The Ministry of Health of Ukraine
Ukrainian Medical Stomatological Academy

Viktor M. Bobyrov, Olena M. Vazhnicha,
Tetyana O. Devyatkina, Natalia M. Devyatkina

PHARMACOLOGY

Textbook for English-speaking students
of higher education institutions
of the Ministry of Health of Ukraine

5th edition, updated

Vinnytsia
Nova Knyha
2020

UDC 615(075)
P56

Recommended by the Ministry of Health of Ukraine as a textbook for students of higher medical educational institutions of the 4th level of accreditation with English as the language of instruction (the letter № 08.01-47/1159 of 02.07.2009)

Recommended by the Academic Council of the Ukrainian Medical Stomatological Academy as a textbook for foreign students-graduands of Master's degree studying "Medicine" in higher educational institutions of the Ministry of Health of Ukraine (protocol of the meeting of the Academic Council No 11 of 24.06.2020)

Reviewers:

Kresyun V. I. — Professor of the Department of Pharmacology of Odessa National Medical University, Corresponding member of National Academy of Medical Scienses of Ukraine, Ukraine State Prize laureate, Honored Scientist of Ukraine, M.D., Ph.D., Professor.
Sheremeta L. M. — Head of the Department of Pharmacology of Ivano-Frankivsk National Medical University, M.D., Ph.D., Professor.
Neporada K. S. – Head of the Department of Biological and Bioorganic Chemistry of Ukrainian Medical Stomatological Academy, M.D., Ph.D., Professor.
Belyaeva O. M. – Head of the Department of Foreign Languages with Latin Language and medical terminology, Ph.D., Associated professor

Authors:

Bobyrov V. M. – Professor of the Department of Experimental and Clinical Pharmacology of Ukrainian Medical Stomatological Academy, Ukraine State Prize laureate, Honored Scientist of Ukraine, M.D., Ph.D., Professor.
Vaznicha O. M. – Professor of the Department of Experimental and Clinical Pharmacology of Ukrainian Medical Stomatological Academy, M.D., Ph.D., Professor.
Devyatkina T. O. – Professor of the Department of Experimental and Clinical Pharmacology of Ukrainian Medical Stomatological Academy, M.D., Ph.D., Professor.
Devyatkina N. M. – Associated professor of the Department of Experimental and Clinical Pharmacology of Ukrainian Medical Stomatological Academy, Ph.D., Associated professor.

Pharmacology : textbook / Viktor M. Bobyrov, Olena M. Vazhnicha, Tetyana O. Devyatkina, Natalia M. Devyatkina. – 5th ed., updated. – Vinnytsia : Nova Knyha, 2020. – 552 p. : il.
P56
ISBN

The textbook for students of higher education institutions of the Ministry of Health of Ukraine has been written according to Pharmacology syllabus and addressed to English-speaking students. The textbook contains main chapters of Pharmacology, outlines the characteristics of medicinal drugs based on modern data concerning their mechanisms of action and usage.

UDC 615(075)

ISBN

УДК 615(075)
Ф24

Рекомендовано Міністерством охорони здоров'я України як підручник для студентів вищих медичних навчальних закладів IV рівня акредитації, які опановують дисципліну англійською мовою (лист № 08.01-47/1159 від 02.07.2009 р.)

Рекомендовано вченою радою Української медичної стоматологічної академії як підручник для іноземних студентів – здобувачів вищої освіти ступеня магістра, які навчаються за спеціальністю № 222 "Медицина" у закладах вищої освіти МОЗ України" (протокол засідання вченої ради № 11 від 24.06.2020 р.)

Рецензенти:

Кресюн В. Й. – професор кафедри фармакології Одеського державного медичного університету, член-кореспондент НАМН України, лауреат Державної премії України, заслужений діяч науки і техніки України, д. мед. н., професор.

Шеремета Л. М. – завідувачка кафедри фармакології Івано-Франківського національного медичного університету, д. мед. н., професор.

Непорада К. С. – завідувачка кафедри біологічної та біоорганічної хімії Української медичної стоматологічної академії, д.мед.н., професор.

Бєляєва О. М. – завідувачка кафедри іноземних мов з латинською мовою та медичною термінологією, к.пед.н., доцент.

Автори:

Бобирьов В. М. – професор кафедри експериментальної та клінічної фармакології Української медичної стоматологічної академії, лауреат Державної премії України, заслужений діяч науки і техніки України, д. мед. н., професор.
Важнича О. М. – професор кафедри експериментальної та клінічної фармакології Української медичної стоматологічної академії, д. мед. н., професор.
Дев'яткіна Т. О. – професор кафедри експериментальної та клінічної фармакології Української медичної стоматологічної академії, д. мед. н., професор.
Дев'яткіна Н. М. – доцент кафедри експериментальної та клінічної фармакології Української медичної стоматологічної академії, к. мед. н., доцент

Фармакологія : підручник для студ. вищих мед. навч. закладів /
Ф24 В. М. Бобирьов, О. М. Важнича, Т. О. Дев'яткіна, Н. М. Дев'яткіна. – 5-те, вид., оновл. та переробл. – Вінниця : Нова Книга, 2020. – 552 с. : іл.
ISBN

Підручник для студентів закладів вищої медичної освіти МОЗ України складено згідно з програмою з фармакології та адресовано студентам з англомовною формою навчання. У підручнику викладено основні розділи фармакології, наведено характеристику лікарських засобів з урахуванням сучасних поглядів на їх механізми дії та застосування.

УДК 615(075)

ISBN

CONTENTS

ABBREVIATIONS

ACE – angiotensin converting enzyme
Ach – acetylcholine
ACTH – adrenocorticotropic hormone
ADH – antidiuretic hormone
AIDS – acquired immune deficiency syndrome
AP – action potential
ATP – adenosin triphosphate
AV – atrioventricular
AZT – azidothymidine
BAL – British antilewisite
BP – blood pressure
cAMP – cyclic adenosyl monophosphate
CBD – cannabidiol
CDCA – chenodeoxycholic acid
CHF – congestive heart failure
Chy – chylomicrones
cGMP – cyclic guanylyl monophosphate
CNS – central nervous system
COMT – catechol-orto-methyltransferase
COX – cyclooxygenase
CTZ – chemoreceptor trigger zone
DHFR – dehydrofolate reductase
DHPS – dehydropteroate synthase
DNA – desoxyribonucleic acid
ECG – electrocardiogram
EDRF – endogenous endothelial-derived relaxation factor
EDTA – edentate (ethylendiamine tetraacetic acid)
FAD – flavine adenine dinucleotide
FMN – flavine adenine mononucleotide
FSH – follicle-stimulating hormone
GABA – γ-aminobutyric acid
GI tract – gastrointestinal tract
GnRH – gonadotropin releasing hormone
HAART – highly active antiretroviral therapy
HDL – high density lipoproteins
hCG – human chorionic gonadotropin
hMG – human menopaustic gonadotropin
HMG CoA – 3-hydroxy-3-methyl-glutaryl-coenzyme A
HIV – human immunodeficiency virus
5HT-receptor – serotonin receptor
IDDM – insulin-dependent diabetes mellitus
IFN – interferon
IHD – ischemic heart desease
IM – intramuscular (-ly)
INH – isoniazid
IV – intravenous (-ly)
LD – lethal dose
LDL – low density lipoproteins
LH – luteinizing hormone
MAO – monoamine oxidase
mRNA – matrix RNA
MRSA – meticillin-resistant staphylococcus aureus
NAD – nicotinamide adenine dinucleotide
NADP – nicotinamide adenine dinucleotide phosphate
NIDDM – non-insulin-dependent diabetes mellitus
NREM-sleep – non-rapid eye movement sleep
NRTI – nucleoside reverse transcriptase inhibitor
NSAID – non-steroidal anti-inflammatory drug
PABA – para-aminobenzoic acid
PANS – parasympathetic autonomic nervous system
PBP – penicillin binding proteins
PDE – phosphodiesterase
PFOR – pyruvate ferredoxine oxyreductase
Pg – prostaglandin
PPAR – peroxisome proliferator-activated receptor
REM-sleep – rapid eye movement sleep
RNA – ribonucleic acid
SA – sinoatrial
SANS – sympathetic autonomic nervous system
SC – subcutaneous (-ly)
spp – speciei (Latin)
SSRI – selective serotonin reuptake inhibitor
STH – somatotropic hormone
T_3 – triiodthyronine
T_4 – thyroxine
THC – Δ^9-tetrahydrocannabinol
TRH – thyrotropin releasing hormone
t-PA – tissue plasminogen activator
tRNA – transport RNA
UDCA – ursodeoxycholic acid
VLDL – very low density lipoproteins
WPW-syndrome – Wolf – Parkinson – White syndrome

PREFACE

Pharmacology is a branch of medical science being a base for all clinical sciences. The knowledge about drugs, their mechanisms of action and usage is necessary for every doctor regardless the speciality.

The purpose of the textbook is to help the students of higher education institutions of the Ministry of Health of Ukraine to study general concepts of Pharmacology and properties of drugs acting on different systems of the human body. This textbook has been prepared in order to improve the students' self-training for the lessons, module controles, and license exam STEP-1. It has been written according to Pharmacology syllabus approved by the Ministry of Health of Ukraine.

The textbook consists of 36 chapters. Chapters 1 and 2 are devoted to General Pharmacology. All others, except chapter 36, include definitions of the respective groups, classification, data on pharmacokinetics, mechanism of action, pharmacodynamics, indications, side effects, and contraindications of existing drugs. Chapter 36 contains information about prescription of different medicinal forms that is practical skill on Pharmacology.

Some modern data concerning pharmacodynamics and toxicodynamics of nicotine and cannabinoids were included into the 5nd edition of the textbook. Serious revision was also made in the part of the textbook devoted to antiviral drugs.

The textbook contains many illustrations which are necessary to understand better the drugs mechanisms and effects.To illustrate this book we have used figures created by ourselves as well as illustrations from Color Atlas on Pharmacology (Lullman H, Albrecht Z., Klaus M, Detlef B. Color Atlas of Pharmacology. – Thieme: Stuttgart – New-York, 2000. – 386 p.). Some figures are from the well known book "Lippincott's Illustrated Reviews: Pharmacology, 4th Edition" edited by R. Finkel, M. A. Clark, L. X. Cubeddu (Lippincott Williams and Wilkins, 2008. – 560 p.), Internet search systems, and other sources.

The textbook contains a bibliography for further study.

All remarks and comments concerning the contents of present textbook will be taken into consideration by the authors for a future edition.

Chapter 1 GENERAL PHARMACOLOGY. PHARMACOKINETICS

DEFINITION OF PHARMACOLOGY

Pharmacology is a science about drugs. It studies their properties and use. The main task of Pharmacology is to create new more effective medicinal drugs for the treatment and prophylaxis of diseases.

Pharmacology is integrated into the system of medical and biological sciences. It receives necessary information from Chemistry, Biochemistry, Genetics, Microbiology, Immunology, etc. At the same time, Pharmacology is the ground of the pharmacotherapy in all branches of the clinical medicine.

MAIN CONCEPTS OF PHARMACOLOGY

Medicinal drug is a medicinal remedy in the shape of medicinal form.

Medicinal remedy is a medicinal substance approved for use in clinic by the special committee of the country.

Medicinal substance is a chemical substance or biologically active substance which can prevent or lessen pathological processes and do a medical action.

Medicinal form is a distinctive size, shape and external appearance of medicinal substance convenient for use.

DRUG DEVELOPMENT

Drug development includes many stages. It is very difficult and expensive.

The process starts with the ***synthesis of novel chemical compounds or obtaining of medicinal substances*** from various sources (plants, animal tissues, microbial cultures, human cells).

The next stage of drug development is ***preclinical testing*** with biochemical-pharmacological investigations, toxicological investigations, study of pharmacokinetics and pharmaceutical technology (methods of drug formulation).

Clinical testing starts with ***Phase I***. During this phase the future drug is studied on healthy subjects and seeks to determine whether effects observed in animal experiments also occur in humans. In ***Phase II*** potential drug is tested on selected patients for therapeutic effecacy in those diseases for which it is intended. In ***Phase III*** the drug is tested on large groups of patients and compared with standard treatments. During clinical trials many drugs are revealed to be unusable. It is known that only one new drug remains from approximately 10000 newly synthesized substances.

The ***decision to approve*** a new drug is made by a National Regulatory Body. Following approval, the new drug may be marketed under a trade name. Long-term postlicensing studies are the purpose of ***Phase IV*** of clinical trials.

GENERAL PHARMACOLOGY

General Pharmacology is a section of Pharmacology which studies general concepts of this science. These concepts are connected with pharmacokinetics and pharmacodynamics (Fig. 1.1).

PHARMACOLOGY = PHARMACOKINETICS + PHARMACODYNAMICS

Fig. 1.1. Two sections of Pharmacology

PHARMACOKINETICS

Pharmacokinetics is a section of Pharmacology that studies how the body acts on the drug. It studies:

- Routes of administration;
- Absorption;
- Distribution;
- Biotransformation;
- Elimination;
- Excretion.

ROUTES OF DRUGS ADMINISTRATION

Routes of drugs administration are divided into ***enteral routes*** (through the gut), ***parenteral routes*** (not through the gut), and ***topical application*** for the local action (Table 1.1).

Table 1.1. **Routes of drugs administration**

Enteral routes	***Parenteral routes***	***Topical application***
1. Sublingual (under the tongue) 2. Oral (by mouth, per os) 3. Rectal (into the rectum)	1. Injections 2. Inhalations (through the respiratory pathways) 3. Intranasal 4. Transcutaneous	1. On the surface of skin 2. On the surface of mucous membrane

After the IV administration a drug has rapid onset and short duration of action. After the oral administration it has slow onset of action, lower concentration, and more durative effect (Fig. 1.2).

After the administration a drug is absorbed and enter the blood. Then it is transported with blood and distributed in the body. After that drug is biotransformed and excreted. These processes results in drugs' inactivation and elimination (Fig. 1.3).

DRUGS ABSORPTION

Absorption is the enter of a drug into the blood from the site of administration.

First-pass metabolism can occur with orally administered drugs. Drugs administered orally are fist exposed to the liver and may be extensively metabolized before reaching the rest of the body. Drugs administered IV enter directly into the systemic circulation and has direct access to the rest of the body.

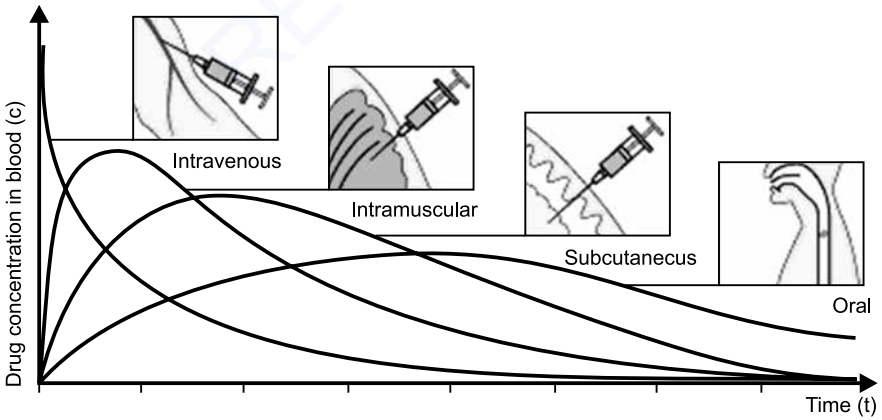

Fig. 1.2. The comparison of drug concentration in the blood in different routes of administration *(by H. Lüllmann, 2000)*

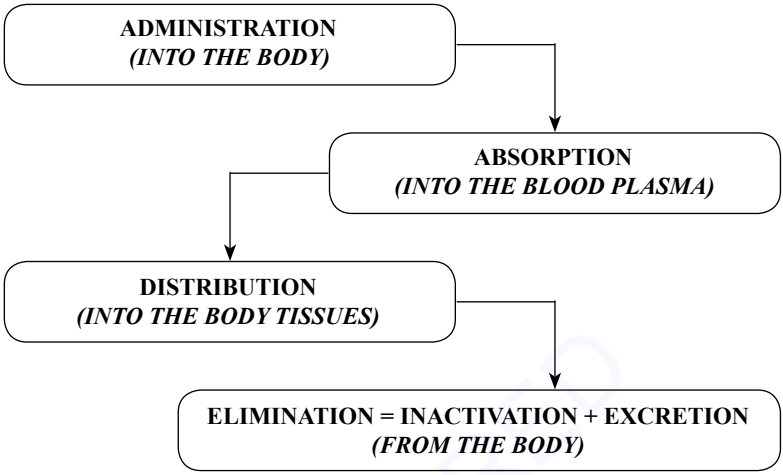

Fig. 1.3. Schematic representation of drug absorption, distribution, and elimination

During the absorption drug crosses cell membranes. There are such kinds of this crossing as passive diffusion, filtration, active transport, and endocytosis (Fig. 1.4).

Passive diffusion is directed down concentration gradient (Fig. 1.5). It does not require energy or carrier and is not saturable. ***Facilitated diffusion (or filtration)*** also is down gradient and energy independent, but needs carrier and is saturable. ***Active transport*** is against gradient, needs energy ATP and carrier, it is saturable. ***Endocytosis*** is a transport of large molecules of molecular complexes with formation of vesicles.

Factors influencing absorption are:

- Chemical structure
- Water- or lipid-solubility
- Ionization
- A medicinal form
- A route of administration
- State of tissues in the site of administration.

Bioavailability is a fraction of administered drug that reaches the systemic circulation. Factors that influence bioavailability are solubility of a drug, nature of a drug, chemical instability, first-pass hepatic metabolism.

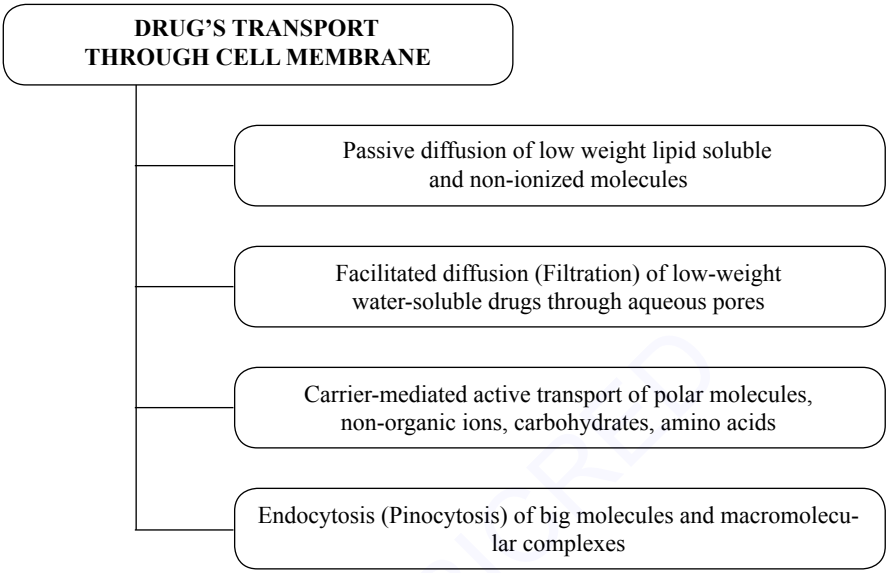

Fig. 1.4. Schematic representation of drug crossing through the cell membrane

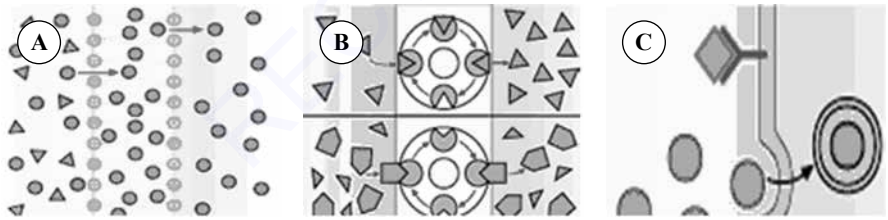

Fig. 1.5. Passive diffusion (A), active transport (B), and endocytosis (C)

DRUGS TRANSPORT IN THE ORGANISM

Drugs transport in the body is realized:

- by proteins of the plasma (e.g., aspirin, sulfa drugs, hormonal preparations, iron);
- by lipoproteins of the plasma (e.g., vitamin A, vitamin D);
- by blood cells (e.g., antibiotics-macrolides);
- by the water fraction of the plasma (e.g., ions of sodium and potassium, glucose).

DRUGS DISTRIBUTION

Distribution is the process by which a drug leaves the blood stream and enters the intersticium (extracellular fluid or the cells of tissues).

Distribution depends on:

- the drug structure;
- the binding of drugs to plasma proteins;
- the blood flow;
- the capillary permeability (blood-tissue barriers, e.g., the blood-brain barrier, placental barrier).

The transfer of drugs into the brain is regulated by the ***blood-brain barrier***. The capillary membrane between the plasma and brain cells is much less permeable to water-soluble drugs than is the membrane between plasma and other tissues. The blood vessels of the fetus and mother are separated by a number of tissue layers that collectively constitute the ***placental barrier***. Drugs that traverse this barrier will reach the fetal circulation. The placental barrier, like the blood-brain barrier, does not prevent transport of all drugs, but is selective, and factors that regulate passage of drugs through any membrane are applicable here.

BIOTRANSFORMATION OF DRUGS

Biotransformation is the metabolism of drugs in the body. The main organ for drugs metabolism is the liver. Biotransformation is realized in two stages (Fig. 1.6).

Stage I reactions are non-synthetic and include oxidation, reduction, hydrolysis. Microsomal oxidation/reduction with participation of enzymes of cytochrome P-450 system is an important way of biotransformation of many drugs. The result of stage I is the formation of active or inactive products which enter the stage II reactions.

Stage II reactions are synthetic (conjugation with glucuronic and sulfuric acids, methylation, acethylation). They lead to the formation of inactve metabolits excreted from the body.

Drugs which increase the activity of microsomal enzymes in the liver are named the ***inductors of microsomal oxidation*** (e.g., phenobarbital, chlorpromazine).

Drugs which decrease the activity of microsomal enzymes in the liver are named the ***inhibitors of microsomal oxidation*** (e.g., metronidazole).

MAIN PATHWAYS OF DRUGS EXCRETION

Excretion is a process by which a drug leaves the body.

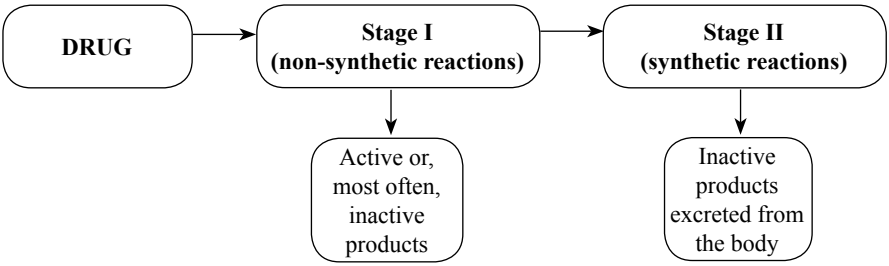

Fig. 1.6. Stages of drugs biotransformation

Drugs are excreted:

- with urine (e.g., sulfa drugs, hypnotics and majority of other drugs);
- with bile (e.g., antibiotic tetracycline);
- with mother's milk (e.g., hypnotics, antibiotics, antihistamines);
- with saliva (e.g., bismuth preparations);
- with sweat (e.g., bromides, chlorides);
- with air (ether for narcosis).

The majority of drugs are excreted by the kidneys. Hydrophilic drugs may be excreted through the kidney in an unchanged form; lipophilic drugs are converted into hydrophilic metabolites which are excreted with urine (Fig. 1.7).

Drugs and their metabolites enter primary urine by glomerular filtration and active secretion in proximal tubules (Fig. 1.8). After that lipid soluble and un-ionized drugs are reabsorbed in distal tubules. Ionized, lipid-insoluble substances stay in urine and are excreted.

PHARMACOKINETIC METRICS

Pharmacokinetics is the mathematical description of the rate and extent of uptake, distribution of drugs in the body. The following are the most commonly measured pharmacokinetic metrics. Some of them are measured directly (maximal and minimal concentration, time to reach maximal concentration), other ones are calculated (volume of distribution, elimination half-life, elimination rate constant, area under the curve, clearance, bioavailability).

Bioavailability is a systemically available fraction of the drug. Bioavailability is a subcategory of absorption and is the fraction of administered dose of unchanged drug that reaches the systemic circulation. When a medication is administered intravenously, its bioavailability is 100%. When the medication is ad-

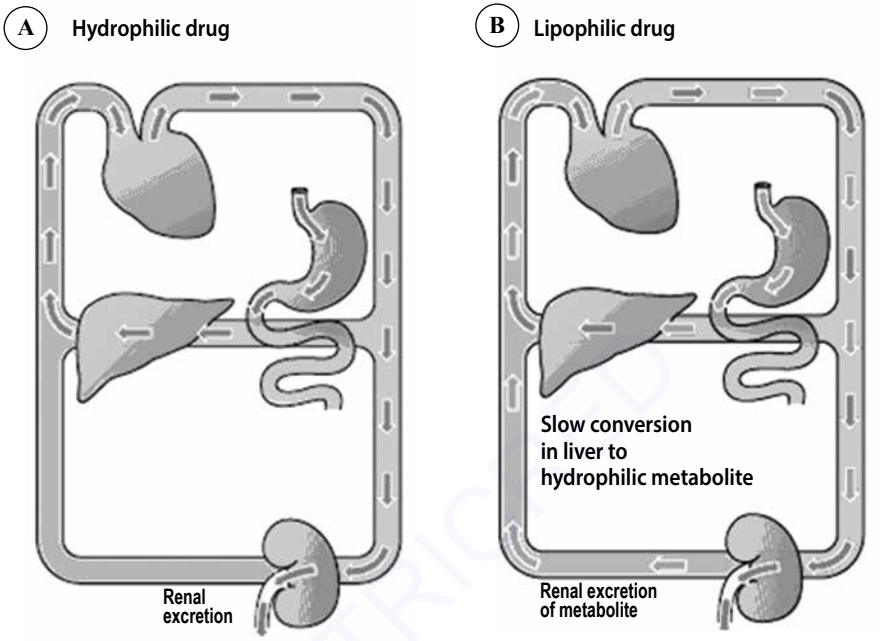

Fig. 1.7. Renal excretion of hydrophilic (A) and lipophilic drugs (B) *(by H. Lüllmann, 2000)*

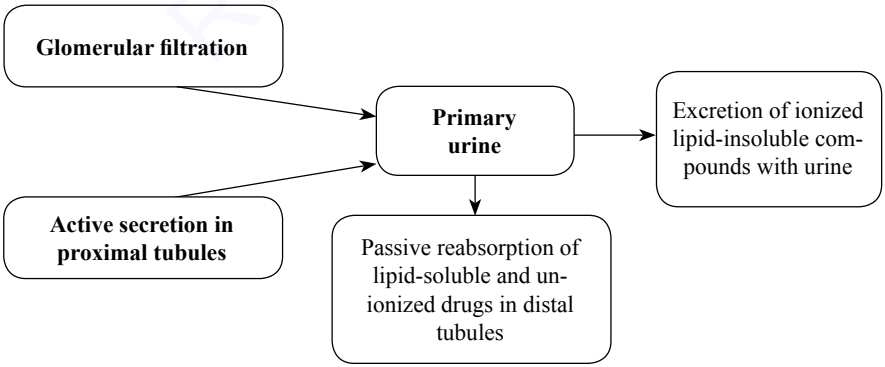

Fig. 1.8. Drugs elimination in the kidney

ministered via other routes, its bioavailability decreases. Absolute bioavailability compares the bioavailability of the active drug in systemic circulation following non-intravenous administration with the bioavailability of the same drug following intravenous administration. Relative bioavailability measures the bioavailability of a formulation of certain drug when compared with another formulation of the same drug, usually an established standard, or through administration via a different route. Relative bioavailability is one of the measures used to assess ***bioequivalence*** between two drug products.

Volume of distribution is the apparent volume in which a drug is distributed (i.e., the parameter relating drug concentration to drug amount in the body).

Elimination half-life is the time required for the concentration of the drug to reach half of its original value.

Steady state concentration is the concentration at stedy state, the situation where the overall intake of a drug is fairly in dynamic equilibrium with its elimination. Steady state is reached when a period of 4 to 5 times the half-life for a drug after regular dosing is started (Fig. 1.9).

Area under the curve is the integral of the concentration-time curve after a single dose or in the steady state.

Clearance is the volume of plasma cleared of the drug per unit time.

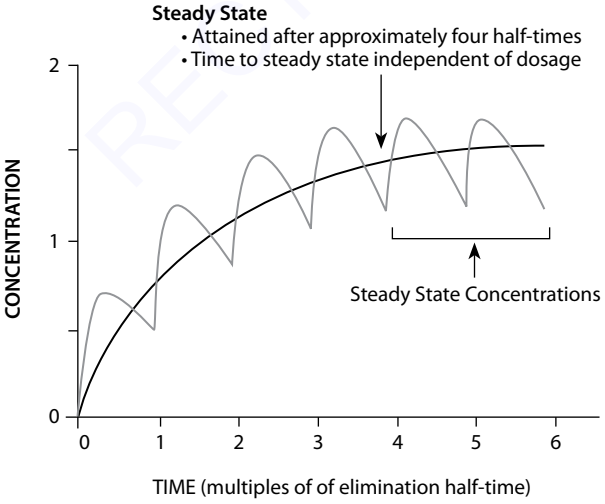

Fig. 1.9. Steady state concentration

TESTS FOR SELF-CONTROL

1. Absorption is:
A. Drug's penetration from the site of administration into the blood
B. Drug's penetration from the blood into tissues
C. Chemical transformation of the drug
D. Drugs interaction
E. Binding to plasma proteins.

2. In the blood plasma drugs are transported:
A. In connection with albumens
B. In connection with lipoproteins
C. In connection with blood cells
D. In water fraction
E. All the listed.

3. The energy-independent mechanisms of drugs crossing through the cell membrane are:
A. Active transport
B. Endocytosis
C. Passive diffusion
D. "Biological pumps"
E. Filtration through pores.

4. Drugs administered by injections:
A. Have a slow onset of action
B. Must be sterile
C. Are suitable for emergency help
D. Need the special equipment
E. Are accompanied by trauma and pain.

5. Phenobarbital is the inducer of microsomal oxidation in the liver. Warfarin is an anticoagulant also biotranformed in microsomes of the liver. What changes in warfarin dosage may be necessary if it is co-administered with phenobarbital?
A. The dose should be decreased due to the inhibition of metabolism of the drug
B. The dose should be increased due to the stimulation of metabolism of the drug
C. The dose should be without any changes
D. The dose should be abolished due to its accumulation
E. All is false.

Answers

1 – A; 2 – E; 3 – C, E; 4 – B, C, D, E; 5 – B.

Chapter 2 GENERAL PHARMACOLOGY. PHARMACODYNAMICS

PHARMACODYNAMICS

Pharmacodynamics is a section of Pharmacology which studies how the drug acts on the body.

It describes:

- effects;
- mechanisms of action;
- drugs interactions;
- doses;
- dose-effect dependence;
- factors influencing a drug action.

TYPES OF DRUGS DOSES

A ***dose*** is the amount of a drugs administered into the body.

The dose may be:

- single (for single administration), daily (for the day of treatment), total (for the course of treatment);
- threshold (minimal dose which begins to act);
- therapeutic (minimal, average, maximal) – the dose which has therapeutic action;
- toxic (minimal, average, maximal) – the dose which causes toxic action;
- mortal (the dose which causes the death of animals in experiments);
- striking dose (a large dose at the start of treatment), supporting dose (an individual dose for supporting a therapeutic effect during long-term treatment).

TYPES OF DRUGS ACTION

Drugs action is displayed as changes in the function of organs and systems.

There are such types of drugs action:

- local (in the site of administration), resorptive (after the absorption into the blood);
- direct (in the organ with target cells), indirect (in other organs, but due to the action on the target organ), reflexive (by reflexes);
- non-selective (on all cells), selective (on celected cells and tissues);
- reversible (with restoration to the initial state after the elimination of the drug), irreversible (without the restoration to the initial state after the elimination of the drug);
- main effects (for which the drug is used), side effects (unwanted effects of a therapeutic dose of the drug).

The factors influencing drug action are the age, weight, gender, physiological state, illness and genetic factors.

Genetic factors represent an important source of interindividual variation in drug response. Relatively few adverse drug effects with a pharmacodynamic basis are known, and most of the well characterised inherited traits take the form of genetic polymorphisms of drug metabolism. Monogenic control of N-acetylation, S-methylation and cytochrome P-450-catalysed oxidation of drugs can have important clinical consequences. Individuals who inherit an impaired ability to perform one or more of these reactions may be at increased risk of concentration-related toxicity. ***Pharmacogenetics*** is the study of inherited genetic differences in drug metabolic pathways which can affect individual responses to drugs, both in terms of therapeutic effect as well as adverse effects. The term pharmacogenetics is often used interchangeably with the term ***pharmacogenomics*** which also investigates the role of genetic differences in relation to drug response and drug behaviour through examination of genes, gene products, and inter- and intra-individual variation in gene expression and function.

Circadian rhythms are genetically determined and are regulated by external synchronizers (light/day cycle). Several biological processes involved in the pharmacokinetics and pharmacodynamics of drugs are subject to circadian variations. ***Chronopharmacology*** studies how biological rhythms impact on drug pharmacokinetics, pharmacodynamics, and toxicity and determines whether time of day administration modifies drug's pharmacological characteristics.

MECHANISMS OF ACTION

Mechanisms of action are events in cells caused by the drug.
Medicinal substances realize their action by:

- changing of the enzymes activity (e.g., neostigmine as acethylcholinesterase inhibitor);
- interaction with receptors (e.g., atropine as M-cholinoblocker);
- influence on ion channels (e.g., local anesthetics);
- influence on the transport systems;
- the antimetabolic mechanism (e.g., methotrexate as folate antagonist);
- the action at the genes level (e.g., anticancer drugs).

RECEPTOR THEORY

Drug receptor is a specialized target macromolecule. The drug binds to the receptor with formation of a drug-receptor complex producing primary pharmacological effect (Fig. 2.1).

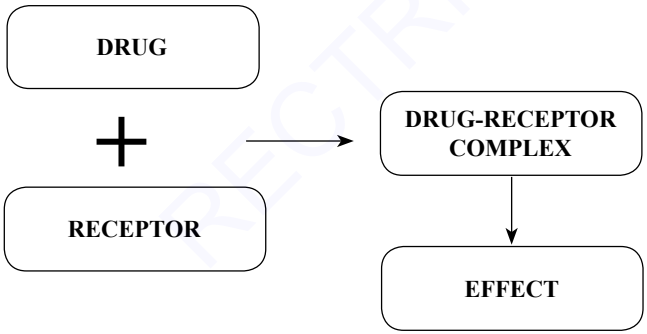

Fig. 2.1. Schematic representation of drug-receptor relationship

Receptors are located:
– in the membrane;
– in the cytoplasma;
– in the nuclei.

Receptors functions are achieved by:
– ion channels (Fig. 2.2);
– cyclic nucleotides (c AMP);

– G- proteins (Fig. 2.2);
– Ca^{++} and protein-kinases.

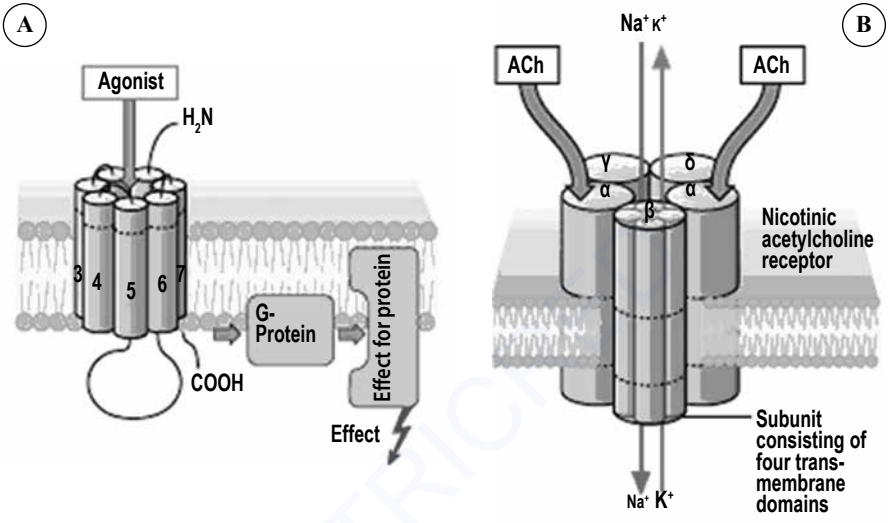

Fig. 2.2. Connection of receptors with G-proteins (A) and ion channels (B) *(by H. Lüllmann, 2000)*

Drugs interaction with receptors (Fig. 2.3):

Agonist is a drug which stimulates the receptor, induces its conformation and causes a specific cell answer (e.g., morphine is a strong agonist of opioid receptors).

Antagonist is a drug which inhibits the receptor – it interacts with the receptor without its conformation, prevents binding of ligand to the receptor resulting in the absence of a specific cell answer (e.g., naloxone is an antgagonist of opioid receptors).

Agonist-antagonist is a drug which stimulates one subtype of the receptor, but blocks another one (e.g., pentazocine is an agonist-antagonist of opioid receptors).

DRUGS INTERACTION

Drugs interaction is the action of one drug on another one (Table 2.1).

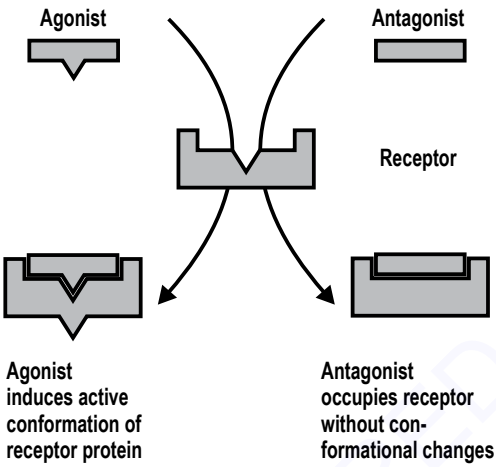

Fig. 2.3. Interaction of an agonist and an antagonist with the pharmacological receptor *(adapted from H. Lüllmann, 2000)*

Table 2.1. **Two types of drugs interaction**

Pharmaceutical (before the administration, outside the body)	***Pharmacological*** (after the administration, inside the body)
1. Physical (changes in agregate state of the drugs). 2. Chemical (chemical reactions between the drugs)	1. Pharmacokinetic (interaction during absorption, distribution, biotransformation, and excretion). 2. Pharmacodynamic (intraction in the tissues during binding to receptors)

COMBINED ACTION OF DRUGS

Combined action of drugs is the action of two or more co-administered drugs on the organism (Table 2.2).

SIDE EFFECTS

Side effects are non-useful effects of drugs in the therapeutic doses:

- direct toxic effects (e.g., ototoxicity, neurotoxicity, and nefrotoxicity of streptomycin);

Table 2.2. **Main kinds of drugs combined action**

Synergism (the strengthening of the effect)	***Antagonism*** (the weakening of the effect)
1. Addition (C = A + B). 2. Potentiation (C > A + B).	1. Chemical. 2. Physical. 3. Physiological (competition in binding to receptors, action on different receptors with the opposite effect).

- allergic reactions as immune reactions of hypersensitivity (e.g., anaphylaxis caused by penicillin) (Fig. 2.4);

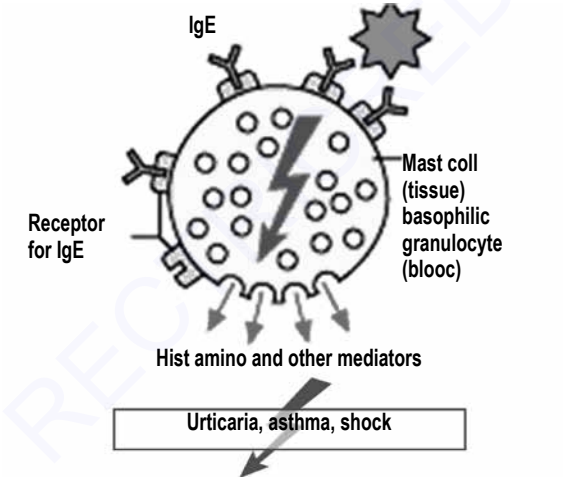

Fig. 2.4. Allergic reaction *(by H. Lüllmann, 2000)*

- idiosyncrasy as abnormal reaction occurred after the fist drug administration and caused by genetic factors (e.g., hemolysis of erythrocytes afer the use of quinine in patients deficient on glucose-6-phosphate dehydrogenase);
- embryotoxic, fetotoxic and teratogenic effects as a negative influence on the embrio and the fetus during pregnancy (e.g., hypoplasia of tooth enamel caused by tetracyclin) (Table 2.3);
- a cancerogenic and mutagenic action as the ability to provoke the development of malignant tumors (e.g., secondary malignancy caused by leukopoiesis inhibitors).

Table 2.3. **Drugs negative influence on the embryo and fetus**

Age of the fetus (weeks)	***1–2***	***2.5–12***	***12–38***
Development stage	Nidation	Embryo: organ development	Fetus: growth and maturation
Result of the negative drug influence	Fetal death	Malformations	Functional disturbances

EFFECTS OF REPEATED DOSES OF DRUGS

Accumulation (material and functional) is the accumulation of a drug or its effects (e.g., material accumulation of digitoxin, functional accumulation of antidepressants).

Tolerance (habituation) is a decrease of drug's action after its repeated administration (e.g., tolerance to hypnotics, alcohol, nitroglycerine or laxatives).

Tachyphylaxis is the rapid form of tolerance developing during the first day of treatment (e.g, tachyphylaxis to ephedrine).

Drug dependence is irresistible aspiration to take the drug for euphoria or improvement of condition.

There are two types of drug dependence:

- ***physical dependence*** – if a patent wants to take the drug for altering general state and mood. It is characterized by abstinence. ***Abstinence*** is a phenomenon of deprivation. Ethyl alcohol and narcotic analgesics may cause physical dependence;
- ***psychological dependence*** – if a patient wants to take the drug for altering the mood (for euphoria). Such kind of drug dependence is caused by psychomotor stimulants.

TESTS FOR SELF-CONTROL

1. All concerning doses of drugs is correct, except:

A. Single dose is a dose for one administration
B. Therapeutic dose may be minimal, overage, and maximal
C. LD-50 causes the death of 50% of animals in the experiments
D. Supporting dose is a high dose at the start of treatment
E. Toxic dose is the amount of the drug causing poisoning.

2. The notions connected with a combined action of medications are:
A. Synergism and antagonism
B. Material accumulation
C. Drug dependence
D. Tolerance and tachyphylaxis
E. Elimination and excretion.

3. Types of drugs action are represented by:
A. A local and resorptive action
B. A reversible and irreversible action
C. A direct and indirect action
D. Pharmaceutical drugs interaction
E. A combined action of drugs.

4. The true information concerning the receptor mechanism of action is:
A. A drug stimulating the receptor is its agonist
B. A drug inhibiting the receptor is its antagonist
C. A drug stimulating one subtype of receptor and inhibiting another one is an agonist-antagonist
D. A drug bound to the receptor with low affinity is a partial agonist
E. A drug without affinity to the receptor is its strong agonist.

5. A patient with malaria was treated with quinine. Treatment was complicated by hemolysis of red blood cells. Such a side effect caused by quinine in patients with deficit of glucose-6- phosphate dehydrogenase is:
A. A direct toxic action
B. Idiosyncrasy
C. An allergic reaction
D. A cancerogenic action
E. A teratogenic action.

Answers

1 – D; 2 – A; 3 – A, B, C; 4 – A, B, C, D; 5 – B.

Chapter 3 DRUGS INHIBITING AFFERENT INNERVATION

DRUGS INHIBITING AFFERENT INNERVATION

Drugs inhibiting afferent innervation are divided into local anesthetics, astringents, adsorbents, and protectives (coverings).

DRUGS FOR LOCAL ANESTHESIA

Local anesthesia

Local anesthesia is a reversible inhibition of the pain sensation in a limited area of the body without impairment of consciousness.

The kinds of local anesthesia are:

- surface anesthesia;
- infiltration anesthesia;
- conduction anesthesia;
- spinal anesthesia.

LOCAL ANESTHETICS

Local anesthetics are the drugs for local anesthesia. Their molecules have 3 common structural elements: lipophilic aromatic part, hydrophylic amine and ester or amide linkage. All local anesthetics are weak bases and alkalic pH increases their ability to penetrate lipophilic barriers and cell membranes (Fig. 3.1).

CLASSIFICATION

1. Esters of para-aminobenzoic acid:
   – Procaine (Novocaine);

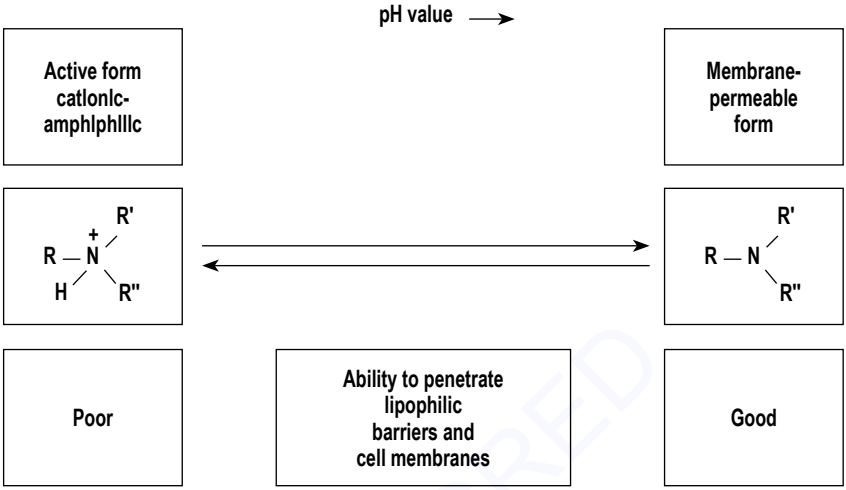

Fig. 3.1. The influence of pH on properties of local anesthetics

- Benzocaine (Anaesthesine);
- Tetracaine (Dicaine).

2. Substituted amides of acetalinidin:
   - Lidocaine (Xycaine);
   - Trimecaine;
   - Piromecaine;
   - Articaine, Ultracaine;
   - Marcaine (Bupivacaine).

Distinctive features of local anesthetics of different groups

Existing groups of local anesthetics differ from one another on duration of action, biotransformation, stability in the site of inflammation, and the interaction with sulfonamides (Table 3.1).

Table 3.1. **Distinguishes between the esters and amides**

Esters	***Amides***
Have short action	Have long action
Are metabolized by esterases of the blood	Are metabolized in the liver
Are not active at acidic pH (in the site of purulent inflammation)	Are active at acidic pH (in the site of purulent inflammation)
Decrease the effect of sulfa drugs.	Do not interact with sulfa drugs.

Mechanism of action

Local anesthetics plug sodium-ion channels and in such a way block initiation and propagation of action potential (AP) (Fig. 3.2).

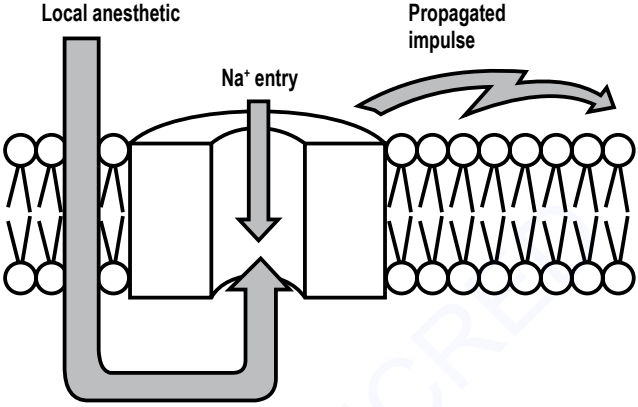

Fig. 3.2. Mechanism of action of local anesthetics *(by H. Lüllmann, 2000)*

Purpose of adrenaline addition to local anesthetics

Addition of adrenaline to solutions of local anesthetics causes constriction of blood vessels. That results in a decrease of the absorption of a local anesthetic and leads to the prolongation of anesthesia.

PECULIARITIES OF PREPARATIONS

Procaine (Novocaine) is an ester; dilates blood vessels; is used for infiltration, conductive and spinal anesthesia; other indications are spasms of blood vessels and smooth muscles, pain syndromes, arrhythmia, toxicosis of pregnancy; may cause allergic complications including anaphylaxis, collapse, hypotension, seizures (in overdose).

Tetracaine (Dicaine) is an ester; dilates blood vessels; is more active and more toxic than procaine; is used only for surface anesthesia.

Benzocaine (Anaesthesine) is an ester; is less active than procaine; is not dissolved in water; is used only for surface anesthesia in burns, wounds, diseases of skin and mucous membranes; is not toxic, but may cause methemoglobin formation when is used on large areas of skin lesions.

Lidocaine (Xycaine) is an amide; acts longer than procaine; is more active; is suitable for all types of anesthesia; is used for the treatment of ventricular tachyarrhythmia (IV).

Trimecaine is an amide; pharmacological properties are similar to lidocaine.

Bupivacaine (Marcaine) is an amide; is one of the most active local anesthetics; is used for infiltration, conductive and spinal anesthesia; has toxic action on the heart.

Articaine is an amide; more active than lidocaine and procaine; acts during 1–5 hrs; is used for infiltration and conductive anesthesia; is widely used in dentistry. Combination of articaine with vasoconstrictor is known as ***Ultracaine***.

ASTRINGENTS

Astringents are the agents that precipitate proteins and form albuminates on the surface of the damaged skin or mucous membrane, thus protecting the receptors from irritating factors and relieving pain.

CLASSIFICATION

1. Organic substances:
   - Tannin;
   - Tannalbin;
   - herb of Saint-John's-wort *(herba Hyperici)*;
   - flowers of chamomile *(flos Chamommillae)*;
   - leaves of salvia *(folium Salviae)*;
   - bark of oak *(cortex Quercus)*;
2. Non-organic substances:
   - Bismuth subnitrate.

PECULIARITIES OF PREPARATIONS

Tannin is an organic astringent; is used in the form of solution, ointment, powder for external use; has astringent and antitoxic action (is an antidote in poisonings with alkaloids and salts of metals); is used for gargling in diseases of oral mucosa, for processing of burns, for lavage of the stomach in acute poisonings; may disturb digestion if it is taken orally.

Tannalbin is a compound of tannin; is taken orally to treat dyspepsia, enteritis, enterocolitis; does not bind to enzymes in the gut and does not disturb digestion.

Bark of oak (cortex Quercus) (Fig. 3.3) is used in the form of decoction; is applied for gargling in stomatitis, gingivitis, paradontitis; may be also used to treat burns, wounds.

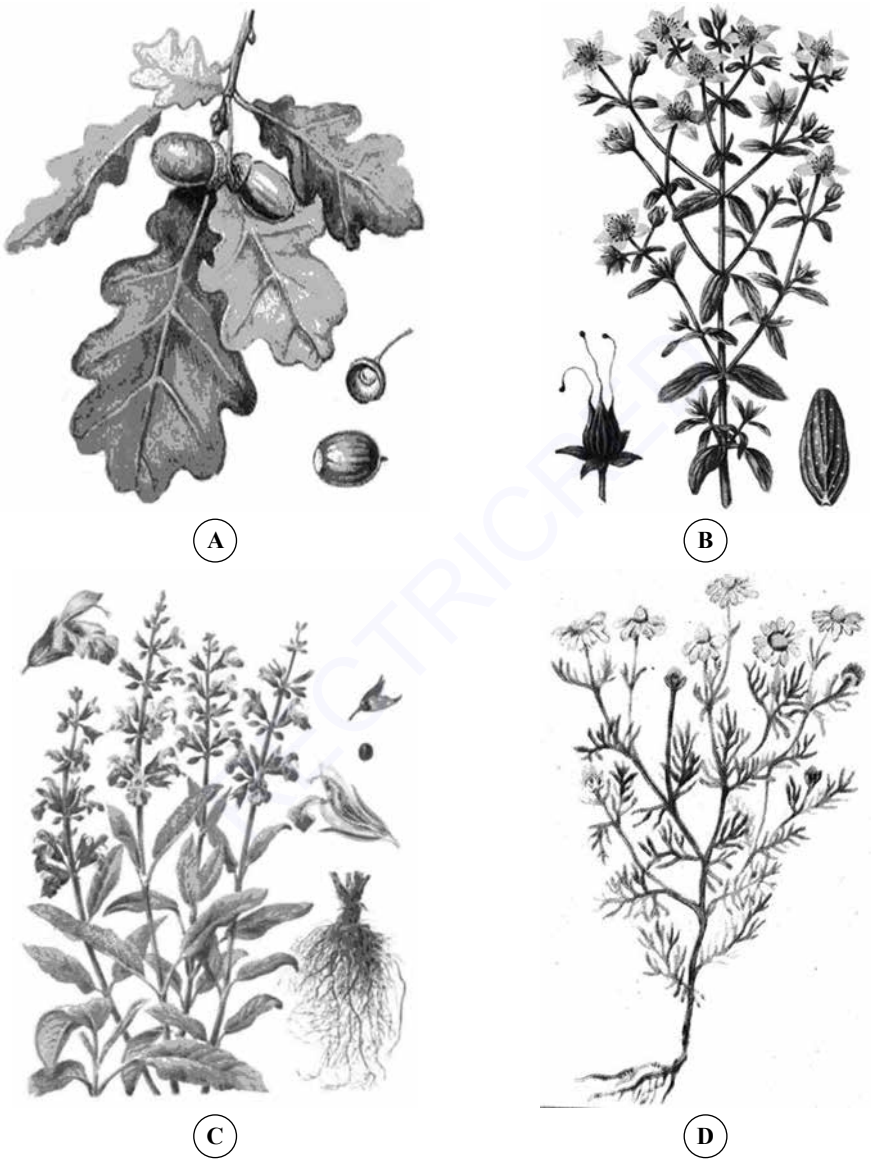

Fig. 3.3. Medicinal plants containing astringent substances:
A – oak; B – saint john's-wort; C – salvia; D – chamomile

Leaves of salvia (Folium Salviae), herb of saint-john's-wort (herba Hyperici), flowers of chamomile (flos Chamommillae) (Fig. 3.3) are used in the form of infusions; they have astringent, anti-inflammatory, antimicrobial effects, stimulate regeneration of tissues; indications are similar to indications for the use of the oak bark; are widely used in dentistry.

Bismuth subnitrate is non-organic astringent; is taken orally in ulcer of the stomach and duodenum, enterocolitis; is applied topically to treat wounds, ulcers, and burns of the skin.

ADSORBENTS

Adsorbents are insoluble fine powders which have a large active surface capable of fixing irritating and poisonous substances dissolved in water and gases, thus preventing their absorption in the GI tract and protecting receptors.

PECULIARITIES OF PREPARATIONS

Activated charcoal (Carbo activatus) is administered orally in the form of tablets or non-dosed powder; is used in acute poisonings (as a universal antidote) as well as in enterocolitis, enteritis, dyspepsia, meteorism.

Enterosgel has porous structure of hydrophobic silicone matrix, which is characterized by a sorption action with respect only to toxic metabolites of molecular weight 70–1000. In the lumen of the GI tract, the drug binds and removes from the body endogenous and exogenous toxic substances of various nature. Enterosgel does not reduce the absorption of vitamins and trace elements. It is used in adults and children as a detoxification agent.

PROTECTIVES

Protectives are the substances that form colloidal solutions covering the skin and mucous membranes and prevent stimulation of receptors. ***Mucus of starch (Mucilago Amyli)*** *and* ***decoction from seeds of flax (Linum)*** belong to this group. They are applied topically to treat burns, wounds, ulcers in mucous membranes and are taken orally in acute gastritis, enterocolitis or together with drugs which irritate gastric mucosa.

TESTS FOR SELF-CONTROL

1. Local anesthetics from esters group are all, except:

A. Procaine

B. Tetracaine
C. Benzocaine
D. Cocaine
E. Lidocaine.

2. Tannin realizes its anti-inflammatory action due to:
A. The formation of albuminates on the surface of the mucous membrane
B. The absorption of toxic substances
C. The formation of colloidal covering on the mucous membrane
D. Local anesthesia
E. The irritation of sensitive nerve endings.

3. Local anesthetics have the following common properties:
A. They are bases
B. The anesthetic activity rises at alkaline pH
C. Ester local anesthetics are metabolized by esterases in blood
D. Amide local anesthetics are metabolized by hepatocytes
E. The duration of action of esters is longer than that of amides.

4. The starch mucus realizes its action due to:
A. The formation of albuminates on the surface of the mucous membrane
B. The absorption of toxic substances
C. The formation of colloidal covering on the mucous membrane
D. Local anesthesia
E. The protection of sensitive nerve endings from irritation.

5. Lidocaine was administered to the patient with ventricular tachyarrhythmia and caused stabilization of the heart rate. Its mechanism of action is:
A. The blockage of sodium ion channels
B. The blockage of calcium ion channels
C. The opening of potassium channels
D. The blockage of adrenergic receptors
E. None of the listed above.

Answers

1 – E; 2 – A; 3 – A, B, C, D; 4 – C, E; 5 – A.

Chapter 4 DRUGS STIMULATING AFFERENT INNERVATION

DRUGS STIMULATING AFFERENT INNERVATION

They are represented by drugs increasing the frequency of afferent impulses running from sensitive nerve endings to CNS.

CLASSIFICATION

A. *Irritants:*
- Menthol;
- Mustard seeds;
- Solution of ammonia;
- Camphor;
- Purified turpentine (Turpentine oil).

B. *Expectorants (reflexly acting):*
- Herb of *Thermopsis;*
- Root of *Althea;*
- Mucaltin.

C. *Bitters:*
- Tincture of *Absinthium.*

D. *Emetic drugs (reflexly acting):*
- Root of *Ipecacuanna;*
- Copper sulfate;
- Zinc sulfate.

E. *Laxatives and purgatives:*

1. Acting in the small intestine:
   - Castor oil;

2. Acting in bowels:
   – Root of *Rheum;*
   – Leaves of *Senna;*
   – Bisacodyl.
3. Acting in all sections of the intestine:
   – Magnesium sulfate;
   – Sodium sulfate.

IRRITANTS

Irritants are medications irritating sensetive nerve endings in the skin and mucous membranes and producing local vascular reactions, reflexive actions, and distractive effects.

MENTHOL

- is crystals with pleasant aroma dissolved in lipids and alcohol;
- is contained in mint (Fig. 4.1);
- is applied topically, is administered sublingually (as ***validol***) or by inhalations

Fig. 4.1. Medicinal plants containing irritants: A – mint; B – mustard

- irritates cold-sensitive nerve endings in the skin and mucous membranes, constricts blood vessels in the site of application, that's why locally decreases the edema and exudation; initiates reflexes changing vascular tone in the heart and brain tunics; decreases pain from internal organs and deep tissues (due to prevalence of pain impulses from the covering tissues over the impulsation from the internal tissues);
- indications: myositis, myalgia, peripheral neuritis, neuralgia, arthritis, arthralgia, bronchitis, inflammation of respiratory airways, rhinitis, headache, spasm of coronary blood vessels (in the form of validol), in dentistry is used as drops for the diminishing a toothache and for the improvement of taste and odor of dental pastes, dental powders;
- may cause disturbances of breathing if it is used for inhalation in high concentration.

MUSTARD SEEDS

- is a plant preparation (Fig. 4.1) in the form of a mustard plaster or mustard bags;
- is applied topically;
- contains glycoside synegrin and enzyme myrosin; in warm water (38 ºC) myrosin destroys synegrin with release of mustard oil; this oil irritates sensitive nerve endings in the skin, dilates blood vessels and improves trophy in the site of application; has reflexive action and decreases pain in the internal tissues; reflexly lowers BP, decreases anginal pain, accelerates recovering from pneumonia;
- indications: myositis, myalgia, peripheral neuritis, neuralgia, arthritis, arthralgia, pneumonia (is applied on the skin projections of the lungs), angina pectoris (on the area of the heart), hypertension (on the occipital area);
- may cause severe irritation and burn of the skin.

SOLUTION OF AMMONIA

- has antimicrobial, weak detergent, irritating and reflexive actions;
- is used for reflexive stimulation of respiration in syncope. For this purpose it is applied on a small piece of the cotton wool and used for inhalation through the nose, irritates sensitive nerve endings in the nasal mucosa, initiates reflexes, stimulates the centers in the medulla of the brain and in such a way stimulates respiration and increases BP;
- is used for processing of surgeon's hands;
- high concentration of ammonia vapors may cause burn of the mucous membrane and arrest of breathing.

CAMPHOR

Camphor is a neurotropic drug (analeptic) with antimicrobial and irritative effects. It is used topically to treat myositis, myalgia, peripheral neuritis, neuralgia, arthritis, arthralgia, external otitis, for prevention of the skin necrosis in immobilized patients.

PURIFIED TURPENTINE

Purified turpentine (turpentine oil) is made from conifers, mainly pine trees. It has disinfecting, distracting, irritating, and analgesic effects. Irritant effect is exerted by active substances, which are released under the influence of turpentine: histamine and other mediators cause skin reddening, minor swelling, vasodilation; endorphins and enkephalins produce anesthesia. Purified turpentine is used as ingredient of liniments and ointments in diseases of peripheral nerves, muscles, joints as well as in acute and chronic diseases of the bronchi and lungs.

EXPECTORANTS

Expectorants are drugs which stimulate the secretion and expelling of liquid sputum from the bronchi.

Reflexly acting expectorants irritate receptors of the stomach mucosa, initiate reflexes, due to which increases the secretion of bronchial glands, the contractility of the epithelium and muscles and help mucus expelling. ***Infusion from the herb of Thermopsis*** (Fig. 4.2) also excites the respiratory center. ***Decoction from the root of Althea and mucaltin*** (Fig. 4.2) have a covering effect.

BITTERS

Bitters are drugs stimulating appetite (appetizers) by irritation of receptors in the oral cavity. ***Tincture of Absinthium*** (Fig. 4.3) is a representative of this pharmacological group.

Irritation of taste-sensitive nerve endings initiates reflexes resulting in the stimulation of gastric juice production. The reflexive mechanism of the action of bitters was investigated by a Russian physiologist I. P. Pavlov.

Bitters are taken orally before meals in asthenia, a loss of appetite after surgeries and infections, in hypoacidic gastritis.

Bitters may cause inhibition of gastric secretion if they are taken during or after meals.

Fig. 4.2. Medicinal plants containing expectorants: A – *Thermopsis;* B – *Althea*

Fig. 4.3. *Arthemisia absinthium* containing bitter

EMETIC DRUGS

Emetic drugs are medications provoking vomiting.

They are divided into:

1. Drugs of central action – ***apomorphine hydrochloride*** acting on the chemoreceptors of the trigger zone (CTZ) connecting to the emetic center. Apomorphine is a dopaminergic preparation. It causes stimulation of CTZ and provokes vomiting; is used in acute poisonings; may cause the rupture of stomach wall and esophagus, an increase in BP; is contraindicated in poisonings with acids and alkalis, ulcer of the stomach, acute abdomen, severe hypertension and pregnancy.

2. Drugs of the peripheral action – ***plant drugs of Thermopsis, Ipecacuanna, sulfates of zinc and copper.*** They are administered orally, irritate sensitive nerve endings in the stomach and cause vomiting reflexly. Now these preparations are used rarely.

LAXATIVES AND PURGATIVES (CATHARTICS)

Laxatives and purgatives (cathartics) stimulate afferent nerves to initiate a reflex increase in the gut motility (Fig. 4.4).

Laxatives are classified according the site of action as well as by the origin.

Plant cathartics are divided into oils (Castor oil) and the drugs consisting of anthraquinone derivatives.

Castor oil (Oleum Ricini) is bean oil which is hydrolyzed in the gut to the ricinoleic acid and glycerol. The ricinoleic acid acts on the ileum and colon to in-

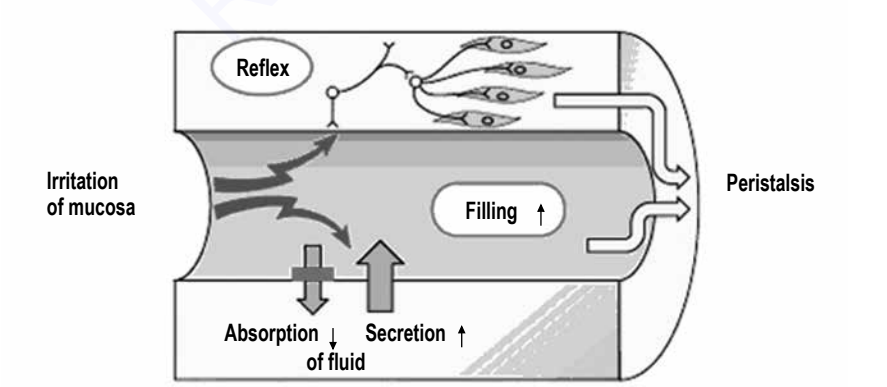

Fig. 4.4. Stimulation of peristalsis by mucosal irritation *(by H. Lüllmann, 2000)*

duce an increased fluid secretion and colonic contraction (Fig. 4.5). It is used in acute constipation.

Anthraquinone derivatives (drugs of Senna, Rheum, Aloe, etc). They are transformed to anthranol which irritates receptors of colon and produces evacuation in 8–10 hrs (Fig. 4.6). The main drugs are ***senadexin, senade, cafiol,*** etc.

Synthetic drugs – isaphenin, bisacodyl, sodium picosulfate (guttalax) also irritate colon receptors and are used as antaguinone derivatives in chronic constipation.

Osmotic purgatives (magnesium sulfate, sodium sulfate) increase lumen osmolarity, drive additional fluid into the GI tract, and irritate intestine receptors. They are used in the intoxication, acute constipation, before some diagnostic procedures, or in treatment with some antihelminthics.

TESTS FOR SELF-CONTROL

1. Mustard seeds realize their action by:
A. The formation of albuminates
B. The absorption of toxic substances
C. The formation of colloidal covering
D. The stimulation of nerve endings in the gut
E. The irritation of sensitive nerve endings in the skin.

2. Menthol is characterized by all, except:
A. The irritation of sensitive nerve endings
B. A reflexive action on coronary blood vessels
C. The constriction of blood vessels in the site of application
D. Vasodilation in the site of application
E. The improvement of taste and odor of dental powders and pastes.

3. The reflexly acting expectorants are:
A. Sodium bicarbonate
B. Trypsin
C. Mucaltin
D. Infusion from the herb of *Thermopsis*
E. Decoction from the root of *Althea*.

4. Bitters are:
A. Stimulants of appetite
B. Suppressors of appetite

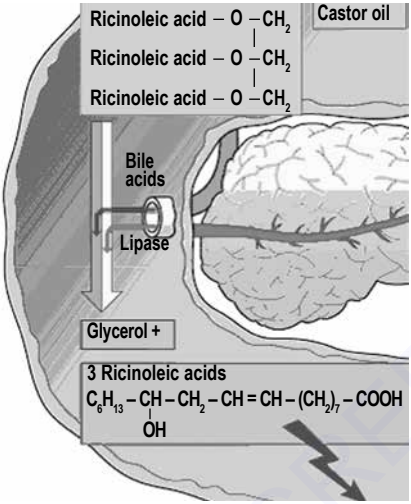

Fig. 4.5. Mechanism of action of Castor oil *(by H. Lüllmann, 2000)*

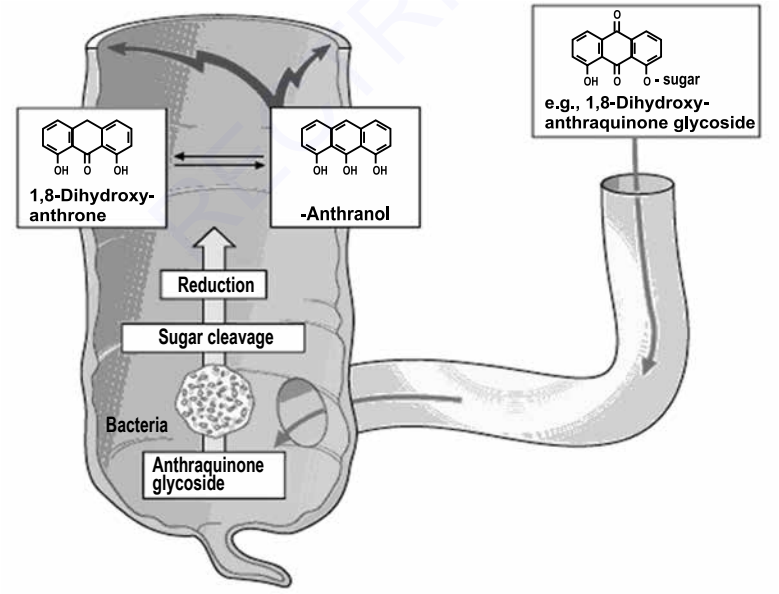

Fig. 4.6. Mechanism of action of anthraquinone derivatives – large-bowel irritant laxatives *(by H. Lüllmann, 2000)*

C. Drugs for replacement therapy
D. Antimicrobial drugs for the treatment of peptic ulcer
E. Stimulants of gastric secretion.

5. A patient with chronic constipation was prescribed with a synthetic laxative. This drug is in the form of rectal suppositories. It is transformed into diphenol and acts in the bowels. What drug was prescibed?
A. Castor oil
B. Phenolphtalein
C. Magnesium sulphate
D. Root of *Rheum*
E. Bisacodyl.

Answers

1 – E; 2 – D; 3 – C, D, E; 4 – A, E; 5 – E.

Chapter 5 CHOLINERGIC AGONISTS

AUTONOMIC NERVOUS SYSTEM

The ***autonomic nervous system*** regulates a function of the internal organs. It is divided into two sections: ***the sympathetic system (SANS)*** and ***the parasympathetic system (PANS)*** which exert opposite actions (Table 5.1).

Table 5.1. **Some distinguishing features in the structure of parasympathetic and sympathetic nervous systems**

Part of the system	***Parasympathetic system***	***Sympathetic system***
Centers (the 1st neuron)	Medulla of the brain, sacral region of the spinal cord	Thoraco-lumbar region of the spinal cord
Ganglia (the 2nd neuron)	In the tissues of effector organs or near them	Near the spinal cord

CHOLINERGIC SYNAPSE

The nerve endings of postganglionic parasympathetic nerves release a neurotransmitter ***acetylcholine*** (Fig. 5.1). Such synapses are named ***cholinergic synapses.***

Each synapse contains a presynaptic membrane, a synaptic gap (cleft), and a postsynaptic membrane with cholinergic receptors (Fig. 5.2). Acetylcholine is synthesized in the presynaptic part of the nerve ending. It is deposited in vesicles, is released into the synaptic gap, and interacts with cholinoreceptors on the postsynaptic membrane. ***Acetylcholinesterase*** produces degradation of the neurotransmitter in the synaptic gap. Choline is taken up by the neuron and used for the synthesis of acetylcholine.

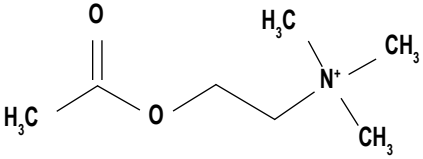

Fig. 5.1. Structure of acetylcholine

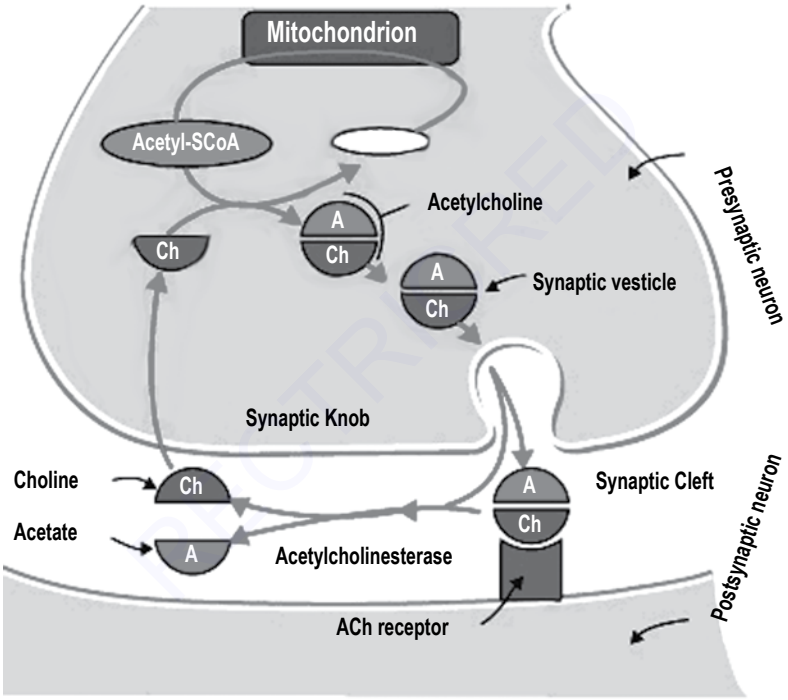

Fig. 5.2. Structure and function of cholinergic synapse *(http://images.yandex.ru)*

CHOLINORECEPTORS

There are two types of cholinergic receptors:

– ***M-cholinoreceptors (muscarinic)*** with subtypes M_1, M_2, M_3, M_4, M_5

– ***N-cholinoreceptors (nicotinic)*** with neuronal and muscular subtypes.

Cholinoreceptors are located in different organs and tissues, but some of these tissues are characterized by prevalence of M- or N-cholinergic receptors (Table 5.2).

Table 5.2. **Location of cholinergic receptors**

M-cholinoreceptors	***N-cholinoreceptors***
CNS	CNS
Eye	Adrenal medulla
Heart	Carotid glomerulus
Blood vessels	Sympathetic and parasympathetic ganglia
Bronchi (smooth muscles, glands)	Skeletal muscles
Gut (smooth muscles, glands)	
Urinary bladder	
Uterus	
Sweat glands	

CHOLINERGIC DRUGS

Cholinergic drugs are preparations acting on cholinergic neurotransmission. They are divided into ***cholinergic agonists*** (= ***cholinomimetics, cholino-positive drugs***) and ***cholinergic antagonists*** (= ***cholinoblockers, cholino-negative drugs***) (Fig. 5.3). Cholinomimetics increase cholinergic neurotransmission. Cholinoblockers decrease cholinergic neurotransmission.

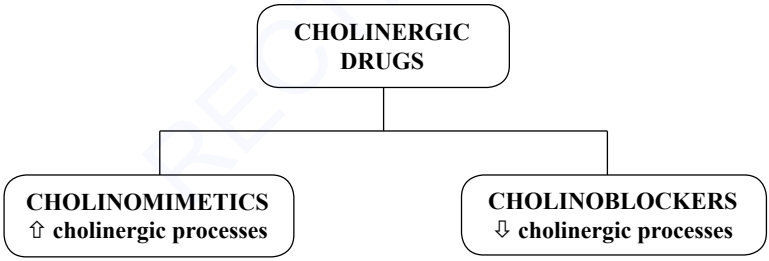

Fig. 5.3. Cholinergic drugs

CHOLINOMIMETICS

CLASSIFICATION

A. *M-,N-cholinomimetics:*

1. Direct-acting:
   - Acetylcholine;
   - Carbachol (Carbocholine).

2. Indirect-acting (anticholinesterases):
   – Neostigmine methylsulfate (Proserine);
   – Physostigmine salicylate;
   – Pyridostigmine bromide;
   – Galanthamine hydrobromide;
   – Isoflurophate.

B. *M-cholinomimetics:*
   – Pilocarpine hydrochloride;
   – Aceclidine.

C. *N-cholinomimetics:*
   – Cytisine (Cytiton);
   – Lobeline hydrochloride.

DRUGS WITH M-CHOLINOMIMETIC EFFECTS

Carbahol, pilocarpine, and anticholinesterases have clinically significant M-cholinomimetic activity and indications grounded on such activity (Table 5.3).

Table 5.3. **Pharmacodynamics and indications for M-,N- and M-cholinomimetics**

M-cholinomimetic effects	***Indications***
Miosis (constriction of eye pupils) Spasm of accommodation (regulation of the eye lens for near vision) A decrease in intra-eye pressure	Glaucoma
Stimulation of glands secretion An increase in the salivation	Xerostomia
An increase in smooth muscles tone	Atonia of the intestine and urinary bladder after surgeries
Bradycardia Blood vessels dilation	Heart arrhythmia

Side effects

1. Hypersalivation
2. Pain in the abdomen
3. Diarrhea
4. Spasm of the bronchi
5. Bradycardia
6. Frequent urination
7. Sweatiness.

PECULIARITIES OF PREPARATIONS

Carbachol (Carbacholine) has a chemical structure similar to acetylcholine, but is not destroyed by cholinesterases; is a direct acting M-, N-cholinomimetic with the prevalence of M-cholinergic activity; now is applied topically for the treatment of glaucoma (eye drops).

Pilocarpine is an alkaloid from *Pilocarpus pinnatifolius* (Fig. 5.4), is M-cholinomimetic; has a strong systemic M-cholinomimetic activity, but is toxic; nowadays is used only for the treatment of glaucoma (eye drops, eye ointment, or eye membranes), seldom is used in xerostomia.

Aceclidine is a synthetic preparation; is administered SC, IM, or topically (eye drops); is not toxic; does not penetrate CNS; is M-cholinomimetic; is used for the treatment of atonia of the intestine and urinary bladder as well as for glaucoma.

ANTICHOLINESTERASES

Anticholinesterases are indirect-acting M-, N-cholinomimetics with a reversible or irreversible type of action.

Mechanism of action

Anticholinesterases bind to acetylcholinesterase in the synaptic gap, inhibit it and decrease acetylcholine destruction.

Fig. 5.4. *Pilocarpus pinnatifolius* containing pilocarpine

The result is the accumulation of acetylcholine in the synaptic gap and an increase in acetylcholine interaction with M- and N-cholinoreceptors (Fig. 5.5).

Pharmacodynamics

- all M-cholinomimetic effects on the internal organs (similar to those of carbachol and pilocarpine);
- an increase in neuromuscular transmission resulting from the accumulation of acetylcholine at the neuromuscular junction.

Side effects

They are the same as the side effects of direct M-,N- and M-cholinomimetics.

PECULIARITIES OF PREPARATIONS

Physostigmine is an alkaloid from *Phyzostigma venenosum* (Fig. 5.6); is well absorbed; penetrates CNS; has a reversible anticholinesterase action; is used for

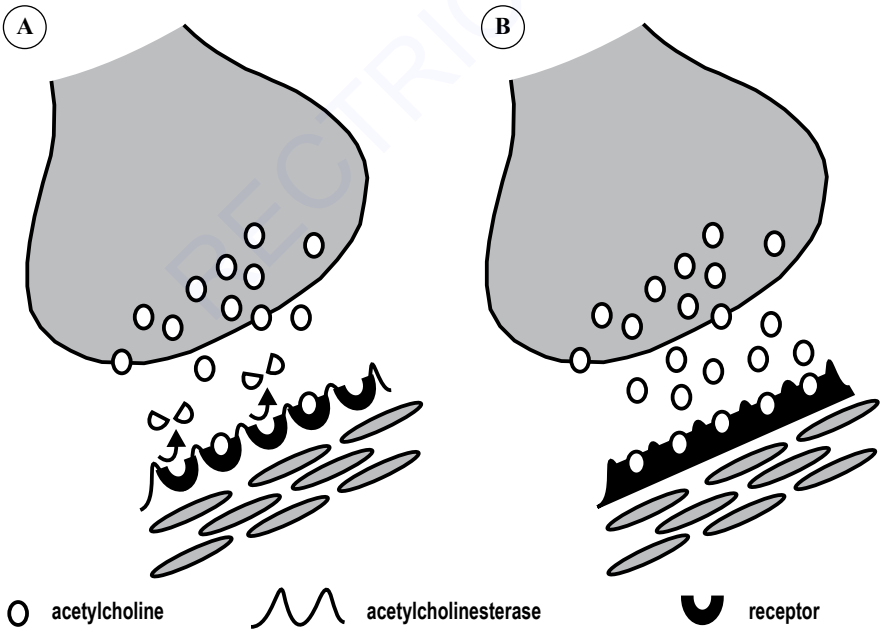

Fig. 5.5. Mechanism of action of anticholinesterases *(http://www.picsearch.com)*
A – *normal condittion of synapse;* B – *synapse after the use of anticholinesterase*

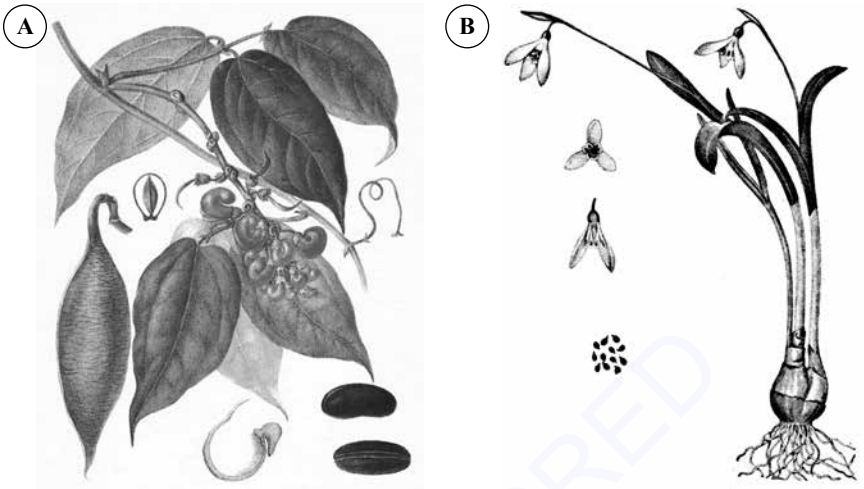

Fig. 5.6. Medicinal plants containing anticholinesterases:
A – *Physostigma venenosum;* **B –** *Galanthus Woronowi*

the treatment of glaucoma, intoxication by atropine, cholinoblockers, and tricyclic antidepressants, early stages of Alzheimer's disease; is toxic.

Galantamine is an alkaloid from *Galanthus Woronowi* (Fig. 5.6); is administered SC, IM; penetrates CNS; has a reversible anticholinesterase action; is used for the treatment of paralysis, neuritis, early stages of Alzheimer's disease and other neurological diseases; is not used in glaucoma due to its irritative action.

Neostigmine is a synthetic preparation; is administered orally, SC, IV, topically (eye drops); does not penetrate CNS; has a reversible anticholinesterase action (4–6 hrs); is used for paralysis, neuritis, myasthenia gravis, atonia of the intestine and urinary bladder, some kinds of arrhythmia, glaucoma, poisoning with atropine, overdose of tubocurarine; may be used for stimulation of labor activity; in dentistry is applied for xerostomia; is less toxic than physostigmine.

Pyridostigmine acts longer, but is less potent than neostigmine; is used orally for the treatment of neurological diseases and myasthenia gravis.

Isoflurophate is an irreversibly acting anticholinesterase with long-lasting action; is toxic and used only for glaucoma (eye drops).

Acute poisoning with organophosphates (irreversible anticholinesterases)

Signs:
– hypersalivation;
– nausea, vomiting;
– spasm of bronchi, edema of the lungs;
– convulsions;
– unconcsiousness.

Emergency help:
– Reactivators of cholinesterase ***(dipyroxim, alloxim, izonitrozin)***, IM;
– Atropine, IM.

N-CHOLINOMIMETICS

N-cholinomimetics are cholinergic agonists stimulating N-cholinoreceptors.

PHARMACODYNAMICS

They stimulate N-cholinoreceptors in *zona carotis* and initiate a reflexive increase in the activity of the respiratory and vasomotor centers resulting in the short stimulation of breathing and elevation of BP.

They also stimulate N-cholinoreceptors in the adrenal medulla, increase the secretion of epinephrine, which causes vasoconstriction and the elevation of BP (Fig. 5.7).

PECULIARITIES OF PREPARATIONS

Cytiton is a name of cytisine solution; is administered IV, acts 3–5 min; stimulates N-cholinoreceptors; reflexly stimulates respiration and increases BP; is used for emergency help in the respiratory arrest and collapse; is an ingredient of combined tablets against tobacco abuse.

Lobeline is an alkaloid; is administered IV and acts during 3–5 min; the mechanism of action is similar to cytiton; is used for emergency help in the respiratory arrest, asphyxia, asphyxia of newborns; is used to treat tobacco abuse in the form of combined tablets “Lobesil”; is not used for collapse due to its ability to provoke transitory decrease in BP resulting from the stimulation of *n. vagus* center.

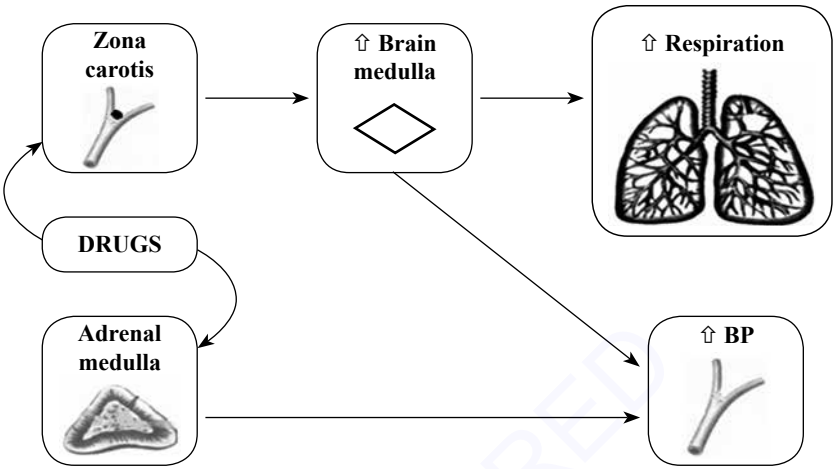

Fig. 5.7. Mechanism of action of N-cholinomimetics

NICOTINE

Nicotine is a parasympathomimetic alkaloid that is naturally produced in tobacco and some other plants. It is well known as addictive psychoactive substance relating to tobacco smoking. At the same time, medicinal forms of nicotine are used for smoking cessation to relieve withdrawal symptoms. That's why below we present short review on pharmacology and toxicology of nicotine.

- it is distributed quickly and crosses the blood–brain barrier reaching the brain within 10–20 sec after inhalation; the elimination half-life is around 2 hrs; is metabolized in the liver by cytochrome P450 enzymes (a major metabolite is cotinine); is primarily excreted in urine; crosses the placenta and is found in the breast milk of mothers;
- acts as a receptor agonist at most N-cholinoreceptors; by binding to N-cholinoreceptors in the brain, nicotine elicits its psychoactive effects and increases the levels of several neurotransmitters in various brain structures (it appears to cause the release of dopamine and endogenous opioids); has a higher affinity for nicotinic receptors in the brain than those in skeletal muscle;
- has positive effects on motor abilities, alerting and orienting attention, and episodic and working memory;
- activates the sympathetic nervous system, stimulates a release of epinephrine by binding to N-cholinoreceptors in the adrenal medulla and increases

flow of epinephrine, that results in an increase in heart rate, BP, and respiration, as well as higher blood glucose levels;

- decreases hunger and food consumption, reduces body weight that is a result from the nicotine's stimulation of N-cholinoreceptors in the arcuate nucleus and subsequently the melanocortin system, especially in the paraventricular nucleus of the hypothalamus;
- the primary therapeutic use of nicotine is treating nicotine dependence to eliminate smoking; controlled levels of nicotine are given to patients through gums, dermal patches, lozenges, inhalers, electronic/substitute cigarettes or nasal sprays, which are designed to minimize addictiveness and are characterized by slow nicotine delivery and absorption;
- side effects of nicotine replacement therapy: a mild analgesic effect (at low amounts), nausea, vomiting, diarrhea, salivation, bradyarrhythmia, heart palpitation, non-ischemic chest pain, seizures, and hypoventilation (at high doses);
- nicotine replacement therapy is not recommended to adolescents or during pregnancy and breastfeeding; precautions are needed in people who have had a myocardial infarction within two weeks, a serious angina pectoris, and heart arrhythmia;
- is highly addictive. It is one of the most commonly abused drugs (as tobacco products). Nicotine dependence involves tolerance, sensitization, physical dependence, and psychological dependence. The drug itself is associated with some health harms: it can harm adolescent brain development, is possible teratogen and a tumor promoter. Withdrawal symptoms in the nicotine abuse include depressed mood, stress, anxiety, irritability, difficulty concentrating, sleep disturbances and peak in 1–3 days, but can persist for several weeks;
- a nicotine overdose typically include nausea, vomiting, diarrhea, hypersalivation, abdominal pain, tachycardia, hypertension, tachypnea, headache, dizziness, pallor, auditory or visual disturbances, and perspiration, followed shortly after by bradycardia, bradypnea, and hypotension. Somnolence, disturbances in sleep structure, confusion, syncope, shortness of breath, marked weakness, seizures, and coma may occur.

TESTS FOR SELF-CONTROL

1. Cholinomimetics may cause all the following side effects, except:

A. Bradycardia
B. Bronchospasm
C. Hypersalivation

D. Constipation and urinary retention
E. Sweating.

2. Only one preparation is N-cholinomimetic:
A. Carbachol
B. Lobeline
C. Neostigmine
D. Aceclidine
E. Pilocarpine.

3. Anticholinesterases are used for the treatment of:
A. Atropine *(Belladonna)* poisoning
B. Postoperative paralytic ileus (atony of intestines)
C. Overdose of depolarizing myorelaxants
D. Myasthenia gravis
E. Glaucoma.

4. N-cholinomimetics:
A. Are stimulants of respiration
B. Are drugs for emergency help
C. Have long duration of action
D. Are used for the treatment of glaucoma and atony of the GI tract
E. Are drugs for relief of tobacco smoking.

5. In the complex treatment of a child suffering from cerebral palsy, a doctor decided to include anticholinesterase drug penetrating CNS and moderately improving mental development. Choose this drug.
A. Aceclidine
B. Neostigmine
C. Galanthamine
D. Pilocarpine
E. Cytitonum.

Answers

1 – D; 2 – B; 3 – A, B, D, E; 4 – A, B, E; 5 – C.

Chapter 6 CHOLINERGIC ANTAGONISTS

ANTICHOLINERGIC DRUGS

Cholinergic antagonists are also called cholinergic blockers. They bind to cholinoreceptors, but do not trigger the usual receptor-mediated intracellular effects. These drugs are divided into two groups: M-cholinoblockers (antimuscarinic agents) and N-cholinoblockers (ganglionic blockers and neuromuscular blockers (Fig. 6.1).

M-CHOLINOBLOCKERS

M-cholinoblockers are the drugs which block neurotransmission in the muscarinic synapses of the parasympathetic nerves and decrease the effects of parasympathetic innervation. They also block M-cholinoreceptors in the sympathetic neurons innervating sweat glands.

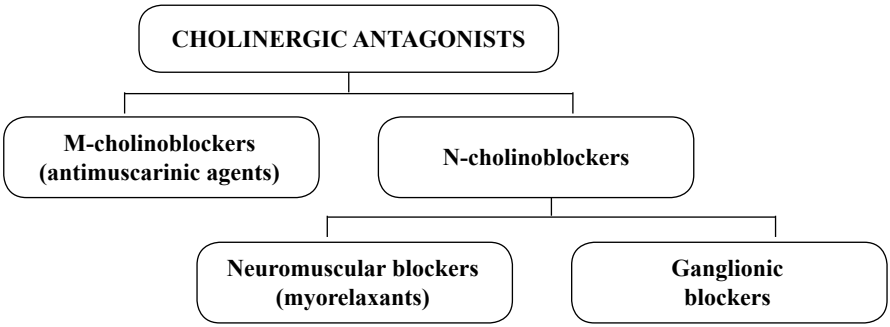

Fig. 6.1. Groups of cholinergic antagonists

CLASSIFICATION

A. *Non-selective:*

1. Natural agents:
   - Atropine sulfate;
   - Hyoscine (Scopolamine hydrobromide);
   - Platyphylline hydrotartrate;
   - *Belladonna* dry extract.
2. Synthetic and semisynthetic agents:
   - Butylscopolamine (Buscopan);
   - Prifinium bromide (Riabal);
   - Ipratropium bromide (Atrovent);
   - Tropicamide.

B. *Selective:*

- Pirenzepine (Gastrocepine).

ATROPINE SULFATE

Atropine is an alkaloid, tropine derivative (Fig. 6.2). It is water- and alcohol soluble.

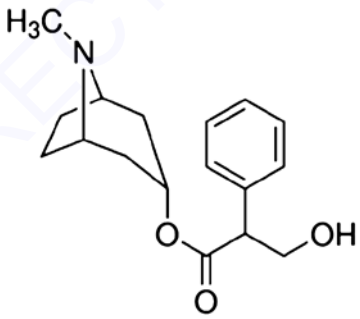

Fig. 6.2. Chemical structure of atropine

Atropine is contained in such medicinal plants as *Atropa Belladonna* (deadly nightshade), *Hyoscianus niger, Datura stramonium* (Fig. 6.3)

Pharmacokinetics

- is administered orally, IM, SC; is applied topically (eye drops);
- is rapidly, but poorly absorbed in the gut;

Fig. 6.3. *Atropa Belladonna* containing atropine

- binds to plasma proteins (18%);
- penetrates CNS and placenta;
- is metabolized in the liver by atropinase;
- is excreted with urine;
- has $T_{½}$ = 2 hrs; acts on the internal organs during 4 hrs; influences eye tissues during 7–10 days after instillation into the conjunctival sack.

Mechanism of action

- atropine competes reversibly with acetylcholine at M-cholinoreceptor;
- it binds to receptors and prevents binding of acetylcholine to these sites (Fig. 6.4);
- atropine has a non-selective action: it interacts with all the subtypes of M-cholinoreceptors;
- atropine is both a central and peripheral muscarinic blocker.

Pharmacodynamics

- weak local anesthesia in the site of application;
- in the CNS: therapeutic doses – sedation and antiparkinsonian effect; large doses – excitation, hallucinations, and coma;

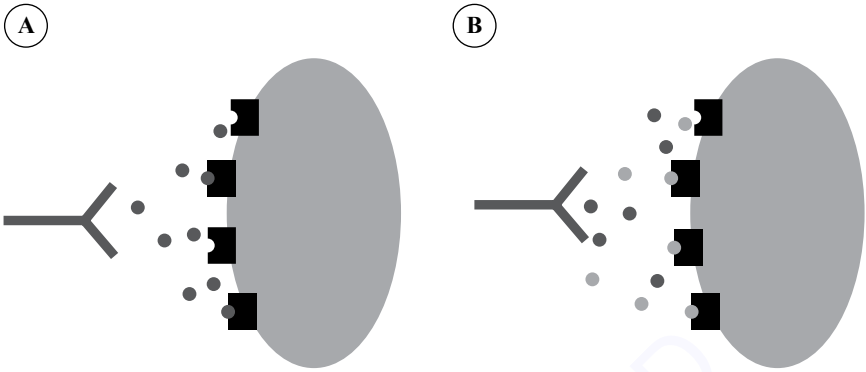

Fig. 6.4. Mechanism of action of atropine: A – normal condition of cholinergic synapse; B – synapse condition in the presence of atropine *(http://www.picsearch.com)*

- in the eye: dilation of the eye pupil (mydriasis), inability to focus for near vision (= cycloplegia, paralysis of accomodation), an increase of intraocular pressure;
- in the cardiovascular system: therapeutic doses – tachycardia, no effect on BP;
- in the respiratory system: dilation of bronchi and a decrease in the secretion of bronchial glands;
- in the gut: reducing of the secretion of saliva and gastric juice, a decrease in the tone and motility; antispasmotic activity;
- in the urinary system: relaxation of the smooth muscles of the urinary bladder and urinary pathways;
- the inhibition of sweat secretion;
- antidote properties in acute poisonings with M-cholinomimetics, anticholinesterases and toxic mushrooms containing muscarine; reducing of the vagal action of morphine and some adverse effects of general anesthetics.

Indications

- trauma of the eye, inflammation in the eye (cycloplegia and mydriasis are "pharmacological bandage" producing eye immobilization);
- diagnostics of eye diseases, the measurement of refraction for the correct selection of the eye glasses;
- bradycardia, AV block;
- hypersalivation;

- gastric ulcer;
- acute pancreatitis;
- cholecystitis;
- billiary or renal colic;
- enuresis;
- premedication;
- acute poisoning with muscarine-containing mushrooms, M-cholinomimetics, anticholinesterases, or morphine.

Side effects

1. Dilated pupils resulting in photophobia
2. Blurred vision
3. An increase in intraocular pressure, an attack of glaucoma in someone with latent condition
4. Tachycardia
5. Dry mouth
6. Constipation
7. Retention of urine
8. Flushed skin
9. A rise in body temperature.

Contraindications

1. Glaucoma
2. Tachycardia, tachyarrhythmia
3. Atonia of the GI tract, achalasia, ulcerative colitis
4. Prostate hyperplasia, adenoma of prostate
5. Hepatic insufficiency
6. Hyperthyroidism
7. High body temperature
8. Toxicosis of pregnancy
9. Cerebral pathology in children
10. Childhood or old age.

Acute poisoning with atropine

Signs:

– restlessness, disorientation, hallucinations, delirium, coma;
– mydriasis, absence of pupils' reaction to the light;
– dryness of the skin and mucous membranes;
– dysphagia;
– retention of urine;
– hyperemia of the skin;
– elevated body temperature.

Emergency help:

– neostigmine or other anticholinesterases (as an antidote); they cause accumulation of acetylcholine in synapses that results in the liberation of receptors from atropine;
– chlorpromazine (to decrease psychotic disorders);
– barbiturates (to decrease seizures).

PECULIARITIES OF OTHER PREPARATIONS

Scopolamine is another alkaloid containing in *Atropa Belladonna* and *Scopolia*. It has pharmacokinetics and peripheral effects similar to atropine; the central action is greater and longer than that of atropine; inhibits activity of VIII pair of cranial nerves and decreases motion sickness, produces sedation and short-memory blocking, has antiparkinsonian effect; as eye drops has a strong and long (4–6 days) action on the eye; is used for the prevention and treatment of motion sickness, for the complex therapy of psychic diseases, Parkinson's disease, for premedication; has side effects similar to those of atropine.

Platyphylline is an alkaloid from *Senecio platyphylus*; has a central action less than that of atropine; has a short (5–6 hrs) action on the eye; causes inhibition of the vasomotor center and a direct myotropic action on blood vessels, that's why dilates blood vessels and lowers BP; may be used to treat spasms of cerebral and coronary blood vessels as well as to treat hypertension.

Preparations of Belladonna (extracts, tinctures) are used as antispasmodic and analgesic agents for stomach ulcer, cholelithiasis and other diseases accompanied by spasms of smooth muscles of the abdominal cavity organs, bradycardia due to overexcitation of *n. vagus*. They are the ingredients of some combined preparations.

Butylscopolamine is a semisynthetic derivative of scopolamine which does not penetrate blood-brain barrier and has not central action. It is used to treat crampy abdominal pain, esophageal spasms, renal colic, and bladder spasms. The drug is effective in reducing the duration of the first stage of labor. Side effects may include sleepiness, vision changes, triggering of glaucoma, and allergy.

Prifinium bromide (Riabal) is slowly absorbed into the gut and quickly excreted; blocks peripheral M-cholinoreceptors in the GI tract that leads to inhibition of acid secretion and peptic activity of gastric juice; reduces the exocrine activity of the pancreas, the tone of smooth muscles of the gut, normalizes the peristalsis of the stomach, corrects increased motor activity of the GI tract. The drug is used in nausea and vomiting caused by functional spasms in infants, abdominal pain syndrome with functional disorders of the colon; spasms of smooth muscles of the GI tract. Side effects are dry mouth, mydriasis, disturbances of accommodation, drowsiness.

Ipratropium bromide is a quaternary derivative of atropine, non-selective M-cholinoblocker in the form of aerosol; is not absorbed in the lungs and acts on M-cholinoreceptors only in the bronchi; dilates bronchi; is used for prevention of bronchial asthma attack; has not significant side effects (may cause unpleasant taste).

Pirenzepine is a selective M_1-cholinoblocker inhibiting gastric secretion; is administered orally, IM, IV; produces maximal concentration in the blood plasma in 2–3 hrs after oral administration; has a half-life of 10–12 hrs; does not penetrate CNS and placenta; is used for the treatment of ulcer of the stomach and duodenum, Zollinger – Ellison's syndrome, prevention of peptic ulcers caused by stress; may cause dry mouth, blurred vision, retention of urine, but side effects are minimal in comparison with atropine.

Tropicamide blocks M-cholinoreceptors of the sphincter in the iris and ciliary muscle, causing short-term mydriasis and accommodation paralysis; is used in the ophthalmology for examination of the ocular fundus, investigation of refraction as well as in the inflammatory processes of the eye. It is applied as eye drops.

N-CHOLINOBLOCKERS

N-cholinoblockers are the drugs which block neurotransmission in the nicotinic synapses in the ganglia or in the skeletal muscles.

GANGLIONIC BLOCKERS

Ganglionic blockers are preparations which block N-cholinorecepors in the ganglia.

CLASSIFICATION

1. Quaternary amines:
   - Hexamethonium (Benzohexonium);
   - Hygronium;
   - Pentamine;
2. Tertiary amines:
   - Pachycarpine hydroiodide;
   - Pempidine.

HEXAMETHONIUM

It is a synthetic compound containing quaternary nitrogen.

Pharmacokinetics

- is administered IM, IV, and orally;
- is poorly aborbed in the GI tract;
- does not penetrate CNS;
- acts during 3–4 hrs.

Mechanism of action

- the drug blocks N-cholinoreceptors in the sympathetic and parasympathetic ganglia and disturbs autonomic regulation of the internal organs (pharmacological denervation) (Fig. 6.5);
- it inhibits the propagation of the nervous impulses running to effector organs along both sympathetic and parasympathetic fibres;
- the main result of sympathetic ganglia blockade is a decrease of BP;
- the blockade of parasympathetic ganglia is manifested by spasmolytic and antisecretory effects;
- under these conditions sensitivity of effector organs to humoral stimuli stays normal or is increased.

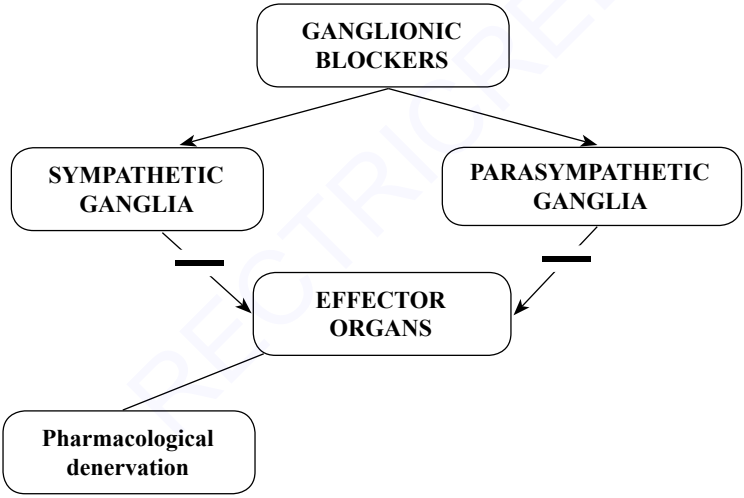

Fig. 6.5. Mechanism of action of ganglionic blockers

Pharmacodynamics

- the dilation of blood vessels, redistribution of blood in the body, lowering of BP;
- the dilation of bronchi;
- a decrease in secretion and motility of the bowels, spasmolytic action;
- a decrease in the tone of the urinary bladder and urinary pathways;
- an increase in the sensitivity of myometrium to oxytocin resulting in the stimulation of uterus contractions in the labor;

- a decrease in sweat secretion;
- changes in the intraocular pressure which depends on the type of glaucoma.

Indications

- Hypertensive emergency;
- Hypertension (rarely);
- Controlled hypotension in surgeries;
- Edema of the lungs;
- Edema of the brain;
- Bronchial asthma attack;
- Colic;
- Ulcer of the stomach (rarely).

Side effects

1. Hypotension.
2. Orthostatic collapse (postural hypotension).
3. Dry mouth.
4. Constipation.
5. Retention of urination.
6. An increase of intraocular pressure in patients with closed-angle glaucoma

Contraindications

1. Hypotension, collapse.
2. Severe atherosclerosis.
3. Closed-angle glaucoma.
4. Atony of the gut.
5. Adenome of prostate.
6. Severe diseases of the heart, liver, and kidney

PECULIARITIES OF OTHER PREPARATIONS

Hygronium is a short-acting potent ganglia blocker; is administered only by IV infusion; is used for controlled hypotension in surgeries, edema of the lungs, edema of the brain, severe hypertensive crisis, for the control of BP in patients with aortha anevrism emergency.

Pentamine is less potent than hexamethonium, acts during 1.5 hrs, is administered IV, IM for emergency help in acute hypertension, bronchial asthma attack, colic as well as for controlled hypotension in surgeries.

Pempidine is a synthetic preparation with the structure of tertiary amine, that's why is taken by mouth, is well absorbed in the gut, penetrates CNS, acts during 6–8 hrs; is used to treat gangliolitis, spasms of peripheral blood vessels, bronchial asthma, gastric ulcer (rarely); has side effects similar to that of hexamethonium.

Fig. 6.6. *Sophora pachycarpa* containing pachycarpine

Pachycarpine is an alkaloid from *Sophora pachycarpa* (Fig. 6.6); is administered orally, IM, SC; penetrates CNS, acts during 8–12 hrs; is a ganglia blocker, stimulates uterus contractions, improves functions of skeletal muscles; is used to treat gangliolitis, spasms of blood vessels, nervous diseases, myopathy, may be used for the stimulation of the labor activity; has high toxicity.

MYORELAXANTS

Myorelaxants (neuromuscular blockers) are cholinergic drugs which interfere with the transmission of nervous impulses in the synapses of skeletal muscles causing their relaxation.

CLASSIFICATION

1. Non-depolarizing agents
   - d-Tubocurarine chloride
   - Pancuronium bromide
   - Pipecuronium bromide
   - Rocuronium bromide
2. Depolarizing agents
   - Succinylcholine (Ditiline).

TUBOCURARINE

Tubocurarine is an alkaloid from a plant-derived arrow poison of South American natives. It contains two quaternary nitrogen atoms which are common to all other muscle relaxants (Fig. 6.7).

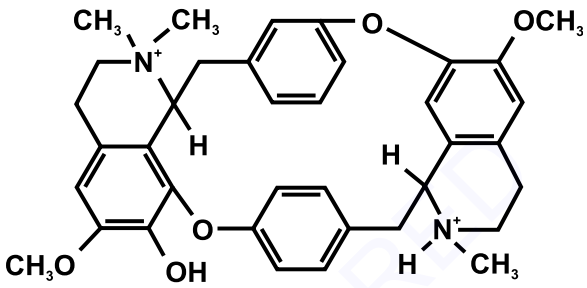

Fig. 6.7. Chemical structure of d-tubocurarine

Pharmacokinetics

- is administered IV;
- is not absorbed in the gut due to the presence of quaternary nitrogen atoms;
- does not penetrate CNS;
- total myorelaxation develops in 20–30 min and lasts about 20–40 min which needs artificial lungs ventilation, restoration of the muscle tone lasts 20–30 min.

Mechanism of action

- it binds to endplate N-cholinoreceptors without exciting them and acts as a competitive antagonist towards acetylcholine;
- it blocks neuromuscular transmission by the prevention of acetylcholine binding to such nicotinic receptors (Fig. 6.8).

Pharmacodynamics

- muscular paralysis which occurres firstly in the muscles of the fingers, neck, face, extremities, trunk, then in the intercostal muscles, and the diaphragm (with the inability to breath).

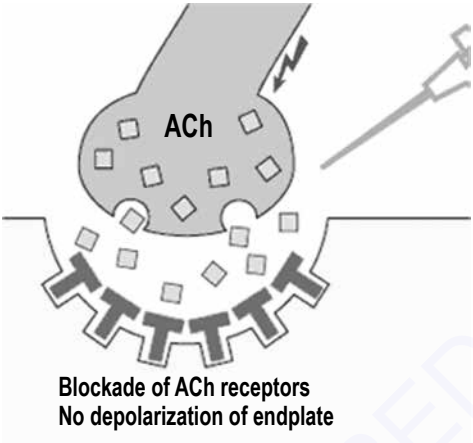

Fig. 6.8. Mechanism of action of d-tubocurarine *(by H. Lüllmann, 2000)*

Indications

- myorelaxation under the conditions of general anesthesia;
- seizures caused by seizure poisons and some infections.

Side effects

1. Spasm of the bronchi and urticaria (due to histamine release from the mast cells).
2. Lowering of BP (due to weak ganglia blocking activity).

Contraindications

Myasthenia gravis, bronchial asthma, childhood.

Decurarization

The duration of the action of d-tubocurarine can be shortened by the administration of neostigmine. Inhibition of acetylcholine esterase causes the concentration of acetylcholine released at the endplate to rise. Competitive "displacement" by acetylcholine of tubocurarine from the receptors allows transmission to be restored.

PECULIARITIES OF OTHER NON-DEPOLARIZING MYORELAXANTS

Pancuronium is a synthetic compound, is more potent than tubocuracine, has a longer duration of action, does not cause release of histamine or ganglionic

blockade, may cause an increased heart rate and BP (due to blockade of M_2 cardiac receptors).

Pipecuronium is similar to pancuronium, does not cause tachycardia and an increase of BP.

Rokuronium is an antagonist of N-cholinergic receptors of skeletal muscles; inhibits neuromuscular transmission and causes myorelaxation, has weak vagolytic effect, does not affect the release of histamine. The duration of action is 22 min in adults.

SUCCINYLCHOLINE

- is a double acetylcholine molecule;
- is administered IV; has a short duration of action (total myorelaxation and stop of breathing lasts 3–5 min) and does not need artificial lungs ventilation; is destroyed by butiryl cholinesrerase in blood;
- like acetylcholine, acts on the endplate N-cholinoreceptors, stimulates them, and causes depolarization of postsynaptic membrane; degradates more slowly than acetylcholine and therefore remains in the synaptic gap for several minutes, causing the endplate depolarization of corresponding duration. This depolarization triggers a propagated action potential. A new AP can be elicited at the endplate only if the membrane has been repolarized, that's why skeletal muscles stay without new nerve impulses and are relaxed (Fig. 6.9). The order of myorelaxation is the same as for tubocurarine;
- is used in the short surgeries, intubation of thrachea, endoscopy, reposition of bone fractures;
- may cause fibrillation of skeletal muscles at the start of action, hyperkalemia, cardiac arrhythmia, an increase of intraocular pressure, pain in the skeletal muscles after the surgery, long-lasting apnoea in patients deficient on butiryl cholinesterase (in this case emergency help is hemotransfusion and artificial lungs ventilation).

In clinic they also use ***centrally acting muscle relaxants***. These agents lower muscle tone by augmenting the activity of intraspinal inhibitory neurons. They are used in the treatment of painful muscle spasms, e.g., in spinal disorders. ***Benzodiazepines*** enhance the effectiveness of the inhibitory transmitter GABA at $GABA_A$ receptors. ***Baclofen*** stimulates $GABA_B$ receptors. ***Clonidine*** acts pesynaptically on α_2-adrenoceptors and inhibits release of exitatory amino acid transmitters.

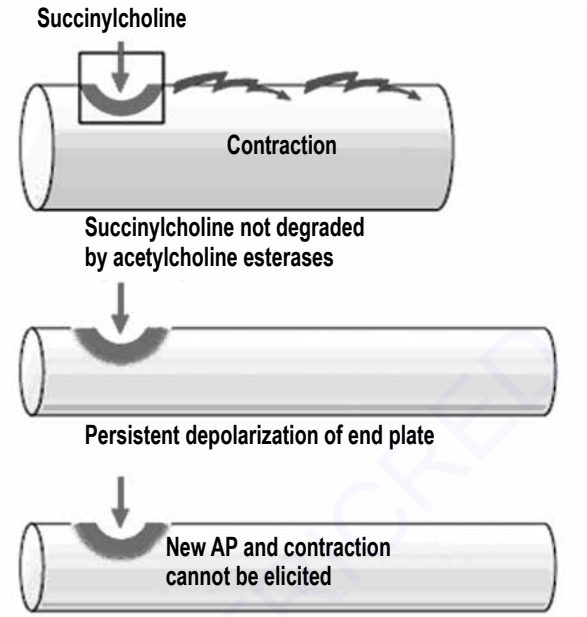

Fig. 6.9. Mechanism of action of succinylcholine *(by H. Lüllmann, 2000)*

TESTS FOR SELF-CONTROL

1. Succinylcholine (Ditiline):
A. Is depolarizing myorelaxant
B. Has a short duration of action
C. May cause lasting apnoea in some patients
D. Is suitable for the short surgeries
E. All the listed.

2. Ganglionic blockers:
A. Block N-cholinoreceptors in the parasympathetic ganglia
B. Block N-cholinoreceptors in the sympathetic ganglia
C. Block N-cholinoreceptors in the skeletal muscles
D. Block N-cholinoreceptors in the CNS
E. Block N-cholinoreceptors both in the parasympathetic and sympathetic ganglia.

3. Indications to the use of atropine are:
A. Gastric ulcer
B. Colic
C. Atonia of the gut after the surgery
D. Bradycardia
E. Preanesthetic medication.

4. The true statements concerning M-cholinoblockers are:
A. Atropine is used to treat glaucoma
B. Scopolamine is used in motion sickness
C. Plathyphylline dilates blood vessels and lowers BP
D. Pirenzepine is for the treatment of gastric ulcer
E. Pirenzepine is for the treatment and diagnostics of eye diseases.

5. The administration of ipratropium in patients with bronchial asthma is not accompanied by numerous side effects which are characteristic for atropine and other M-cholinoblckers due to:
A. The inability to penetrate through the blood-brain barrier
B. The inhibition of M-cholinoreceptors in the bronchi only
C. The inhibition of all the types of M-cholinoreceptors
D. The inhibition of cholinesterase
E. Significant protein binding.

Answers

1 – E; 2 – E; 3 – A, B, D, E; 4 – B, C, D; 5 – B.

Chapter 7 ADRENERGIC AGONISTS

SYMPATHETIC NERVOUS SYSTEM

The sympathetic nervous system is a section of the autonomic nervous system. Centers of SANS are located in thoraco-lumbar segments of the spinal cord (the 1st neuron). Ganglia of SANS are located near the spinal cord and form *Truncus sympathycus* (the 2nd nueron). The neurotransmitter released by sympathetic nerve endings is ***norepinephrine*** (= noradrenaline) (Fig. 7.1).

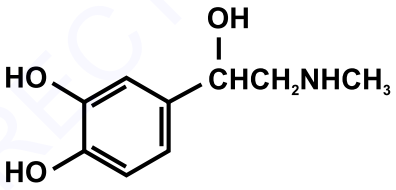

Fig. 7.1. Chemical structure of norepinephrine

ADRENERGIC SYNAPSE

Synapses, in which norepinephrine is the neurotransmitter, are named ***adrenergic synapses*** (Fig. 7.2).

Norepinephrine is synthesized in the presynaptic part of the neuron. It is deposited in vesicles. Non-storaged neurotransmitter is destroyed by monoamine oxidase (MAO). When the nerve impulse arrives, norepinephrine is liberated into the synaptic gap. It interacts with receptors on the presynaptic and postsynaptic membranes. Binding to presynaptic receptors terminates the release of the neurotransmitter. In the synaptic gap 20% of norepinephrine is degradated by catechol-O-

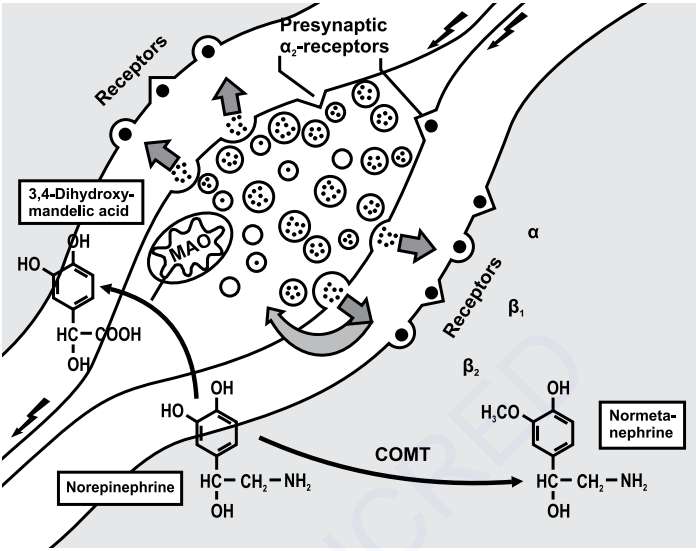

Fig. 7.2. Adrenergic synapse and its function *(by H. Lüllmann, 2000)*

methyltransferase (COMT). Another part of neurotransmitter (80%) is reuptaken by the presynaptic membrane.

ADRENOCEPTORS

There are two types of adrenoceptors and some subtypes in the each family (Fig. 7.3). They are located in the CNS as well as in many peripheral tissues (Table 7.1).

ADRENERGIC DRUGS

Drugs acting on adrenergic synapses are named ***adrenergic drugs***. They are divided into two groups: ***adrenergic agonists*** and ***adrenergic antagonists (adrenoblockers and sympatholytics)*** (Fig. 7.4).

Adrenergic agonists are also named adrenopositive drugs including direct-actig adrenomimetics and indirect-acting adrenomimetics (sympathomimetics).

Adrenergic antagonists are also named adrenonegative agents. Among them there are substances inhibiting adrenergic receptors (adrenoblockers) and substances influencing the store and reuptake of norepinephrine (sympatholytics).

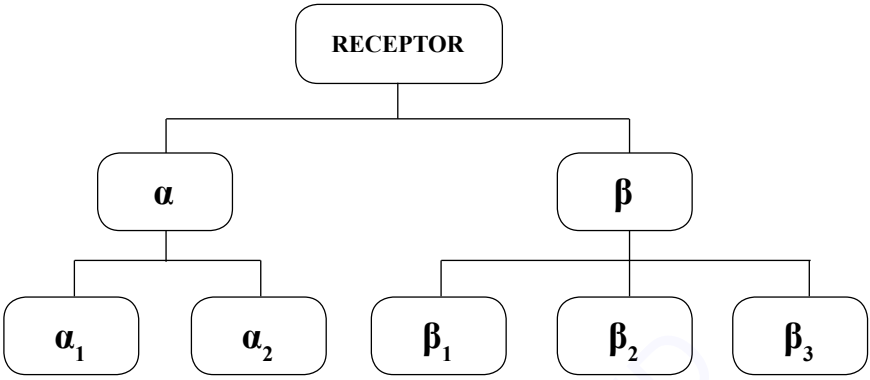

Fig. 7.3. Types and subtypes of adrenoceptors

Table 7.1. **Localization and main effects of adrenoceptors**

Receptor	***Localization***	***Effects***
α_1	Blood vessels	Constriction, ⇧ of blood pressure
	Spleen	Constriction
	Eye	Mydriasis
	Urine bladder	⇧ of sphincter closure
α_2	Blood vessels	Constriction
	Pancreas	⇩ of insulin release
	All adrenergic synapses	⇩ of norepinephrine release
β_1	Heart	⇧ of rate and contractility
	Fat tissue	⇧ of lipolysis
β_2	Blood vessels	Vasodilation
	Bronchi	Dilation
	Uterus	Relaxation
	Pancreas	⇧ of glucagon's release
	Liver	⇧ of glycogenolysis
	Skeletal muscles	⇧ of glycogenolysis
β_3	Pancreas	⇧ of insulin secretion
	Fat tissue	⇧ of lipolysis
	Mast cells	⇩ of degranulation
		⇩ of release of allergy mediators

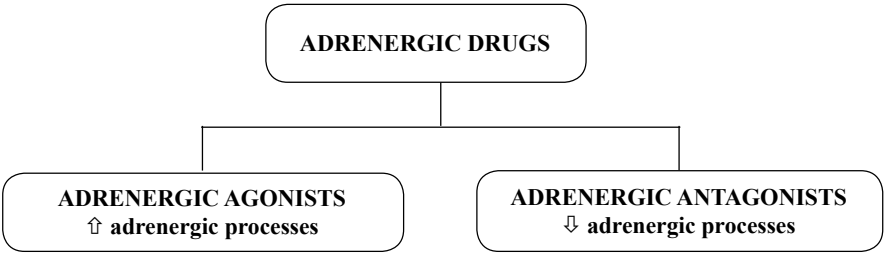

Fig. 7.4. Drugs influencing adrenergic synapses

ADRENERGIC AGONISTS

Adrenergic agonists are drugs stimulating adrenergic neurotransmission.

CLASSIFICATION

A. *α-, β-adrenomimetics:*
1. Direct-acting:
   – Adrenaline hydrochloride (Epinephrine).
2. Indirect-acting (Sympathomimetics):
   – Ephedrine hydrochloride.

B. *α-adrenomimetics:*
1. Non-selective:
   – Noradrenaline hydrotartrate (α_1, $\alpha_2 > \beta$).
2. Selective
   – Phenylephrine (Mesatone) (α_1);
   – Naphazoline (Naphthyzin) (α_2);
   – Halazolin (Xylometazoline) (α_2).

C. *β- adrenomimetics:*
1. Non-selective:
   – Isoprenaline (Isadrine) (β_1, β_2).
2. Selective:
   – Dobutamine (β_1);
   – Salbutamol (Albuterol) (β_2);
   – Fenoterol (β_2).

ADRENALINE

It is a catecholamine, the hormone produced by the adrenal medulla.

Pharmacokinetics

- is administered SC, IV (rarely), intracardially (in the heart arrest), or topically;
- is destroyed in the GI tract, that's why is not administered orally;
- does not penetrate the CNS;
- is biotransformed by enzymes in the blood;
- acts during 15 min on the internal organs and during 30 min on metabolic processes.

Mechanism of action

Adrenaline acts by the stimulation of all the types of adrenoceptors.

Pharmacodynamics	Indications
An increase in automaticity, conductivity, and contractility of the heart	Heart arrest
Constriction of blood vessels	Prolongation of local anethesia Acute inflammation of the mucous membrane of the nose or eye
Elevation of blood pressure	Shock, collapse
Bronchodilation	Bronchial asthma attack
An increase in glucose concentration in the blood	Hypoglycemic coma
Inhibition of allergy	Anaphylactic shock
Mydriasis	Pupil dilatation.
A decrease in intra-eye pressure.	Open-angle glaucoma.

Side effects

1. Excitement, tremor
2. Hypertension
3. Arrhythmia
4. Hyperglycemia.

Contraindications

Hypertension, severe atherosclerosis, heart arrhythmia, diabetes mellitus, hyperthyroidism.

EPHEDRINE

The drug is not a catecholamine by its structure (Fig. 7.5).

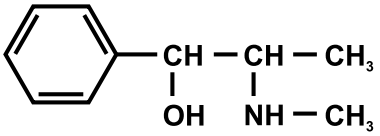

Fig. 7.5. Chemical structure of ephedrine

It is an alkaloid from *Ephedra equisetica* (Fig. 7.6).

Fig. 7.6. *Ephedra equisetica* containing ephedrine

Pharmacokinetics

- is administered orally, SC, IM, IV, or topically
- is absorbed in the GI tract
- penetrates CNS
- is metabolized in the liver
- is excreted by the kidney
- acts during 4–6 hrs.

Mechanism of action

Ephedrine stimulates the release of norepinephrine, inhibits the reuptake of norepinephrine (indirect action) (Fig. 7.7).

It has a weak direct action on adrenoceptors.

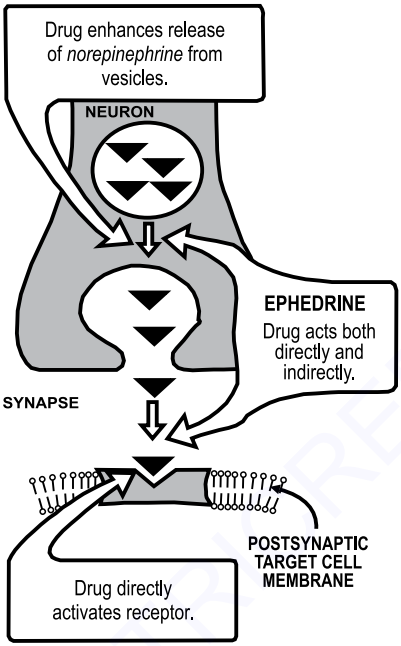

Fig. 7.7. Mechanism of ephedrine's action
(adapted from R. Finkel et al., 2008)

Pharmacodynamics

- the stimulation of CNS, an increase in the ability to mental and physical work, euphoria;
- the stimulation of the heart function;
- vasoconstriction;
- the elevation of BP;
- the dilation of bronchi;
- the inhibition of the gut motility;
- the retention of urine;
- mydriasis.

Indications

- shock, collapse;
- bronchial asthma;
- bronchospasm;

- AV block, bradycardia;
- acute rhinitis;
- acute conjunctivitis;
- for pupil dilation;
- pathological narcolepsia;
- myasthenia;
- enuresis.

Side effects

1. Insomnia.
2. Anxiety, restlessness.
3. Tachycardia.
4. Palpitation.
5. Hypertension.
6. Rash on the skin.
7. Tolerance and tachyphylaxis.
8. Drug dependence.

The drug should not be used in sportsmen (as a doping).

α-ADRENERGIC AGONISTS

α-adrenomimetics are drugs stimulating α-adrenoceptors. Noradrenaline is a natural neurotransmitter which binds to all types of adrenoceptors, but only the stimulation of α-adrenoceptors is clinically significant.

These preparations are characterized by common pharmacological effects and indications (Table 7.2).

Table 7.2. **Common pharmacological effects and indications for α-adrenomimetics**

α-adrenomimetic effects	***Indications***
Vasoconstriction An increase in BP Mydriasis without cycloplegia	Shock, collapse Prolongation of local anesthesia Rhinitis, conjunctivitis Glaucoma, diagnostics of eye diseases

PECULIARITIES OF PREPARATIONS

Noradrenaline is a catecholamine; it has a non-selective action on adrenoceptors with a preferable action on α-adrenoceptors; has a short-durative action, is administered only by IV infusion in collapse and acute hypotension; may cause strong vasoconstriction and necrosis of the soft tissues if it is administered SC or IM; is contraindicated in blood loss, cardiogenic shock, long-lasting shock.

Phenylephrine (Mesatone) is a non-catecholamine; has a selective action on α_1-adrenoceptors; may be taken orally, is administered SC, IM, IV, or topically; has the duration of action of 4–6 hrs; is used in acute and chronic hypotension, for prolongation of local anesthesia, for producing of mydriasis as well as for a decrease in edema of the mucous membrane in acute rhinitis or conjunctivitis.

Naphazoline and halazolin are non-catecholamines; have a selective action on α_2-adrenoceptors, are used as nasal drops for acute rhinitis, nasal bleeding, and rhinoscopia; cause tolerance and tachyphylaxis.

β-ADRENERGIC AGONISTS

β-adrenomimetics are agonists of β-adrenoceptors and increase the neurotransmission in such synapses. They have some common pharmacological properties and indications (Table 7.3).

Table 7.3. **Common effects and indications for β-adrenomimetics**

β-adrenomimetic effects	***Indications***
Dilation of the bronchi An increase in the heart rate An increase in the heart work A decrease in the myometrium tone.	Bronchial asthma, spasm of bronchi Heart block, bradycardia Danger of pregnancy interruption.

PECULIARITIES OF PREPARATIONS

Isoprenaline (Isadrine) is a synthetic catecholamine; has a non-selective action on β_1- and β_2-adrenoceptpors; is administered sublingually, by inhalation, or IV; is used in bronchial asthma attack, heart block, some types of cardiogenic shock.

Salbutamol is a non-catecholamine; has a selective action on β_2-adrenoceptors, acts longer than isoprenaline; does not act on the heart; is used in bronchial asthma, bronchospasm and before bronchoscopia.

Fenoterol (Partusisten) is a non-catecholamine; has a selective action on β_2-adrenoceptors, acts during 4–6 hrs; does not act on the heart; is used in bronchial asthma and in the danger of pregnancy interruption.

Dobutamine has a selective action on β_1-adrenoceptors; increases cardiac output; is administered by IV infusion for the emergency treatment of acute heart insufficiency and cardiogenic shock.

COMPARISON OF ADRENOMIMETICS-CATECHOLAMINS

Adrenomimetics with catecholamine structure are distinguished by their affinity to adrenergic receptors (Fig. 7.8).

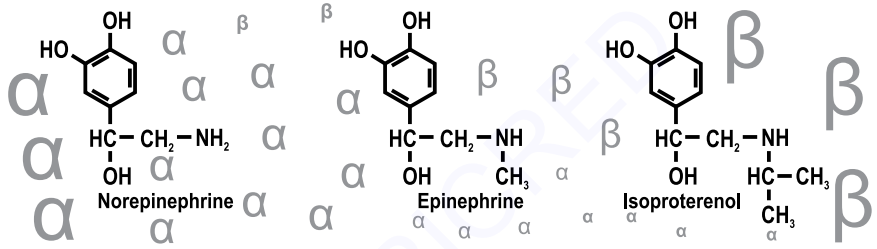

Fig. 7.8. Chemical structure of catecholamines and their affinity to α- and β-adrenoceptors *(by H. Lüllmann, 2000)*

This affinity depends on the structure of substitute radicals. They may be methyl in adrenaline or isopropyl in isoproterenol (isoprenaline). Noradrenaline has not such substitutes in its side chain.

The represented data result in peculiarities of pharmacological effects. It is a typical evidence of dependence of drug's effects on its chemical structure (Table 7.4).

Table 7.4. **Dependence of catecholamines' effects on their chemical structure**

Effect	*Adrenaline*	*Noradrenaline*	*Isoprenaline*
An increase in the heart rate	+ + +	+	+ +
An increase in the blood pressure	+ +	+ + +	–
Dilation of the bronchi	+ +	±	+ + +
A decrease in the gut function	+ + +	+	+ +
An increase in the glucose level (hyperglycemia)	+ + +	±	±
A decrease in the tone of uterus	+ + +	±	+ +

TESTS FOR SELF-CONTROL

1. Adrenaline is used to treat all the conditions, except:
A. Acute bronchial asthma
B. Capillary bleeding after tooth extraction
C. Anaphylactic shock
D. Angina pectoris
E. Hypoglycemia.

2. The drug used to prevent premature labor is:
A. Dobutamine
B. Metoprolol
C. Isadrine
D. Adrenaline
E. Partusisten (Fenoterol).

3. Ephedrine:
A. Releases stored noradrenaline from nerve terminals
B. Produces bronchodilation
C. Stimulates CNS
D. Rises systolic blood pressure
E. Produces AV block.

4. Isoprenaline (Isadrine) is:
A. Contraindicated in tachyarrhythmia
B. A synthetic catecholamine
C. A bronchodilator
D. A stimulant of the heart function
E. A cardioselective adrenomimetic.

5. To perform fundoscopy, an ophthalmologist instilled in the eye an agent capable of causing mydriasis without cycloplegia. Point out this agent.
A. Phenylephrine
B. Noradrenaline
C. Atropine
D. Pilocarpine
E. Isoprenaline.

Answers:

1 – D; 2 – E; 3 – A, B, C, D; 4 – A, B, C, D; 5 – A.

Chapter 8 ADRENERGIC ANTAGONISTS. HISTAMINE, SEROTONIN- AND DOPAMINERGIC DRUGS

ANTI-ADRENERGIC DRUGS

Anti-adrenergic drugs are preparations for a decrease in the neurotransmission in adrenergic synapses due to blockade of adrenoceptors or due to presynaptic inhibition of norepinephine release (Fig. 8.1).

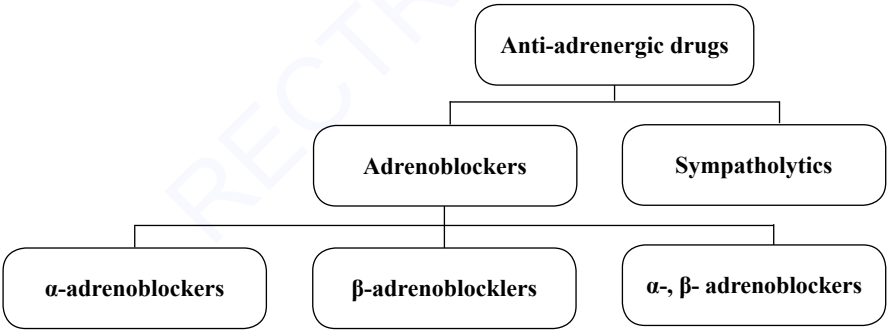

Fig. 8.1. Groups of anti-adrenergic drugs

CLASSIFICATION

A. *α-adrenoblockers:*

1. Non-selective:
   – Phentolamine hydrohloride.
2. Selective:
   – Prazosin;
   – Doxazosin.

B. *β-adrenoblockers:*

1. Non-selective:
   – Propranolol (Anaprilin);
   – Oxprenolol.
2. Selective:
   – Metoprolol;
   – Atenolol;
   – Nebivolol;
   – Bisoprolol.

C. *α-, β-adrenoblockers:*

– Labetalol;
– Carvedilol.

D. *Sympatholytics:*

– Guanethidine (Octadine);
– Reserpine.

α-ADRENOBLOCKERS

α-adrenoblockers are preparations which bind to α-adrenoceptors and prevent their stimulation by norepinephrine.

Mechanism of action

They bind to α-adrenoceptors and make impossible the interaction between norepinephrine and adrenoceptors.

Pharmacodynamics

- the dilation of peripheral blood vessels, reducing of the peripheral resistance, an increase in the venous capacity;
- a decrease in BP;
- the improvement of trophy of the peripheral tissues;
- the stimulation of the gut motility;
- a decrease of the urine retention in patients with prostate hyperplasia.

Indications

- hypertension;
- spasms of peripheral blood vessels (Raynaud's disease);
- frostbites, trophic ulcers;
- pheochromocytoma (diagnostics and treatment);
- prostate hyperplasia.

Side effects

1. Headache, vertigo
2. Hypotension
3. Weakness
4. Insomnia
5. Orthostatic collapse
6. Tachycardia
7. Vomiting, nausea, diarrhea
8. Rhinitis.

PECULIARITIES OF PREPARATIONS

Phentolamine hydrochloride has a non-selective action (blocks α_1- and α_2-adrenoceptors); is administered orally or IV; has a short duration of action; has many side effects; causes tachycardia due to the blockade of α_2-adrenoceptors and disorders in the back-cross regulation of norepinephrine liberation in the synapses.

Prazosin has a selective action on α_1-adrenoceptors; is taken orally; acts during 4–6 hrs; is used for the treatment of hypertension; has less side effects.

Doxazosin has a selective action on α_1-adrenoceptors; is taken orally; has a more durative and strong action than prazosin; decreases urine retention in patients with adenoma of prostate; is used for the treatment of hypertension and adenoma of prostate.

β-ADRENOBLOCKERS

β-adrenoblockers are preparations which bind to β-adrenoceptors and prevent their stimulation by norepinephrine.

PROPRANOLOL (ANAPRILIN)

Pharmacokinetics

- is administered orally, IV, topically (eye drops);
- is absorbed in the GI tract;
- binds to proteins in the blood plasma;
- penetrates CNS;
- is metabolized in the liver;
- is excreted with urine;
- acts during 3–4 hrs.

Mechanism of action

Propranolol blocks β_1-adrenoceptors in the heart and β_2-adrenoceptors in other organs (blood vessels, bronchi, etc).

Pharmacodynamics

- a decrease in automaticity of the myocardium;
- a decrease in excitability of the myocardium;
- a decrease in conductivity of the myocardium;
- a decrease in the heart rate (*antiarrhythmic* effect);
- a decrease of the heart contractility, striking and minute volume;
- a decrease in the consumption of oxygen by myocardium (*antianginal* effect);
- a decrease in the renin's secretion in the kidney;
- the lowering of BP (*antihypertensive* effect);
- the lowering of intraocular pressure;
- sedative action;
- an increase in the tone of bronchi;
- the stimulation of gastric secretion;
- an increase in the peripheral resistance of blood vessels (at the beginning of the therapy);
- antagonism to adrenaline as to its lipolytic and hyperglycemic action.

Indications

- Hypertension;
- Ischemic heart disease (angina pectoris, myocardial infarction);
- Supraventricular tachyarrhythmia;
- Hyperthyroidism;
- Migraine;
- Glaucoma.

Side effects

1. Bradycardia
2. Hypotension
3. Increasing of the heart incompetence
4. Heart block
5. Spasm of the bronchi
6. Hypoglycemia when insulin is given together with propranolol
7. Fatique, drowsiness, vertigo, depression
8. Disturbances of the sexual function in men.

Contraindications

1. Bradycardia
2. Hypotension
3. Severe heart failure
4. Heart block
5. Bronchial asthma
6. Ulcerative disease
7. Diabetes mellitus
8. Disturbances of peripheral blood circulation
9. Pregnancy.

PECULIARITIES OF OTHER PREPARATIONS

Metoprolol has a cardioselective action on β_1-receptors (Fig. 8.2); is used for the treatment of hypertension, angina pectoris, and arrhythmia; does not cause spasm of the bronchi and an increase of gastric secretion; may be used in patients with bronchial asthma, ulcerative disease, and diabetes mellitus.

Talinolol has a cardioselective action on β_1-receptors; has *inner sympathomimetic activity* and membrane stabilizing effect (does not inhibit the heart contractility and conductivity); has less side effects and less contraindications connected with the influence on β_1-adrenoceptors.

Atenolol has a cardioselective action on β_1-receptors in therapeutic doses; is not metabolized in the body, penetrates tissue barriers poorly; therapeutical effect starts slowly (2–4 hrs) and lasts near 24 hrs.

Nebivolol is a cardioselective β_1-adrenoblocker with vasodilation properties which are due to metabolic interaction with L-arginine and NO; is used to treat chronic hypertension and as a part of combined therapy of congestive heart failure (CHF) in old patients.

Bisoprolol is a highly selective β_1-adrenoblocker in all the doses, is taken orally once a day for the treatment of chronic hypertension, angina pectoris and CHF.

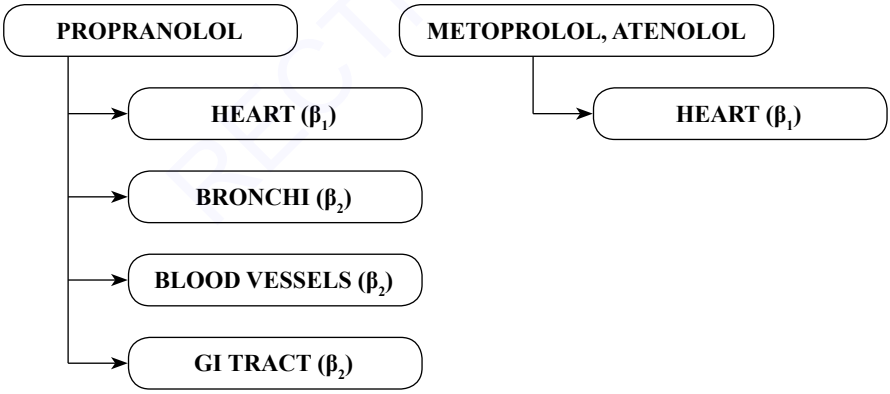

Fig. 8.2. Targets for the action of propranolol and cardioselective β-adrenoblockers

α-, β-ADRENOBLOCKERS

α-, β-adrenoblockers are preparations which bind both to α- and β-adrenoceptors, prevent their stimulation by norepinephrine, and disturb adrenergic neurotransmission.

LABETALOL

– blocks both α- and β-adrenoceptors;
– has the action on β-receptors, which is 3 times more potent than the action on α-receptors;
– is less active than propranolol;
– is less active than phentolamine;
– is taken orally or IV;
– is indicated for the control of hypertension;
– is contraindicated in the heart block, spasm of the bronchi, pregnancy.

CARVEDILOL

Carvedilol is a non-selective β-adrenoblocker and selective α-adrenoblocker. Combination of the blockade of β-adrenoceptors with vasodilation is useful in the treatment of ishchemic heart disease, hypertension, and CHF with disfunction of the left ventricle of the heart. Active metabolites of the drug have an antioxidant effect.

CONCEPT OF INTRINSIC SYMPATHOMIMETIC ACTIVITY

Some β-adrenoblockers (oxprenolol, labetalol) exhibit intrinsic sympathomimetic activity. They are capable of exerting low-level agonist activity at the β-adrenoceptor while simultaneously acting as a receptor site antagonist. These agents may be useful in the individuals exhibiting excessive bradycardia with sustained β-blocker therapy.

SYMPATHOLYTICS

Sympatholytics are adrenergic antagonists of presynaptic action.

RESERPINE

- is an alkaloid from *Rauwolfia serpentina;*
- decreases the storage of norepinephrine that leads to destruction of neurotransmitter by MAO in the axonal cytoplasma resulting in a decrease of neurotransmission in adrenergic synapses (Fig. 8.3);
- penetrates CNS, has a central and peripheral action (Table 8.1);
- has antihypertensive, sedative and antipsychotic action;

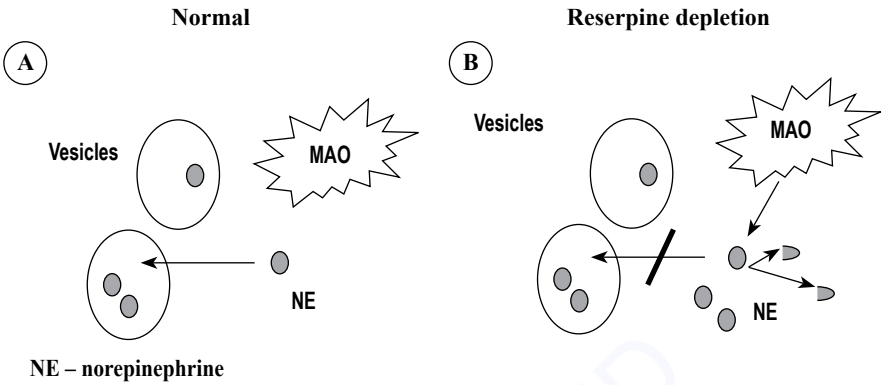

Fig. 8.3. Mechanism of reserpine's action: A – normal condition of adrenergic synapse; B – adrernergic synapse in the presence of reserpine

Table 8.1. **Comparison of sympatholytics**

Drugs	***Reserpine***	***Guanethidine***
Chemical structure	Alkaloid	Synthetic compound
Mechanism of action	Inhibition of biogenic amines storage	Active uptake and storage, not a transmitter
Central action	+	–
Peripheral action	+	+
Main effect	Varicosity, ↓ BP	Varicosity, ↓ BP

- is administered orally, IM or IV;
- acts during 8–12 hrs;
- is indicated in hypertension;
- may cause disturbances of sleep, depression, bradycardia, spasm of the bronchi, stimulation of gastric secretion, diarrhea.

GUANETHIDINE (OCTADINE)

- is a synthetic compound of the simple structure;
- produces active storage and uptake instead of norepinephrine release, decreases neurotransmitter release;
- does not penetrate CNS, has only peripheral action (Table 8.1);
- has antihypertensive action, decreases intraocular pressure;

- is taken orally or topically (in the form of eye drops);
- action is slow and long (it starts to act in 2–4 days after the beginning of treatment and continues to act during 10–14 days after the ending of treatment);
- is indicated for hypertension, glaucoma, some types of arrhythmia;
- may cause orthostatic hypotension and side effects connected with prevalence of PANS (bradycardia, spasm of the bronchi, stimulation of gastric secretion, diarrhea, enlargement of the salivary glands).

HISTAMINERGIC DRUGS

Histaminergic agents include histamine and antihistamines.

HISTAMINE

Histamine is biologically active amine which regulates the tone of smooth muscles, allergy, inflammation, and secretion of exocrine glands. It realizes its action by the binding with histamine receptors. In clinic, histamine is used rarely.

ANTIHISTAMINES

Antihistamines are drugs which antagonize effects of histamine by the blockage of histamine receptors or by a decrease of histamine liberation.

CLASSIFICATION

1. Drugs stabilizing mast cells membranes:
   – Cromolyn sodium (Sodium cromoglycate, Intal);
   – Ketotifen (Zaditen).
2. Blockers of H_1-histamine receptors:
   – Diphenhydramine (Dimedrol);
   – Clemastine (Tavegil);
   – Chloropyramine (Suprastin);
   – Promethazine (Diprazin);
   – Mebhydroline (Diazolin);
   – Quifenadine (Phencarol);
   – Loratadine;
   – Fexofenadine.
3. Blockers of H_2-histamine receptors:
   – Ranitidine;
   – Famotidine.

MAST CELL STABILIZERS

CROMOLYN SODIUM

- is administered by inhalation;
- stabilizes basophiles membranes, prevents the release of histamine and other allergy mediators;
- is used for the prophylaxis of bronchial asthma attack, allergic rhinitis, and conjunctivitis;
- may cause the irritation of respiratory pathways, spasm of the bronchi, headache, cough.

KETOTIFEN

- is administered orally;
- stabilizes basophiles membranes, prevents the release of histamine and other allergy mediators; has a weak antihistamine and sedative action;
- is used for the prophylaxis of bronchial asthma attack;
- may cause such side effects as drowsiness, dry mouth, dizziness, thrombocytopenia;
- is contraindicated for patients whose job needs quick motor reaction.

BLOCKERS OF H_1–HISTAMINE RECEPTORS

DIPHENHYDRAMINE (DIMEDROL)

Diphenhydramine is a synthetic drug, dimethylaminoethanol derivative (Fig. 8.4).

Pharmacokinetics

- is administered orally, IM, IV, rectally, topically (ointment, eye drops);
- is absorbed in the GI tract;

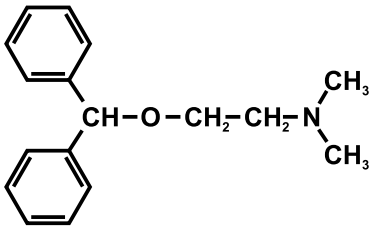

Fig. 8.4. Chemical structure of diphenhydramine

- penetrates CNS and placenta;
- is metabolized in the liver, is the inductor of microsomal oxidation;
- is excreted by urine;
- has the duration of action of 6–8 hrs.

Mechanism of action

- the drug blocks H_1-histamine receptors and inhibits effects of histamine, especially allergic reactions;
- it blocks cholinergic receptors;
- it blocks adrenergic and serotonin receptors.

Pharmacodynamics

- the inhibition of histamine action;
- a decrease of allergic reactions;
- a decrease in edema of tissues due to histamine;
- a decrease in the permeability of blood vessels wall;
- a decrease of inflammation;
- a decrease in spasms of smooth muscles;
- ganglia blocking effect;
- sedative and hypnotic effect;
- antiemetic effect;
- potentiative action.

Indications

1. Allergic diseases (angioneurotic edema, hay fever, urticaria, vasomotor rhinitis, serum sickness).
2. Allergic complications of blood transfusion.
3. Allergic complications of pharmacotherapy.
4. Hemorrhagic capillary toxicosis.
5. Radiation sickness.
6. Motion sickness.
7. Insomnia.
8. The potentiation of general anesthesia.

Side effects

1. Weakness, fatigue, psychomotor impairment, depression.
2. Dry mouth.
3. Blurred vision.
4. Urinary retention.

5. Gastrointestinal disturbances.
6. Changes of the effects of other drugs.

The drug should not be used during driving or together with alcoholic drinks.

PECULIARITIES OF OTHER PREPARATIONS

Clemastine (Tavegil) is taken orally; acts during 12 hrs; has a strong antihistamine and weak sedative effect.

Chloropyramine (Suprastin) is taken orally, IM, IV; has an overage antihistamine and sedative effect accompanied by a significant M-cholinoblocking action.

Promethazine (Diprasin) is administered orally, IM, IV; blocks α-adrenoceptors; has denominated sedative, hypnotic and vestibuloprotective actions; may be used for the treatment of motion sickness and vestibule disturbances; may cause hypotension.

Mebhydroline (Diazolin) is taken orally; acts during 48 hrs; has a minimal sedative action (day-time antihistamine).

Loratadine is taken orally; acts during 48 hrs; has an overage antihistamine action; does not penetrate CNS, has not sedative action (day-time antihistamine).

Quifenadine (Phencarol) is taken orally; blocks H_1-receptors and increases the enzymic inactivation of histamine; has an overage antihistamine and antiserotonin action, but a minimal sedative effect.

BLOCKERS OF H_2-HISTAMINE RECEPTORS

These preparations block H_2-histamine receptors and decrease gastric secretion. They have common indications: ulcerative disease, symptomatic ulcer, gastroesophagitis. Detailed description of these drugs is represented in Chapter 24.

PECULIARITIES OF PREPARATIONS

Ranitidine is administered orally (1–2 times a day), IV; side effects: headache, vertigo, weakness, skin rash, thrombocytopenia.

Famotidine is administered orally or IV (1–2 times a day); inhibits basal gastric secretion as well as stimulated secretion; is more effective; has less side effects.

SEROTONINERGIC DRUGS

Serotoninergic drugs are agents which stimulate or block serotonin (5-HT) receptors.

SEROTONIN ADIPINATE

- is administered IV or IM;
- is the agonist of serotonin receptors;
- decreases the permeability of the blood vessels wall;
- is used as antihemorrhagic agent in hemorrhagic vasculitis, hypo- and aplastic anemia, thrombocytopenia, hemorrhagic syndrome accompanied the anticancer chemotherapy;
- may cause pain in the abdomen, pain in the heart, headache, elevation of BP, GI disturbances, decreases diuresis after a quick IV administration.

CYPROHEPTADIN (PERITOL)

- is taken orally;
- is a strong antagonist of serotonin receptors; also blocks H_1-histamine receptors and cholinergic receptors;
- is an anti-allergic agent; blocks hypersecretion of ACTH and STH;
- is used in allergy, migraine, anorexia;
- may cause somnolence, dry mouth, vertigo, ataxia, skin rash.

SUMATRIPTAN

- is structurally similar to serotonin (5-HT);
- is a 5-HT receptor types 5-HT_{1D} and 5-HT_{1B} agonist;
- causes vasoconstriction of dilated cranial and basilar arteries, decreases the activity of the trigeminal nerve;
- is effective in the treating cluster headaches and migraine.

DOPAMINERGIC DRUGS

DOPAMINE HYDROCHLORIDE

- is an agonist of dopamine receptors;
- has cardiostimulant, vasodilation, and diuretic action;
- is used by IV infusion in shock of different origin, functioinal renal failure, CHF.

TESTS FOR SELF-CONTROL

1. Only one drug belongs to α-adrenoblockers:
A. Carbachol
B. Adrenaline hydrochloride
C. Prazosin
D. Propranolol
E. Guanethidine.

2. All the drugs are used for the treatment of hypertension, except:
A. Prazosin
B. Anaprilin
C. Diphenhydramine
D. Labetalol
E. Reserpine.

3. The following statements concerning guanethidine are correct
A. It is a potent antihypertensive agent
B. It causes vasodilation
C. It blocks β-adrenoceptors
D. It acts presynaptically
E. It blocks α-adrenoceptors.

4. Dimedrol is applied in clinic for:
A. The treatment of bronchial asthma
B. Allergic diseases
C. Allergic complications of pharmacological therapy
D. Hemorrhagical diathesis
E. Hypertension.

5. An adrenoblocking drug was prescribed for the treatment of angina pectoris, but bronchospasm, and gastric ulcer had been developed. What drug was used? What drug from the same pharmacological group may be used for the replacement of the first remedy?
A. Labetalol, propranolol for its replacement
B. Propranolol, metoprolol for its replacement
C. Propranolol, prazosin for its replacement
D. Phentolamine, metoprolol for its replacement
E. Propranolol, diphenhydramine for its replacement.

Answers:

1 – C; 2 – C; 3 – A, B, D; 4 – B, C, D; 5 – B.

Chapter 9

DRUGS FOR GENERAL ANESTHESIA

DRUGS INHIBITING CNS

Drugs inhibiting CNS are divided into eight groups (Fig. 9.1). They include general anesthetics, sedatives, hypnotics, neuroleptics, anxiolytics, analgesics, anticonvulsants, and antiparkinsonian drugs.

GENERAL ANESTHESIA

General anesthesia (narcosis) is a reversible suppression of the CNS with abolishing of pain and all kinds of sensitivity, with myorelaxation and unconsciousness (Fig. 9.2).

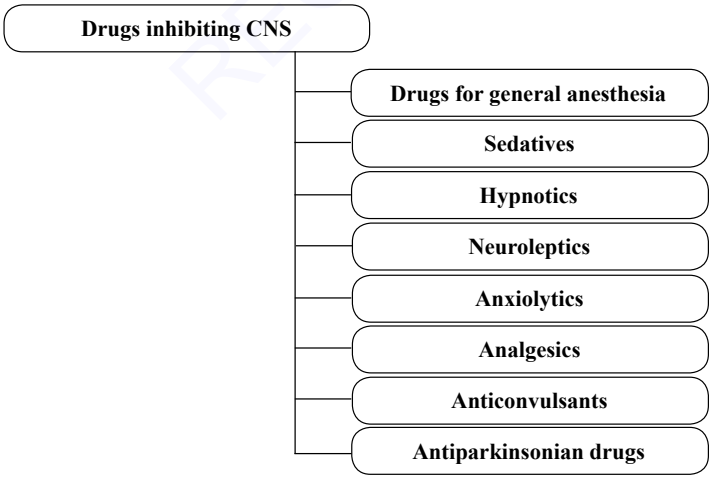

Fig. 9.1. Main groups of CNS inhibitors

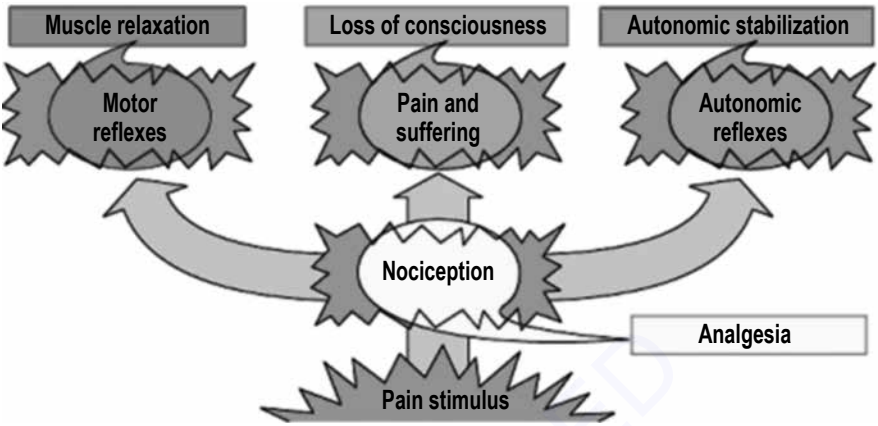

Fig. 9.2. Main goals of general anesthesia *(by H. Lüllmann, 2000)*

Disparities between general and local anesthesia

General anesthesia and local anesthesia both are used for abolishing of pain in the surgery, but they have significant distinctinctive features (Table 9.1).

Table 9.1. **Disparities between general and local anesthesia**

General anesthesia	*Local anesthesia*
– Total abolihing of pain – A loss of consciousness – Relaxation of skeletal muscles – Abolishing of reflexes – Usage for all kinds of surgeries	– Local abolishing of pain – Normal consciousness – Normal muscular tone – Normal reflexes – Usage for uncavitary surgeries

Main concepts of general anesthesia

- induction to anesthesia (inductive narcosis) is the start of narcosis which should be pleasant for a patient;
- basis narcosis is the maintenance of narcosis for all the periods of surgery;
- mixed narcosis is a combined usage of general anesthetics from one pharmacological group (halothane + nitrous oxide);
- combined narcosis (balanced anesthesia) is the combined usage of general anesthetics and preparations from other pharmacological groups (ganglia blockers, myorelaxants, etc) (Fig. 9.3);
- safety margin is the difference between the dose that causes surgical anesthesia and the dose that causes lethal suppression of the respiratory center;

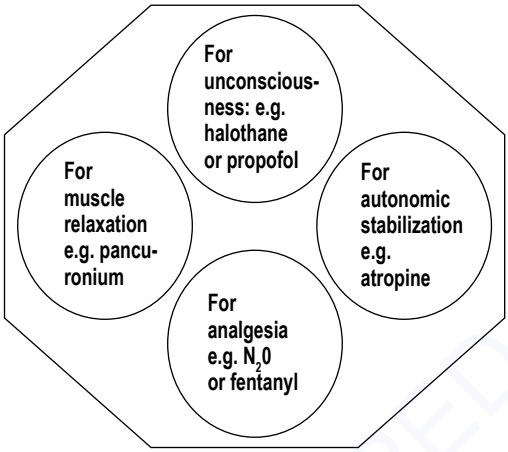

Fig. 9.3. Balanced anesthesia *(by H. Lüllmann, 2000)*

- premedication (preanesthetical medication) is the administration of preparations for the potentiation of narcosis as well as for the prophylaxis of side effects of general anesthesia.

DRUGS FOR GENETRAL ANESTHESIA

According to their routes of administration ***general anesthetics*** are divided into ***inhalation anesthetics and preparations for IV anesthesia***. These two groups are distinguished by some properties (Table 9.2).

Table 9.2. **Distinguishes between inhalation and IV general anesthetics**

Inhalation anesthetics	***Drugs for IV anesthesia***
– Inhalation administration	– IV administration
– Long duration of narcosis	– Short duration of narcosis after a bolus administration
– Strong myorelaxation	– Weak myorelaxation
– Well managed anesthesia	– Unmanaged anesthesia after a bolus administration
– Usage for cavitary surgeries	– Usage for short uncavitary surgeries

INHALATION ANESTHETICS

Inhalation anesthetics are preparations for general anesthesia which are administered by inhalation through a special mask or system.

CLASSIFICATION

1. Volatile liquids:
   - Ether for narcosis;
   - Halothane;
   - Isoflurane;
   - Sevoflurane.
2. Gaseous anesthetics:
   - Nitrous oxide;
   - Xenon.

Mechanism of action

It is based on the lipid solubility of inhalation general anesthetics and their ability to dissolve in the cell membrane lipids resulting in the inhibiting of neurotransmission (Fig. 9.4).

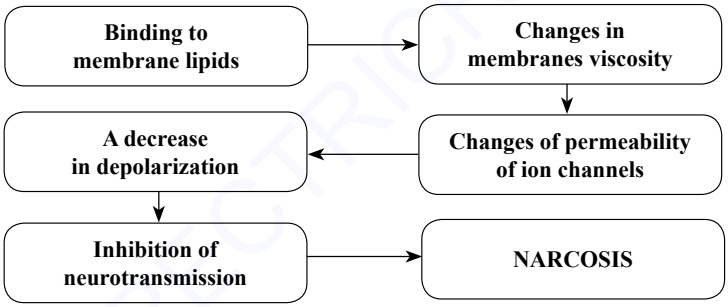

Fig. 9.4. Mechanism of action of inhalation general anesthetics

Stages of narcosis

Deepening of narcosis leads to the development of four stages of general anesthesia:

I. ***Analgesia*** with the absence of pain and the possibility to carry out short surgeries.

II. ***Excitement*** with many disturbances in the organism (motor and speech excitement, heart arrhythmia, heart arrest, changes in BP, irregulary respiration, respiratory arrest, spasm of the bronchi, spasm of the larynx, vomiting, hypersalivation), which make surgical intervention impossible.

III. ***Surgical anesthesia*** (planes 1–4) which is characterized by a loss of pain, unconsciousness, myorelaxation, absence of reflexes, stability of BP and respiration that is suitable for the majority of surgeries.

IV. ***Awakening*** with the restoration of CNS functions (if the concentration of the drug decreases), or ***medulla paralysis*** (if the concentration of the general anesthetic increases).

PECULIARITIES OF PREPARATIONS

Ether for narcosis is volatile inflammable liquid with specific odor; 80% of a dose is excreted unchanged with the air (Fig. 9.5); has a wide safety margin of the narcosis action, but a long stage of excitement; is used for basis mono- and combined narcosis; irritates the upper respiratory pathways; may cause pneumonia after the surgery.

Halothane (Phthorothane) is volatile liquid; contains fluorine; is not inflammable; has a strong narcosis action, but weak analgesia; has a long stage of analgesia without the excitement stage; dilates bronchi (may be used for the termination of severe bronchial asthma attack); dilates blood vessels; lowers BP; increases the myocardium sensitivity to catecholamines (adrenaline and noradrenaline are contraindicated during this narcosis); decreases the tone of uterus; is metabolized in the liver (Fig. 9.5) and may cause liver lesions; is used for combined general anesthesia.

Isoflurane is similar to halothane; displays good myorelaxation and rapid recovery; has a less negative influence on the heart and liver; is the best agent in pediatric patients.

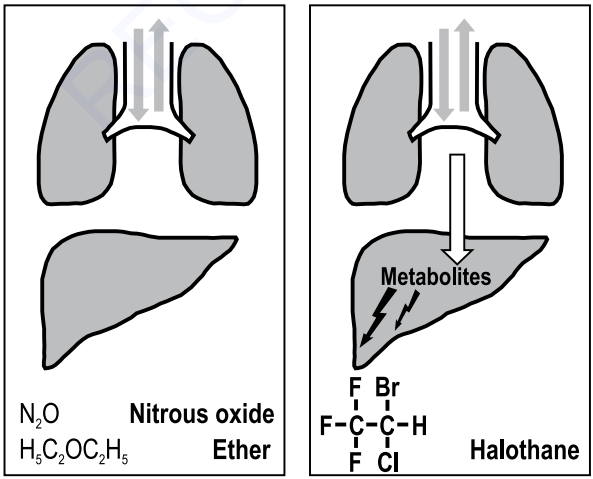

Fig. 9.5. Routes of elimination of inhalation anesthetics *(by H. Lüllmann, 2000)*

Sevoflurane is a sweet-smelling, nonflammable, highly fluorinated methyl isopropyl ether used as inhalational anesthetic for induction and maintenance of general anesthesia; has fast onset and offset; is one of the most commonly used volatile anesthetic agents, particularly for outpatient anesthesia; is often administered in a combination with nitrous oxide and oxygen.

Nitrous oxide is a gaseous anesthetic; is biologically inert (Fig. 9.5); has a weak narcosis action (is not used as a sole anesthetic for surgeries); does not cause good myorelaxation; has strong analgesia; rapid onset of action and recovery; is used for analgesia in traumas, myocardial infarction, or labor as well as for inductive and combined narcosis; is not toxic; may cause hypoxia in a concentration about 80%.

Xenon is the inert gas giving rapid induction and recovery in general anesthesia. The most important positive effects of xenon are cardiovascular stability, cerebral protection and favorable pharmacokinetics.

DRUGS FOR INTRAVENOUS ANESTHESIA

Intravenous anesthetics are drugs for general anesthesia which are administered IV.

CLASSIFICATION

According to the duration of action

1. Long-acting (more than 60 min):
   – Sodium hydroxibutyrate.
2. Intermediate-acting (20–30 min):
   – Thiopental-sodium.
3. Short-acting (10–20 min):
   – Ketamine (Kalipsol).
4. Ultra-short-acting (5–10 min):
   – Propofol.

According to the mechanism of action

1. GABA-ergic:
   – Sodium hydroxibutyrate;
   – Propofol.
2. Barbiturate-ergic:
   – Thiopental-sodium.

3. Glutamatergic:
   – Ketamine.

CHLORIDE CHANNEL

Some IV general anesthetics, hypnotics, tranquilizers, and other CNS inhibitors realize their effects by interaction with receptors of Cl^- channels (Fig. 9.6).

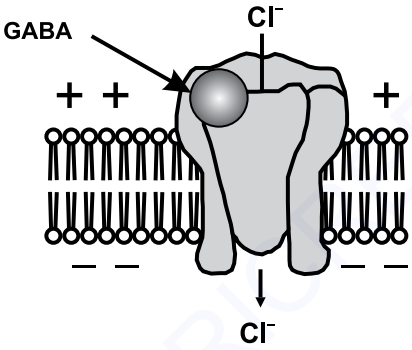

Fig. 9.6. Cloride channel *(adapted from R. Finkel et al., 2008)*

SODIUM HYDROXIBUTYRATE

By its chemical structure, the drug is the analogue of GABA (natural inhibiting neurotransmitter).

Pharmacokinetics

- is administered IV, IM, orally;
- begins to act in 5–7 min after the IV administration;
- acts during 2–4 hrs;
- is completely metabolized in the body.

Mechanism of action

- sodium hydroxibutyrate stimulates GABA-receptors of Cl^- channels (Fig. 9.7);
- a result is the opening of Cl^- channels and an increase in Cl^- influx into the cell;
- increased Cl^- concentration leads to the hyperpolarization of the cell membrane and more difficult depolarization;

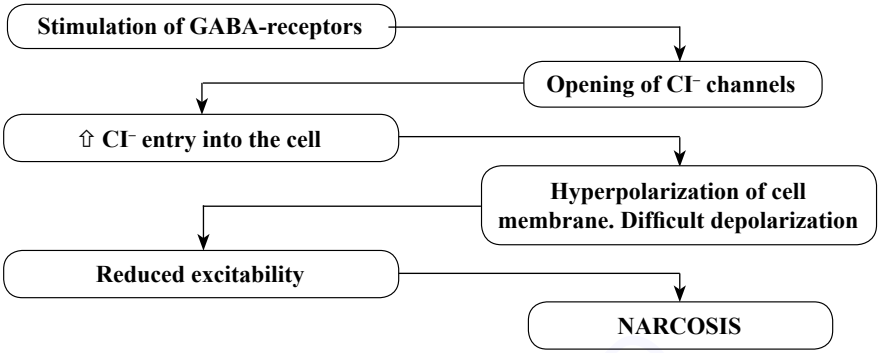

Fig. 9.7. Mechanism of action of sodium hydroxibutyrate

- these processes result in the reduction of neurons excitability, sleep, and general anesthesia.

Pharmacodynamics

- general anesthesia;
- a sedative action;
- a hypnotic action;
- an antiseizure action;
- an antihypoxic action;
- a nootropic action (after a long-term treatment).

Side effects

The drug is not toxic, but may cause hypokalemia.

PECULIARITIES OF OTHER PREPARATIONS

Thiopental sodium is administered IV; begins to act in 1–3 min; acts during 20–30 min; is destroyed in microsomes of the liver; is accumulated in the fat tissue; stimulates barbiturate receptors of Cl^- channels; displays a rapid onset of action; has potent anesthesia, poor analgesia, and little myorelaxation; has a hypnotic action; is used for the induction to narcosis, general anesthesia in short-term surgeries and diagnostic investigations; may cause the suppression of respiration, apnea, bronchospasm, laryngospasm, hypotension, arrhythmia, liver lesions, lower-

ing of the body temperature, thrombophlebitis; is contraindicated in the heart failure, bronchial asthma, diseases of the upper respiratory pathways, shock, acidosis.

Ketamine is administered IV, IM; begins to act in 30–60 sec after the administration; acts during 15–30 min; may be administered repeatedly in a lower dose. Ketamine acts primarily as a selective antagonist of the NMDA receptor. Also it is an agonist of different subtypes of opioid receptors, the agonist of dopamine D_2 receptor and a potentiator of 5-HT receptor. The drug produces "dissociative narcosis"; causes general anesthesia accompanied by strong analgesia during narcosis and after it (6–8 hrs); stimulates blood circulation (increases heart rate, minute volume of the heart and BP); does not inhibit respiration; does not cause myorelaxation and impairment of reflexes; has psychotomimetic action at the start and at the end of narcosis; may cause postoperative hallucinations. It is used for starting and maintaining of anesthesia, for chronic pain and for sedation in the intensive care. The drug can be used in children, in patients with shock or low BP, asthmatics or people with chronic obstructive airway disease, emergency surgery in the field conditions in war zones, and to supplement spinal or epidural anesthesia. Ketamine causes such side effects as muscles regidity, block of the upper respiratory pathways, psychomotor excitement; is contraindicated for patients with hypertension and disturbances of cerebral blood circulation. It can cause drug dependence and is strongly controlled substance.

Propofol is a short-acting IV general anesthetic. It has several mechanisms of action, both through activation of $GABA_A$ receptor and acting as a sodium channel blocker. Endocannabinoid system may contribute significantly to propofol's anesthetic action. Propofol's uses include the starting and maintenance of general anesthesia, sedation for mechanically ventilated adults, procedural sedation, and status epilepticus. Maximal effect takes about 2 min to occur and lasts 5–10 min. Common side effects are irregular heart rate, low BP, burning sensation at the site of injection, and the stopping of breathing. The drug may cause addiction and propofol infusion syndrome.

TESTS FOR SELF-CONTROL

1. Stage III stage of general anesthesia (the stage of surgical anesthesia) is manifested by all, except:

A. 4 planes of its development
B. Excitement
C. A progressive decrease in the muscular tone
D. A progressive decrease in reflexes
E. Stability of BP (at planes 1–2).

2. Only one IV general anesthetic has antihypoxic and nootropic properties:
A. Ketamine
B. Propofol
C. Sodium hydroxibutyrate
D. Kalipsol
E. Thiopental-sodium.

3. Nitrous oxide is characterized by the following properties:
A. Good analgesia
B. Good anesthesia
C. Poor muscle relaxation
D. High liver toxicity
E. Usage in obstetrics.

4. Ketamine is:
A. A long-acting general anesthetic
B. Increasing cardiac output
C. Producing profound analgesia
D. Not abolishing reflexes
E. Used for short operations.

5. Lowering of BP has been developed during the surgery under the combined general anesthesia including halothane. The anesthesiologist chooses phenylephrine for the correction of the patient's condition because adrenaline or noradrnaline are contraindicated in this case. What is a background of such contraindications?
A. Halothane's liver toxicity
B. Halothane's neurotoxicity
C. A combined action of general anesthetics
D. Halothane's ability to dilate blood vessels
E. The sensibilization of the myocardium to catecholamines.

Answers:

1 – B; 2 – C; 3 – A, C, E; 4 – B, C, D, E; 5 – E.

Chapter 10 ETHANOL. HYPNOTICS. ANTIEPILEPTIC AND ANTIPARKINSONIAN DRUGS

ETHANOL

(Alcohol, Spiritus aethylicus)

Ethanol's chemical structure is C_2H_5OH. It is water and lipid-soluble liquid with specific odor.

Pharmacokinetics

- is applied topically, IV, orally, or by inhalation;
- after the oral administration, it is absorbed in the oral cavity, in the stomach (less than 20% of a dose) and in the small intestine (80% of administered dose);
- penetrates CNS and the placenta barrier;
- is metabolized in the liver (Fig. 10.1);
- is excreted with urine and with air.

Pharmacodynamics

Ethanol has local and resorptive actions.

Local action of ethanol

Mechanism of action

- the inhibition of oxidoreductases;
- the denaturation of proteins;
- the irritation of sensitive nerve endings, local hyperemia;
- alcohol vapor changes the surface tension of surfactant in the lungs.

Effects

- an antiseptic action;
- a disinfective action;

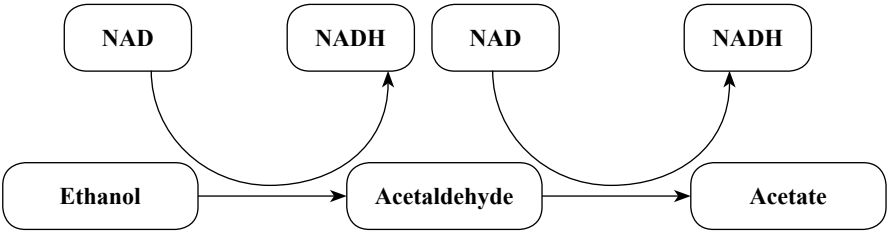

Fig. 10.1. Hepatic metabolism of ethanol

- an irritating action;
- a tannic effect;
- an antifoam action (after the inhalation).

Indications to topical application

- the processing of the surgeon's hands and surgical area (70%);
- the processing of instruments (95%);
- compresses (40%);
- the inhalation in the mixture with oxygen in pulmonary edema;
- preparing alcohol solutions and tinctures.

Resorptive action of ethanol

Mechanism of action

- ethanol acts as inhalation general anesthetic with a narrow safety margin;
- it is an energy substrate for the organism (Fig. 10.1).

Effects

- an anxiolytic action;
- an anti-shock effect;
- the stimulation of energy metabolism;
- an increase in BP;
- an increase in the heat irradiation;
- changes in the gastric secretion (till 20% – stimulation, about of 20% – suppression);
- a diuretic action resulting from the inhibition of vasopressin secretion;
- an antidote action.

Indications to IV and oral administration

- shock (20%, IV);
- abscess or gangrene of the lung (20%, IV);
- cachexia (20%, IV);
- producing sclerosis in the varicose vein (70%, inside the pathological vein);

- alcoholizing of nerves (inside the nerve at the surgery);
- diagnostics of the gastric function (10%, orally);
- acute poisoning with methanol (20%, IV).

Acute poisoning with ethanol

Main signs:	Emergency help:
– a specific odor – euphoria, excitement, then sleeping and coma – hyperemia of the face, then paleness – a decrease in BP – the suppression of respiration – hyporeflexia – hypotermia – unvoluntary urination	– lavage of the stomach with solution of potassium permanganate – analeptics (bemegride) – glucose, insulin, and vitamins preparations (IV) – nootropics (piracetam, IV)

Alcohol abuse (alcoholism)

It is tolerance and physical/psychological dependence (due to the participation of acetaldehyde in the synthesis of opioid peptides).

Main disorders in the organism:

– alcohol encephalopathy;
– alcohol polyneuritis;
– alcohol myocardiopathy;
– alcohol cirrhosis;
– hypoacidic gastritis;
– impotency in men;
– a negative influence on the fetus in pregnant women.

Abstinence is manifested as *alcohol delirium.*

Treatment of alcoholism

The therapy of alcohol abuse is carried out by the production of a conditioned reflex to the alcohol, combining its usage with such drugs as ***Emetine hydrochloride*** or ***Teturam (Disulfiram)*** (Fig. 10.2). Disulfiram blocks acetaldehyde dehydrogenase, inhibits alcohol metabolism with the accumulation of toxic acetaldehyde. Nausea, vomiting and other disturbances caused by this process are the basis of negative reflex to alcohol.

HYPNOTICS

Hypnotics are the drugs for the treatment of insomnia. They induce the onset of sleep and maintain it. Normal sleep is characterized by two stages: REM-sleep

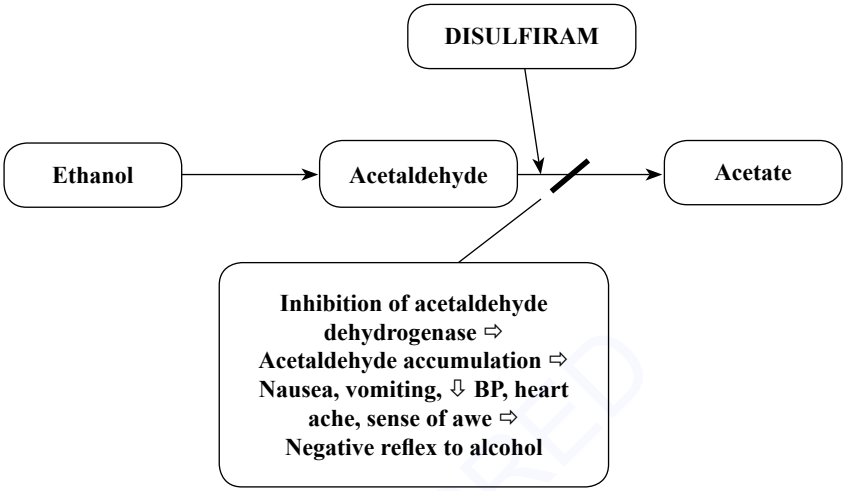

Fig. 10.2. Mechanism of action of disulfiram

(Rapid Eye Movement Sleep) and NREM-sleep (Non-Rapid Eye Movement Sleep). The state of sleep differs from the waking state by the activity of neurotransmitters in the brain (Fig. 10.3).

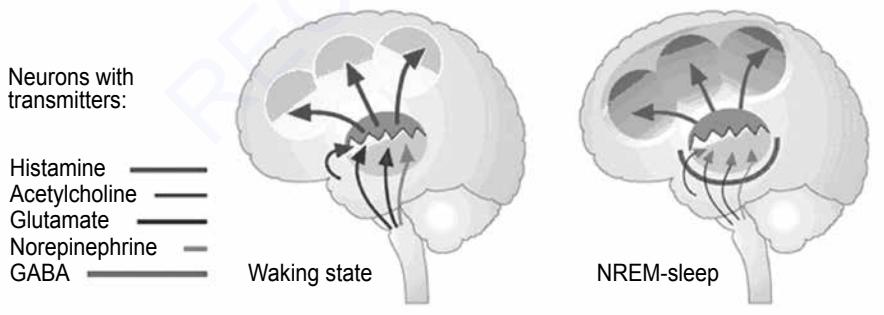

Fig. 10.3. Neurotransmission in the brain in the waking state and NREM sleep *(by H. Lüllmann, 2000)*

CLASSIFICATION

1. Barbiturates:
   – Phenobarbital;

- Barbital;
- Ethaminal.

2. Benzodiazepines:
   - Nitrazepam.
3. Aliphatic compounds:
   - Chloral hydrate.
4. Other preparations:
   - Donormyl;
   - Zopiclone;
   - Zaleplon.

PHENOBARBITAL

It is a derivative of barbituric acid (Fig. 10.4). The substance is not soluble in water, but solubility is increased at alkalic pH.

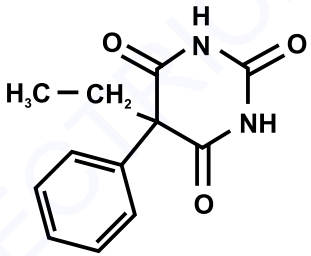

Fig. 10.4. Chemical structure of phenobarbital

Pharmacokinetics

- is taken orally;
- is absorbed in the small intestine;
- is strongly bound to proteins in the blood plasma;
- penetrates CNS and placenta;
- is metabolized in microsomes of the liver;
- is the inductor of microsomal oxidation;
- is excreted with urine;
- is accumulated (material accumulation);
- starts to act in 30–60 min after the administration and acts during 6–8 hrs, stays in the body during 1–2 days.

Mechanism of action

- the drug binds to barbiturate receptors of chloride channels;
- that results in the enhancement of $GABA_A$-receptors' activation and opening of chloride channels;
- an increase in the Cl^- influx leads to the membrane hyperpolarization, difficult depolarization, and the inhibition of neuron functions.

Pharmacodynamics

- a hypnotic action with the change in normal sleep structure (inhibition of REM-sleep);
- a sedative action;
- an antiepileptic action;
- the potentiation of the effect of other drugs inhibiting CNS.

Indications

- insomnia;
- epilepsy with grand mal;
- ictrerus in newborns;
- as the ingredient of combined sedative preparations;
- as the ingredient of combined analgesic preparations.

Side effects

1. The after-action syndrome (weakness, drowsiness, apathy, slow motor reaction in the morning).
2. The return syndrome after rapid cancellation of the drug.
3. Tolerance due to the induction of microsomal oxidation (Fig. 10.5).
4. Drug dependence.
5. Changes in pharmacokinetics of other drugs due to the induction of microsomal oxidation (Fig. 10.5).
6. The suppression of respiration.
7. Hypotension.
8. Liver lesions.

Contraindications

Liver and renal diseases, hypotension, intermitted purpura, age about 60 or till 10 years old, pregnancy.

The drug should not be used in patients whose job needs quick motor reaction as well as for long treatment.

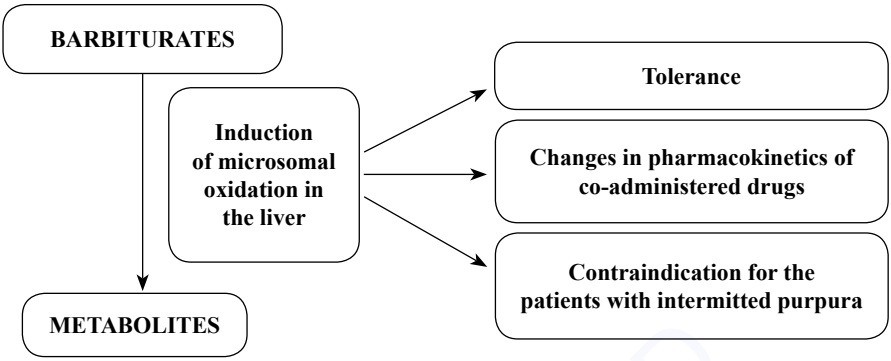

Fig. 10.5. Inhibition of microsomal oxidation by phenobarbital and its result

Acute poisoning with barbiturates

Main signs:

- sleep, coma
- hyporeflexia
- a decrease of the muscles tone
- suppression of respiration
- hypotension
- hypothermia

Emergency help:

- lavage of the stomach
- activated charcoal
- laxatives (magnesium sulfate)
- hemodilution and forced diuresis
- hemodialysis
- analeptic bemegride (an antagonist of barbiturates)

PECULIARITIES OF OTHER PREPARATIONS

Nitrazepam is a benzodiazepine derivative; is an agonist of benzodiazepine receptors of Cl^- channels; has a hypnotic action with minimal changes in the normal sleeping structure; has anxiolytic, sedative, central myorelaxative and potentiative effects; is used in insomnia, neurosis, epilepsy, abstinence in alcoholics; has less side effects than phenobarbital (less tolerance, drug dependence, and return syndrome); does not produce the activation of liver enzymes.

Chloral hydrate is administered orally or rectally; is converted to trichlorethanol; has an antiseizure and sedative action; is applied in seizures, insomnia, and severe cough in children; irritates mucous membranes (is used with the addition of starch mucus).

Donormyl is H_1-histamine blocker from the group of ethanolamines. The drug has a hypnotic, sedative and M-anticholinergic action. Reduces the time of falling

asleep, increases the duration and quality of sleep, while not changing the phase of sleep. The duration of action is 6–8 hrs.

Zopiclone is a cyclopirrolone derivative, which interacts with ω_1- and ω_2-benzodiazepine receptors of the macromolecular GABA-benzodiazepine-chloronophore complex. The drug shortens the period of falling asleep, reduces the number of nocturnal awakenings, improves the quality of sleep, does not change the phase structure of sleep. It is effective in situational insomnia, changes in the usual rhythm of life, and a shift work regime. Sleep occurs within 20–30 min and lasts 6–8 hrs. Side effects are drowsiness, lethargy, headache, dizziness, irritability, confusion, muscle weakness, impaired coordination of movements, diplopia, memory impairment, paradoxal reactions. Addiction, drug dependence, and withdrawal syndrome also are possible.

Zaleplon is a derivative of pyrazolopyrimidine, which selectively binds to ω_0-benzodiazepine receptors and excites them, that leads to the opening of chloride channels, hyperpolarization, and inhibition in the CNS. It reduces the latent time of falling asleep, prolongs the sleep time in the first half of the night, does not change the ratio of the sleep phases. Doses of 5–10 mg do not cause tolerance at 2–4 weeks. The drug has sedative, weak anxiolytic and central myorelaxant effect. Indications to use are short-term treatment of severe forms of sleep disorders (difficulty falling asleep) disturbing day activity. The most common undesirable effects are memory impairment, paresthesia, drowsiness, and dysmenorrhea.

ANTICONVULSANTS

EPILEPSY AND ITS PHARMACOTHERAPY

Epilepsy is a disease of the brain with attacks of seizures. There are some types of epilepsy (Fig. 10.6).

Principles of the treatment of epilepsy

- the choice of the drug according to the type of epilepsy;
- a long-term treatment;
- oral administration of the drugs;
- an equal dose of a new drug if the change of preparation is needed;
- slow cancellation of the drug.

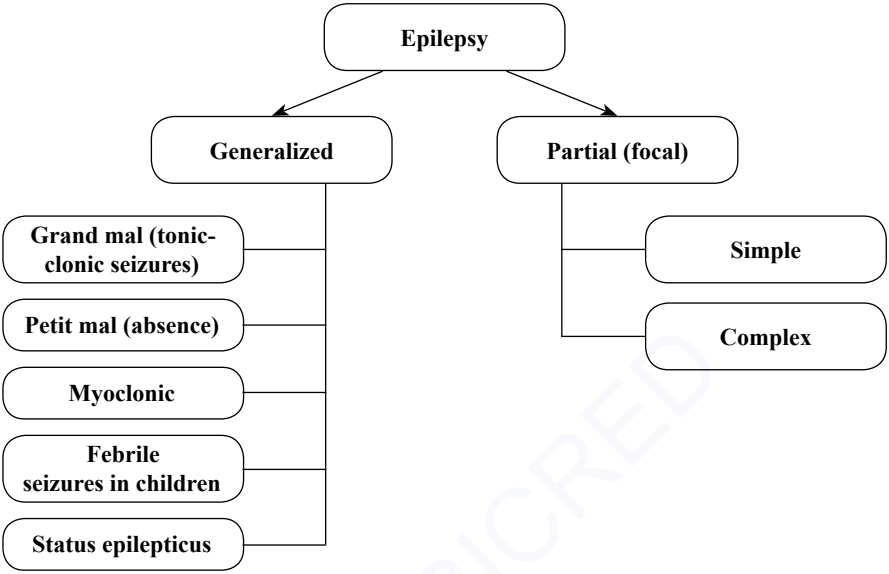

Fig. 10.6. Types of epilepsy as the basis for differential pharmacotherapy

ANTIEPILEPTIC DRUGS

Antiepileptics are drugs of a different chemical structure which prevent attacks of epilesy (Fig. 10.7).

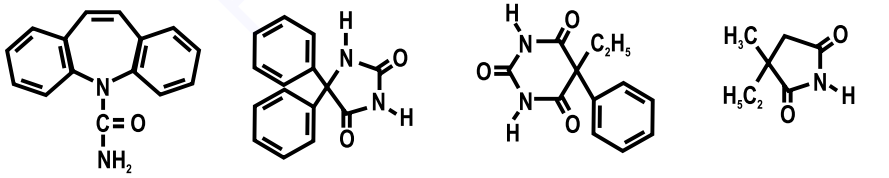

Fig. 10.7. Chemical structure of antiepileptics

CLASSIFICATION

1. Preparations for the treatment of epilepsy with grand mal:
   – Phenobarbital;

– Phenytoin (Diphenine);
– Carbamazepine (Finlepsin);
– Valproic acid, Sodium valproate;
– Clonazepam;
– Lamotrigine.

2. Preparations for the treatment of epilepsy with petit mal:
– Valproic acid;
– Clonazepam;
– Lamotrigine.

Mechanism of action

- most excitory nerve cells utilize glutamate and most inhibitory nerve cells utilize GABA. Glutamate receptors comprise three subtypes, of which the NMDA subtype has the greatest therapeutic importance. N-metyl-D-aspartrate (NMDA) is their synthetic selective agonist. Stimulation of these receptors permits the entry of both Na^+ and Ca^{++} into the cell;
- phenytoin, phenobarbital, and lamotrigine inhibit release of glutamate (Fig. 10.8);
- benzodiazepins and phenobarbital increase the inhibition by the release of physiological amounts of GABA and its interaction with $GABA_A$ receptors of chloride channels;
- valproic acid decreases GABA catabolism by the inhibition of GABA transaminase;
- other preparations realize their actioin by the antagonism to glutamate, a direct GABA-mimetic action or regulation of GABA reuptake.

PHENYTOIN

- is taken orally, is quickly absorbed in the GI tract, is metabolized in the liver, stays in the organism for a long time, is excreted by urine and bile, accumulates;
- promotes carrying out Na^+ from neurons; decreases the Ca^{++} contain and energy processes in the epileptic focal area; increases GABA concentration, as a result, suppresses the induction and irradiation of excitement in the motor areas in the brain;
- has an antiepileptic action; an antiarrhythmic action; a weak sedative action;
- is used in epilepsy with grand mal, tachyarrhythmia (especially in acute poisoning with cardiac glycosides), Menier's disease;

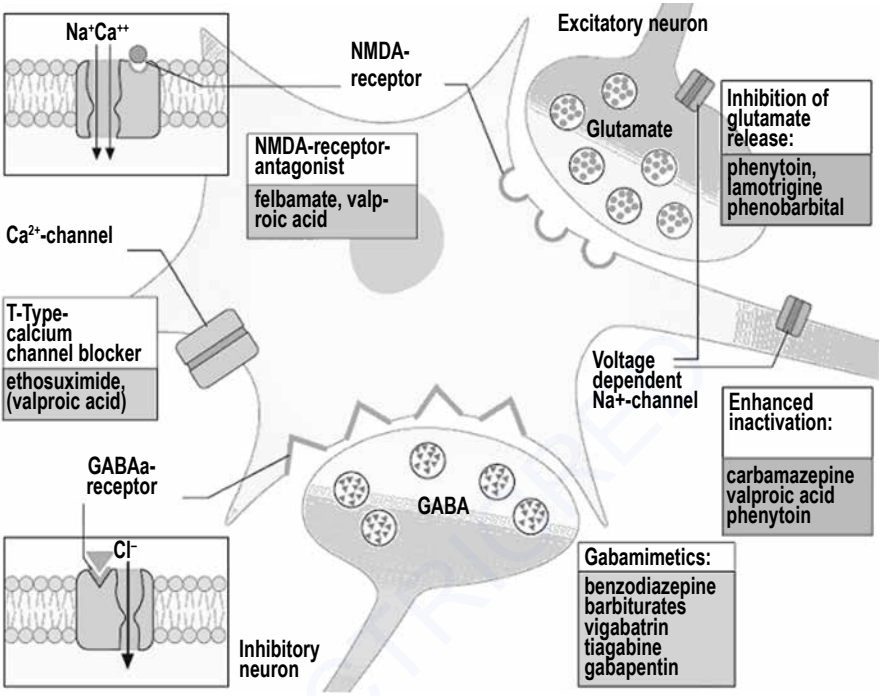

Fig. 10.8. Sites of action of antiepileptic drugs *(by H. Lüllmann, 2000)*

- may cause side effects, such as vertigo, ataxia, tremor, nystagmus, diplopia, respiratory disturbances, an increase of the body temperature, skin rash, hyperplastic gingivitis.

PECULIARITIES OF OTHER PREPARATIONS

Carbamazepine is an agonist of benzodiazepine receptors of Cl^- channels; has antiepileptic and anxiolytic effects, decreases pain syndromes and vestibular disturbances; is indicated in epilepsy with grand mal, petit mal, mixed forms, hyperkinesis, neuralgia of *n. trigeminus*, Menier's disease; may cause nausea, vomiting, drowsiness, ataxia, accomodation disturbances.

Clonazepam suppresses generalized seizures more than focal. It binds to the benzodiazepine site of the $GABA_A$ receptor which increases its sensitivity to GABA, reducing the excitability of neurons. It is used for epilepsy with focal and

generalized seizures, absences (typical and atypical small epileptic attacks), panic disorder, phobias, bipolar disease, and hyperkinesia. Like other benzodiazepines, clonazepam has sedative, anxiolytic, and central myorelaxing effects.

Sodium valproate (or valpoic acid) inhibits GABA transaminase and produces accumulation of GABA in the brain, is used for the treatment of grand mal, petit mal, mixed and local forms of epilepsy; has such side effects as drowsiness, ataxia, dyspepsia, decreasing of blood coagulation.

Lamotrigine enhances the action of GABA in the CNS and inhibits the release of glutamate and aspartate. It is a first-line drug for primary generalised tonic-clonic seizures, an adjuvant therapy in partial seizures, and an alternative drug for absences. Other indications include bipolar disorder, peripheral neuropathy, trigeminal neuralgia, cluster headaches, and migraines. Side effects are life-threatening skin reactions, loss of balance or coordination; vision disturbances, dizziness, drowsiness, insomnia, anxiety, memory problems, mood changes; dry mouth, itch, cough; nausea, abdominal pain, weight loss and dysmenorrhea.

PREPARATIONS FOR EMERGENCY HELP IN SEIZURES ATTACK

- Diazepam (IV or IM);
- Sodium hydroxibutyrate (IV or IM);
- Magnesium sulfate (IV or IM);
- Chloral hydrate (rectally);
- Tubocurarine (IV, under the conditions of artificial lungs ventilation);
- General anesthesia by halothane.

PARKINSON'S DISEASE AND ITS PHARMACOTHERAPY

The main signs of ***Parkinson's disease*** are tremor, muscular rigidity, hypokinesia, hypersalivation. The main disorders in the CNS are lesions in striatum resulting in the diminished amount of dopaminergic neurons in the substantia nigra. This leads to the onset of dopamine/acetylcholine imbalance (Fig. 10.9).

The ways of ***pharmacological management of Parkinson's disease*** are:

1. Stimulation of dopaminergic processes with:
   – Levodopa;
   – Nacom;
   – Madopar;
   – Midantan;
   – Selegeline.

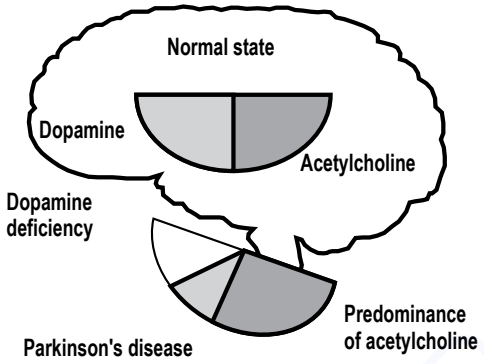

Fig. 10.9. Main disorders in the CNS resulting in Parkinson's disease *(by H. Lüllmann, 2000)*

2. Inhibition of central cholinergic processes by:
   – Trihexyphenidyl (cyclodol).

PECULIARITIES OF PREPARATIONS

Levodopa is a precursor of dopamine (Fig. 10.10). It is administered with a purpose to replenish the dopamine deficiency in specific regions of the brain. Dopamine itself does not cross the blood-brain barrier, but levodopa is actively transported into the CNS and is converted to dopamine in the brain. Large doses of levodopa are required, because much of the drug is decarboxylated to dopamine in the periphery, resulting in the side effects. Levodopa avoids hypokinesia; has a little action on muscles regidity and tremor and is used for the treatment of Parkinson's disease. It may cause dyspepsia, orthostatic hypotension, arrhythmia, psychic disturbances. It is significant to know the following drugs interactions observed during the intaking of levodopa: vitamin B_6 decreases the effect of levodopa; MAO inhibitors administered together with levodopa may cause hypertension.

Nacom is a combined preparation containing levodopa and carbidopa which decreases the metabolism of levodopa in peripheral tissues and enhances the effectiveness of the preparation (Fig. 10.10).

Madopar is a combined remedy for the treatment of Parkinson's disease and restless legs syndrome, contains levodopa and benserazide, an inhibitor of peripheral decarboxylase; is used for fluctuations in the action of levodopa, depletion of the single dose effect, or an increase in the latent period before the onset of the clinical effect of this drug.

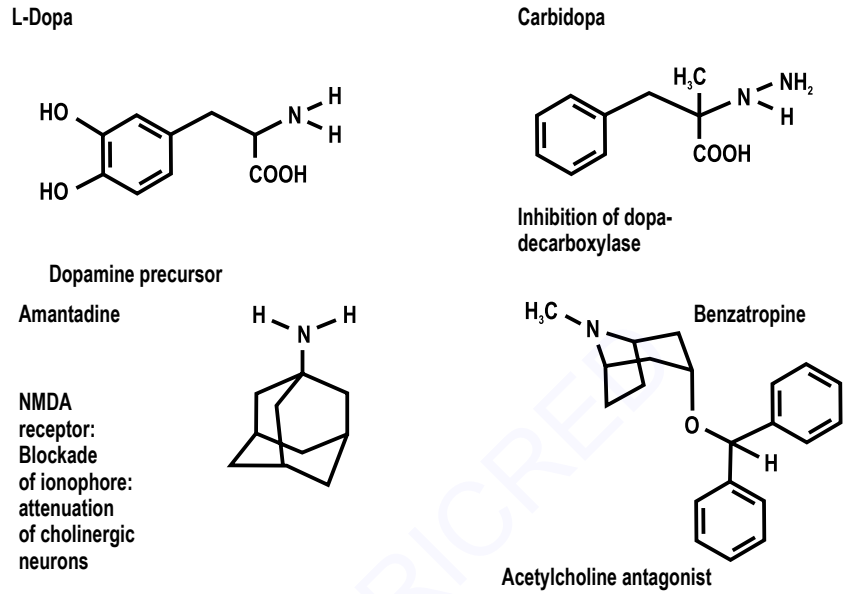

Fig. 10.10. Chemical structure and mechanism of action of levodopa, carbidopa, midantan, and benzatropine *(by H. Lüllmann, 2000)*

Midantan blocks glutamate receptors in the cortex (Fig. 10.10), decreases their influence on the neostriatum, protects neurons in substantia nigra, increases the sensitivity of dopamine receptors to the neurotransmitter; avoids hypokinesia and muscles regidity; has antiviral activity: is used for the treatment of Parkinson's disease and symptomatic parkinsonism; may cause such side effects as insomnia, hallucinations, headache, orthostatic hypotension, dyspepsia.

Selegiline is a selective irreversible MAO-B inhibitor, preventing degradation of dopamine in some areas of the brain. It is used to reduce symptoms in early-stage Parkinson's disease and depression. Side effects include nausea, hallucinations, confusion, depression, a loss of balance, insomnia, agitation, arrhythmia, bradycardia, hypertension, angina pectoris, and syncope. Due to the structural similarity to amphetamine, selegiline is a controlled substance.

Trihexyphenidyl (cyclodol) blocks cholinoreceptors in basal ganglia of the brain; avoids hypokinesia, regidity, and hypersalivation; is used for the treatment of Parkinson's disease and symptomatic parkinsonism; may cause peripheral M-cholinoblocking action. Benzatropine has similar mechanism of action (Fig. 10.9).

TESTS FOR SELF-CONTROL

1. Hypnotic with benzodiazepine structure is only:
A. Phenobarbital
B. Levodopa
C. Donormyl
D. Thiopental sodium
E. Nitrazepam.

2. The concentration of ethanol for IV administration in cachexia is:
A. 40%
B. 96%
C. 70%
D. Absolute ethanol
E. 20%.

3. Phenytoin exerts the following useful effects:
A. Antiepileptic
B. Gum hypertrophy
C. Coarsening of facial features
D. Hyperglycemia
E. Antiarrhythmic.

4. Ethanol is:
A. A long acting general anesthetic
B. A neuronal depressant with local antimicrobial action
C. Causing acute and chronic poisonings
D. Used mainly as antiseptic
E. Used for myorelaxation in the short surgeries.

5. An antiparkinsonian drug influencing dopaminergic processes in basal ganglia of the brain was prescribed to the patient suffering from Parkinson's disease. It is known, that this preparation also has antiviral activity and may be used for the prophylaxis of influenza. Which of the listed drugs was prescribed?
A. Levodopa
B. Nacom
C. Cyclodol
D. Amantadine (midantan)
E. Carbidopa.

Answers:

1 – E; 2 – E; 3 – A, E; 4 – B, C, D; 5 – D.

Chapter 11 NEUROLEPTICS. ANXIOLYTICS. SEDATIVES. LITHIUM SALTS

PSYCHOTROPIC DRUGS

Neuroleptics, anxiolytics, and sedatives are drugs for the treatment of psychic disorders of different severity. Neuroleptics (major tranquilizers) are the strongest among these preparations and have an antipsychotic action (Fig. 11.1). Anxiolytics (minor tranquilizers) are characterized by anxiolytic and sedative effects. Sedative drugs are the least potent and have only a sedative effect. Lithium salts are specific agents to treat mania.

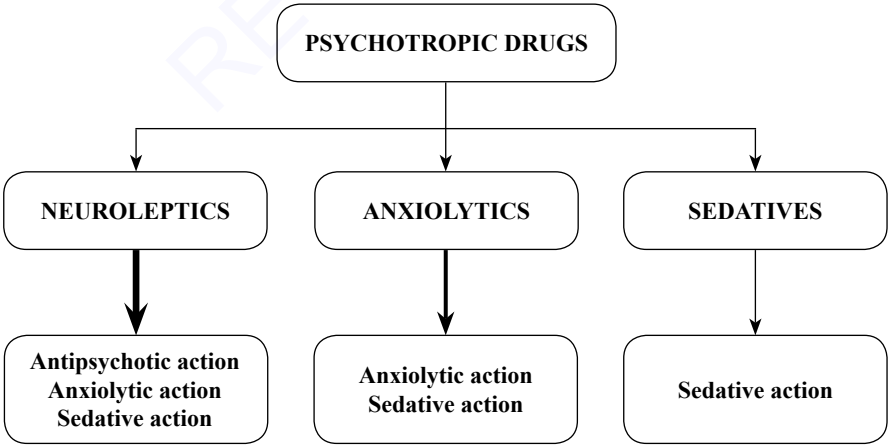

Fig. 11.1. Main groups of psychotropic drugs and their potency

ANTIPSYCHOTIC DRUGS

SCHIZOPHRENIA

Schizophrenia is a type of psychosis characterized by delusions, hallucinations, thinking and speech disturbances. The illness often initially affects people during adolescence and is a chronic and disabling disorder. It has genetic component and reflects some biochemical abnormality in the brain, possibly the overactivity of the mesolimbic dopaminergic neurons.

NEUROLEPTICS

Neuroleptics are drugs which are used to treat schizophrenia and some other psychotic states, such as manic states and delirium.

CLASSIFICATION

A. *Typical neuroleptics:*

1. Phenothiazines:
   - Chlorpromazine (Aminazine);
   - Trifluoperazine (Triftazine);
   - Flunazine (Phthorphenazine).
2. Butyrophenones:
   - Haloperidol;
   - Droperidol.
3. Thioxanthenes:
   - Chlorprothixene.

B. *Atypical neuroleptics:*

1. Dibenzodiazepines:
   - Clozapine.
2. Benzamides:
   - Sulpiride.
3. Benzisoxazoles:
   - Risperidone.

DISTINGUISHES BETWEEN TYPICAL AND ATYPICAL NEUROLEPTICS

Typical neuroleptics block D_2-, D_1-, D_3- and D_4-dopamine receptors; cause extrapyramidal disturbances (drug parkinsonism).

Atypical neuroleptics block 5-HT_2- receptors, α_2-adrenoceptors, D_4-dopamine receptors, have a weak action on D_2-dopamine receptors, do not cause extrapyramidal disturbances.

CHLORPROMAZINE (AMINAZINE)

The drug is a phenothiazine derivative (Fig. 11.2).

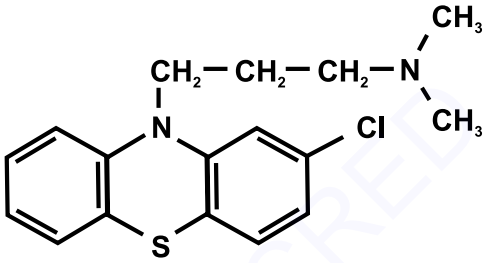

Fig. 11.2. Chemical structure of chlorpromazine

Pharmacokinetics

- is administered orally, IM, IV;
- is absorbed in the GI tract, but absoption is poor;
- maximal concentration is determined in 2–4 hrs;
- penetrates CNS and placenta;
- binds to albumins in the blood plasma (95–98%);
- is metabolized in the liver;
- is the inductor of microsomal oxidation;
- is excreted by urine, bile, and mother's milk;
- acts during 6–8 hrs, $T_{½}$ = 30 hrs;
- accumulates.

Mechanism of action

Chlorpromasine blocks dopamine receptors; exerts preference for D_2-dopamine receptors, prevents the interaction of dopamine with the receptor, decreases intracellular response (Fig. 11.3).

It also blocks serotonin receptors, cholinergic receptors, α-adrenoceptors, H_1-histamine receptors (Fig. 11.4).

Chlorpromazine acts in the mesolimbic system, hypothalamus, extrapyramidal system, trigger zone of the emetic center, ascending reticular system of the brain.

It has a peripheral action (antimuscarinic, anti-adrenergic, and antihistamine).

Pharmacodynamics

- an antipsychotic action (a decrease in hallucinations and agitation);
- an anxiolytic action (a decrease in anxiety and stress);
- a sedative action (a decrease in restlessness);
- a decrease in psychomotor excitement;
- a hypnotic action;
- an antiseizure action;
- cataleptic effect (absence of active movements under the conditions of the normal muscle tone);
- an antiemetic action (a decrease in nausea and vomiting caused by cancer chemotherapy or radiation);
- an antihypertensive effect;
- hypothermia and poikilothermia (lowering in high body temperature as well as normal temperature);
- a potentiative action;
- weak anti-inflammatory and anti-allergic actions.

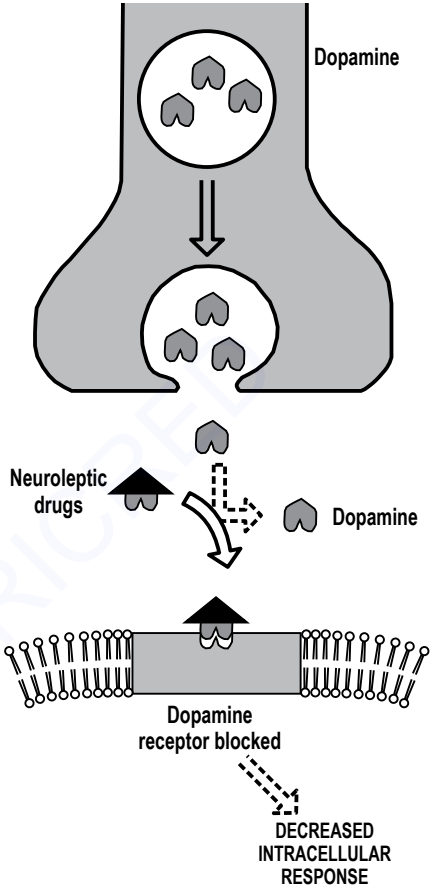

Fig. 11.3. Dopamine-blocking mechanism of action of neuroleptics *(by R. Finkel et al., 2008)*

Indications

- psychosis, schizophrenia;
- psycho-motor excitement;
- seizures attack;
- premedication;
- severe vomiting of central origin;

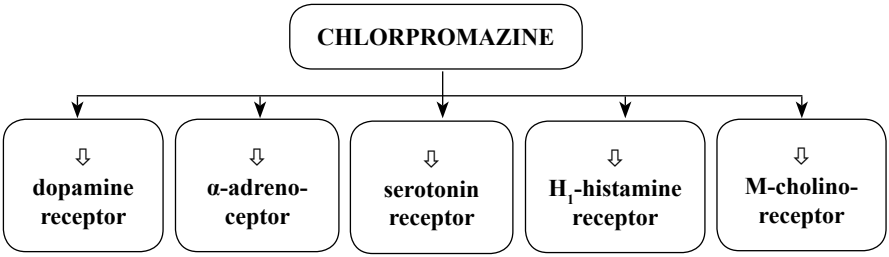

Fig. 11.4. Receptors which are blocked by chlorpromazine

- hypertensive crisis;
- hyperthermia;
- hibernation (a decrease in normal body temperature during surgeries on the brain or on the heart);
- combined therapy of pain syndromes;
- skin diseases accompanied by severe itch.

Side effects

1. Irritation in the place of injection
2. Pain in the stomach
3. Irritation of the skin and mucous membranes
4. Confusion, blurred vision, dry mouth, hyposecretion in the stomach, constipation, urinary retention (due to M-cholinoblockage)
5. Hypotension, orthostatic reactions, lightheadedness (due to the blockage of α-adrenoceptors)
6. Liver lesions, icterus
7. Inhibiting in hemopoiesis (leukopenia, agranulocytosis)
8. Dermatitis, phototoxicity
9. Parkinsonian symptoms, such as akathisia and tardive dyskinesia (due to the blockage of dopaminoreceptors in the nigrostriatal pathway)
10. Neuroleptic syndrome (apathy, depression, parkinsonism)
11. The aggravation of acute agitation accompanying withdrawal from alcohol
12. The aggravation of epilepsy
13. Amenorrhea, galactorrhea, infertility, impotence (due to the depression of hypothalamus)
14. Allergy
15. Tolerance.

Contraindications

1. Diseases of the liver and kidney
2. Diseases of the blood
3. Hypothyroidism
4. Thromboembolism
5. Organic diseases of the brain and spinal cord (trauma, cancer, insult)
6. Gastric ulcer
7. Pregnancy and lactation.

PECULIARITIES OF OTHER PREPARATIONS

Typical neuroleptics

Trifluorperazine (Triftazine) contains fluorine; is more active in its antiemetic action and in the influence on the extrapyramidal system; is less active in potentiation, antiseizure, and antihistamine actions; may cause sedative or stimulating effect according to the form of the disease.

Flunazine (Phthorphenazine) contains fluorine; has strong antipsychotic and antiemetic actions; manifests a stimulating action in lower doses and a sedative action in bigger doses; is effective for the treatment of long durative schizophrenia; may be used in neurosis (lower doses).

Haloperidol is from butyrophenone derivatives; has strong antipsychotic, potentiative, antiemetic and sedative actions, denominated catalepsy; is effective for the treatment of acute psychosis; may be used for neuroleptanalgesia; often causes extrapyramidal disturbances.

Droperidol has a strong and short action; has no cholinoblocking activity; has anti-shock, antiarrhythmic, antihypertensive actions; strong catalepsy; is used for neuroleptanalgesia, before, during and after operations, in shock and myocardial infarction.

Chlorprothixene is a thioxanthene derivative; has a sedative action, decreases depression; has a weak antiseizure effect; does not cause catalepsy; is used in psychoses accompanied by depression, in neurosis (lower doses).

Atypical neuroleptics

Clozapine (Asaleptin) has an antipsychotic action with sedation; does not cause catalepsy and extrapyramidal disturbances; does not cause apathy; is effective in the resistance to other preparations.

Sulpiride has a strong antiemetic action and a weak cataleptic action; has no sedative, antiseizure and potentiative effects; has an antidepressive action; is used for the treatment of psychic diseases accompanied by apathy as well as of psychosomatic diseases.

CONCEPT ABOUT NEUROLEPTANALGESIA

Neuroleptanalgesia is the kind of general anesthesia when neuroleptic (droperidol) and narcotic analgesic (fentanyl) are administered together (IV). In this case neuroleptic produces psychic suppression and narcotic analgesic causes abolishing of pain. Co-administered, they display a synergic action.

ANTI-ANXIETY DRUGS

ANXIETY

Anxiety is a state of tension, apprehension or uneasiness. The symptoms of severe anxiety are mental disturbances accompanied by tachycardia, sweating, trembling, palpitation. Episodes of mild anxiety are common life experiences and do not warrant treatment. The symptoms of severe or chronic anxiety may be treated with anti-anxiety drugs.

ANXIOLYTICS

Anxiolytics are drugs to treat anxiety and stress. They are also named ***minor tranquilizers or ataractics.***

CLASSIFICATION

1. Benzodiazepines:
   - Chlordiazepoxide (Chlosepide);
   - Diazepam (Sibason);
   - Phenazepam;
   - Medazepam (Mezapam, Rudotel);
   - Gidazepam.
2. Preparations of another chemical structure:
   - Buspirone;
   - Benactyzime (Amizyl);
   - Meprobamate (Meprotane).

Antagonist of benzodiazepines is Flumazenil.

CLORDIAZEPOXIDE

The drug is a benzodiazepine derivative (Fig. 11.5)

Pharmacokinetics

- is administered orally, IM, IV;
- is absorbed in the GI tract;
- penetrates CNS;
- is metabolized in the liver;
- is excreted by urine;
- has a long-durative action, $T_{½}$ = 24–48 hrs.

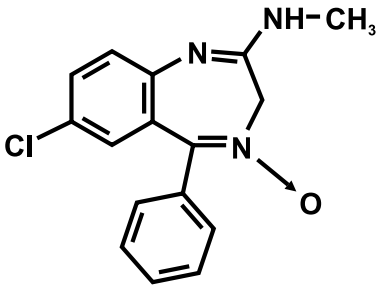

Fig. 11.5. Chemical structure of chlordiazepoxide

Mechanism of action

- benzodiazepine-receptor is a part of the benzodiazepine-GABA-chloride ion channel complex;
- the drug binds to benzodiazepine receptors of Cl^- ion channels and opens them (Fig. 11.6);
- Cl^- ions entry is increased that leads to hyperpolarization of the cell membranes. Depolarization gets worse and decreasing of neurons excitement in the limbic system and midbrain develops. It results in the anxiolytic action.

Pharmacodynamics

- an anxiolytic action (a decrease in anxiety, panic, and stress);
- a sedative action;
- a hypnotic action;
- a central myorelaxative action (due to action on spinal polysynaptic reflexes);
- an antiseizure action;
- a potentiative action (a strengthening of the effect of co-administered analgesics, general anesthetics, or other CNS inhibitors).

Indications

- neuroses;
- stress, emotional overstrain;
- sleeping disorders induced by emotional overstrain;
- neurological diseases with muscle spasticity;
- seizures;
- abstinence in chronic alcoholics;
- psychosomatic diseases;
- premedication.

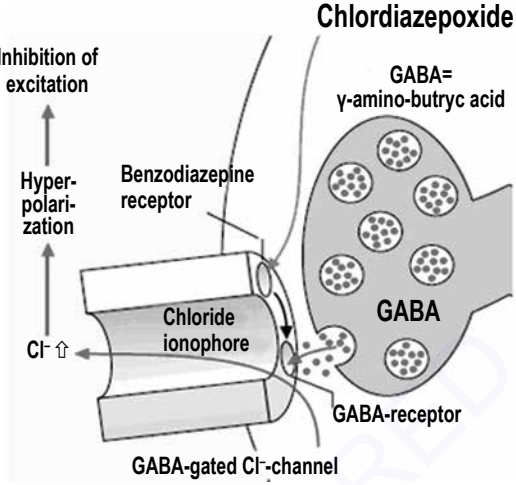

Fig. 11.6. Mechanism of action of chlordiazepoxide *(by H. Lüllmann, 2000)*

Side effects

1. Weakness
2. Drowsiness
3. A decrease in attention and rapidness of motor reactions
4. Ataxia
5. Skin itch
6. Amenorrhea
7. Impotence
8. Drug addition
9. Drug dependence

Contraindications

1. Jobs that needs increased attention
2. Myasthenia
3. Diseases of the liver and kidney
4. Pregnancy

PECULIARITIES OF OTHER PREPARATIONS

Diazepam (Sibazon) is administered orally, IM, IV; maximal concentration after the oral administration develops in 30–90 min; elimination is characterized by two phases (the 1st short phase with distribution of the drug in tissues during 3 hrs and the 2nd long-lasting phase with $T_{½}$ = 48 hrs); is more potent than clordiazepoxide, especially in the antiseizure effect; causes a decrease in night gastric secretion and arrhythmia; is suitable to treat a seizure attack; may be used in the combined therapy of ulcerative disease and heart arrhythmia.

Phenazepam is administered orally; maximal concentration is in 1–2 hrs; has $T_{½}$ = 6–10 hrs; is stronger than clordiazepoxide or diazepam; has a strong hypnotic action and muscle relaxation.

Medazepam is taken orally; is less potent, but does not cause hypnotic effect and myorelaxation (so named "day-time" tranquilizer); may be used in patients who need increased attention for their jobs.

Gidazepam is "day-time" tranquilizer; is taken by mouth; begins to act in 30–60 min and acts during 1–4 hrs; has $T_{½}$ = 87 hrs; has an anxiolytic action, psychostimulating and antidepressant effects; has not a hypnotic effect; is well tolerated; is used to treat neuroses accompanied by asthenia and depression.

CONCEPT ABOUT ATARACTANALGESIA

The ataractanalgesia is a kind of general anesthesia when tranquilizer and the narcotic analgesic are administered together (IV).

SEDATIVES

Sedatives are the drugs to treat restlessness and light forms of anxiety.

CLASSIFICATION

1. Non-organic preparations:
   – Sodium bromide;
   – Potassium bromide.
2. Vegetable preparations:
   – Tincture from valerian;
   – Tincture from *Leonurum*.
3. Metabolic sedatives:
   – Melatonin;
   – Glycised.
4. Combined preparations:
   – Corvalol;
   – Valocormid;
   – Persen;
   – Novo-Passit.

SODIUM BROMIDE

Pharmacokinetics

- is taken orally in the form of solution or mixture;
- quickly penetrates CNS;
- is excreted by urine, saliva, and sweat;
- excretion depends on the concentration of chloride-ions in the blood plasma;
- accumulates in the body.

Mechanism of action

- it increases inhibition in the CNS;
- effective dose depends on the type of higher nervous activity.

Pharmacodynamics

- a sedative action (a decrease in restlessness and anxiety);
- a hypnotic action;
- an antiepileptic action.

Indications

- light forms of neuroses, neurasthenia, hysteria;
- restlessness;
- insomnia;
- epilepsy;
- light forms of hypertension.

Side effects

The accumulation of bromides results in ***bromism.***

Main signs:

– drowsiness, weakness, apathy, memory disturbances;
– skin rash;
– rhinitis;
– cough.

Treatment:

– to drink much liquid;
– sodium chloride with meal;
– diuretics, especially ethacrynic acid.

VEGETABLE PREPARATIONS

Sedatives of vegetable origin are galenic preparations from medicinal plants, such as *Valeriana, Leonurum* and some other plants (Fig. 11.7).

They have common pharmacological properties:

- are taken orally;
- the mechanism of action is not known;
- the main effects are sedative, hypnotic, spasmolytic;
- the indications to use are light forms of neurosis, neurasthenia, insomnia, cardioneurosis, somatic diseases with neurotic syndrome, spasms of the stomach and intestine.

METABOLIC SEDATIVES

Melatonin is a hormone produced by the pineal gland and regulating circadian rhythms through activation of melatonin receptors and having an antioxidant action. As a medicine, it is used for the treatment of insomnia, jet lag and shift work, headaches, protection from radiation. Side effects are minimal.

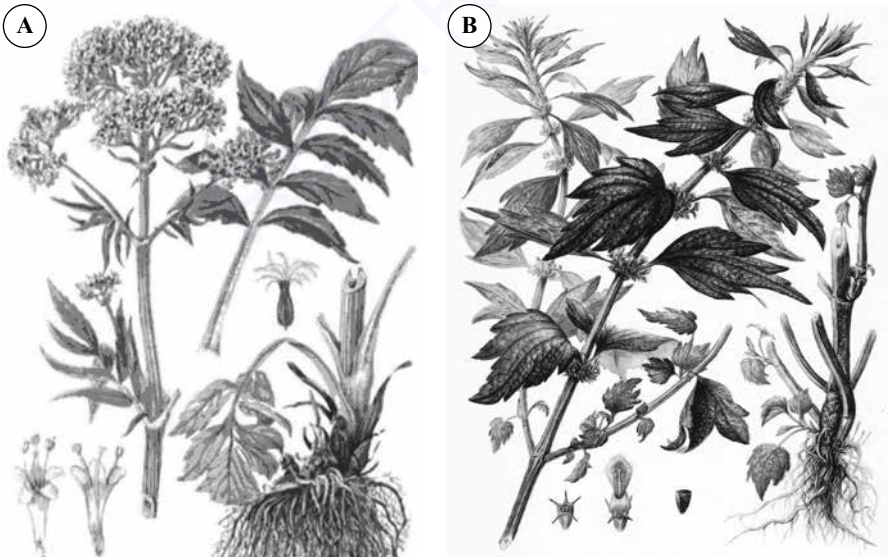

Fig. 11.7. Medicinal plants containing sedatives:
A – *Valeriana;* B – *Leonurum*

Glycised has a mild sedative, anti-anxiety, nootropic and antitoxic action. An active component of the preparation is the amino acid glycine which participates in the neurotransmission in glycinergic and GABA-ergic synapses as well as in the synthesis of proteins, phospholipids, etc. The greatest bioavailability is observed with sublingual administration. The drug is used for asthenia, neurocirculatory dystonia, alcohol abstinence, psychoemotional stress, depression, sleep disorders, increased irritability. It is well tolerated by patients.

COMBINED SEDATIVE PREPARATIONS

Corvalol is a mixture for oral administration (drops for taking inside); contains ethylic ester of bromine-isovalerianic acid, 2% of phenobarbital, 3% of mint oil, sodium hydroxide, alcohol, and water; has sedative, spasmolytic, and light hypnotic actions; is used in neuroses, spasms of coronary blood vessels, tachycardia, spasms in the gut.

Valocormid contains tincture from valerian, tincture from the lily of the valley, tincture from *Belladonna*, sodium bromide, menthol, and distil water; is used in neuroses accompanied by bradycardia.

Persen is made on the basis of plant extracts of valerian *(Valeriana)*, lemon balm *(Melissa)* and peppermint *(Mentha piperita)*, which have a mild sedative effect; is used for light neuroses, after the abolition of potent sedatives; for vascular dystonia and stress.

Novo-Passit is a combined preparation consisting of extracts of medicinal plants and guaifenesin; has sedative, anxiolytic and spasmolytic effects; is used for mild forms of neurasthenia and sleep disorders; headaches caused by nervous tension; climacteric syndrome; functional diseases of the GI tract and cardiovascular system.

DRUGS USED TO TREAT MANIA

MANIA AND BIPOLAR (MANIC-DEPRESSIVE) DISORDER

Mania is an affective disorder characterized by elevated, expansive, or irritable mood, accompanied by increased activity, pressure of speech, flight of ideas, decreased need for sleep, distractibility, or involvement in activities that have high potential for painful consequences. Patients that cycle between depression and mania have the diagnosis of ***bipolar affective disorder***.

CLASSIFICATION

1. Lithium salts:
   – Lithium carbonate;
   – Lithium hydroxybutyrate.
2. Other preparations:
   – Carbamazepine;
   – Clonazepam;
   – Valproic acid.

LITHIUM CARBONATE

Pharmacokinetics

- is taken orally;
- is absorbed in the gut completely, but absorption lasts during 8 hrs;
- maximal concentration develops in 2–4 hrs;
- does not bind to plasma proteins;
- 95% of a dose is excreted with urine and 5% – with sweat;
- $T_{½}$ = 19 hrs;
- therapeutic effect developes in 1–3 weeks after the start of treatment.

Mechanism of action

- lithium disturbs sodium transport and in such a way inhibits Ca-dependent liberation of norepinephrine and dopamine in synapses of the brain;
- lithium salt also inhibits the reuptake of norepinephrine and dopamine;
- at the same time, it does not influence serotonin.

Pharmacodynamics

- a decrease in manic behavior;
- the stabilization of mood, reduce in frequency and magnitude of mood swings;
- the prevention of phase of mania in patients with bipolar disorder.

Indications

- bipolar affective disorder (manic-depressive disease);
- manias.

Side effects

1. Weakness, tremor, ataxia, pseudotumor of the brain, hyperreflexia, extrapyramidal disturbances, headache, vision disturbances.
2. Nausea, vomiting, diarrhea, abdominal pain, an increase in size of salivary glands, dry mouth.
3. Renal dysfunction (glucosuria, proteinuria, creatinuria).
4. Thyroid enlargement, hypo- or hyperthyroidism.
5. Skin rash.
6. Teratogenic action (congenital cardiac anomalies).

A small therapeutic index of the drug necessitates frequent monitoring of the lithium level in the blood plasma.

TESTS FOR SELF-CONTROL

1. Only one preparation in the list belongs to "day-time" tranquilizers:
A. Chlorpromazepine
B. Chlorprothixene
C. Chlordiazepoxide
D. Gidazepam
E. Diazepam.

2. All of the following are observed in patients taking neuroleptics, except:
A. Increased BP
B. Orthostatic hypotension
C. Parkinsonian symptoms
D. Altered endocrine function
E. Phototoxicity.

3. Anxiolytics:
A. Are the drugs to treat a manic-depressive disorder
B. Are the drugs to treat panic and phobia
C. Bind to dopamine receptors in the brain
D. Bind to benzodiazepine receptors of chloride ion channels
E. Act in the limbic system, midbrain, and hypothalamus.

4. Lithium salts are characterized by:
A. Complete and durative absorption in the gut
B. Competition with sodium in cells of the brain

C. A small therapeutic index
D. Minimal side effects and low toxicity
E. The ability to prevent neurosis.

5. A 60 year-old woman addressed her doctor complaining of side effects which appeared during the treatment with chlorpromazine (Aminazine). She was troubled with tremor and disturbances of movements. What is the mechanism of these side effects?
A. The activation of hyppocampus
B. The inhibition of reticular formation (α_1-adrenoceptors)
C. The inhibition of neostriatum (D_2-receptors)
D. The inhibition of hypothalamus
E. The inhibition of neocortex.

Answers

1 – D; 2 – A; 3 – B, D, E; 4 – A, B, C; 5 – C.

Chapter 12 OPIOID (NARCOTIC) ANALGESICS. MEDICAL CANNABINOIDS

PAIN SENSATION AND LIMITATION OF PAIN

Nociception

Pain is a signal about the danger for the organism. At the same time, it causes discomfort, decreases the quality of life, may be unbearable, may cause a pain shock.

Nociception is pain sensation. It includes sensative nerve endings, afferent nerves, afferent pathways in the spinal cord, thalamus, and cortex of the brain (Fig. 12.1).

Thalamus is the main collector of pain impulses. Strong nociceptive stimuli irradiate on the medulla of the brain resulting in pain shock.

Nociception is realized in the following way. Nociceptive terminals of primary sensory neurons are stimulated by noxious stimuli. Action potentials are generated, pass along the peripheral afferent sensory fiber and arrive at junctions between the peripheral afferent fibers and the spinal cord neurons in the dorsal horn. The arrival of the action potentials causes the opening of voltage-gated Ca^{++} channels in the presynaptic membrane. An increased influx of Ca^{++} causes vesicles containing neurotransmitter to release their contents into the synaptic gap. Neurotransmitters (glutamate, substance P) bind to receptors on the postsynaptic membrane. Activation of such receptors enables the efflux of K^+ and influx of Ca^{++} and Na^+ into the postsynaptic cell that leads to the transmission of impulses along the axons of the spinal cord neurons to the brain. Information about pain is received and processed by higher centers in the brain and the individual perceives pain.

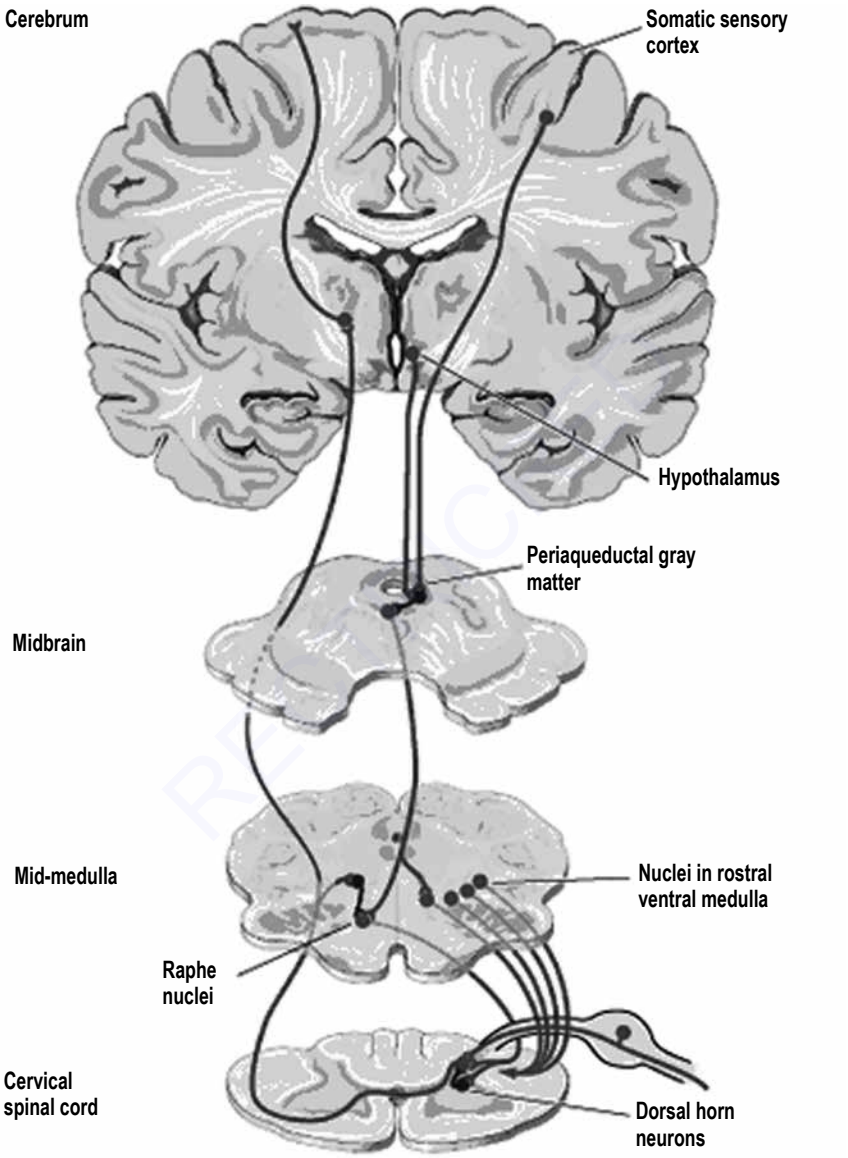

Fig. 12.1. Anatomy structures connected with nociception
(http://www.picsearch.com)

Antinociception

Antinociception is the limitation of pain in the body. It is realized by ***opioid receptors and their ligands***.

The main subtypes of opioid receptors are mu (μ)- , kappa (κ)-, sigma (σ), and delta (δ)-receptors (Fig. 12.2).

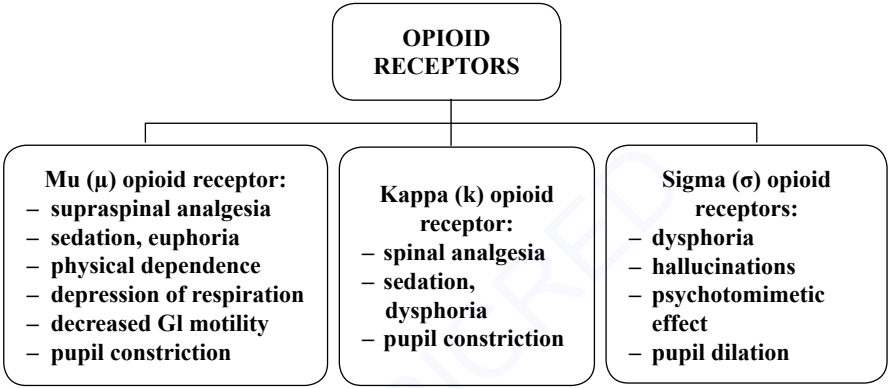

Fig. 12.2. Subtypes of opioid receptors and processes mediated by them

They are located in the CNS (brainstem, medial thalamus, spinal cord, hypothalamus, limbic system), sensory nerve fibers and their terminals. Opioid receptors are also located in the peripheral tissues (myocardium, GI tract, immune organs, bones).

Ligands of opioid receptors are endorphins, enkephalins and dynorphins.

Opioid receptors take part in the limitation of pain, limitation of stress, regulation of sleeping, and emotional behavior. They mediate respiration, cough, nausea, vomiting, maintenance of BP, pupillary diameter and stomach secretion (Fig. 12.2).

The stimulation of opioid receptors results in the inhibition of adenyl cyclase and a decrease in the cAMP content. Coupling of receptors to G-proteins of K^+ channels leads to the opening of channels and hyperpolarisation. Coupling to G-proteins of Ca^{++} channels leads to the inhibition of these channels and a decrease in the Ca^{++} influx (Fig. 12.3).

To reduce the level of perceived pain, endogenous opioids are released by interneurons in the dorsal horn in response to severe or persistent pain. The opioids bind to G proteins associated with μ type opioid receptors with the following results: the inhibition of the presynaptic release of glutamate and an increased K^+

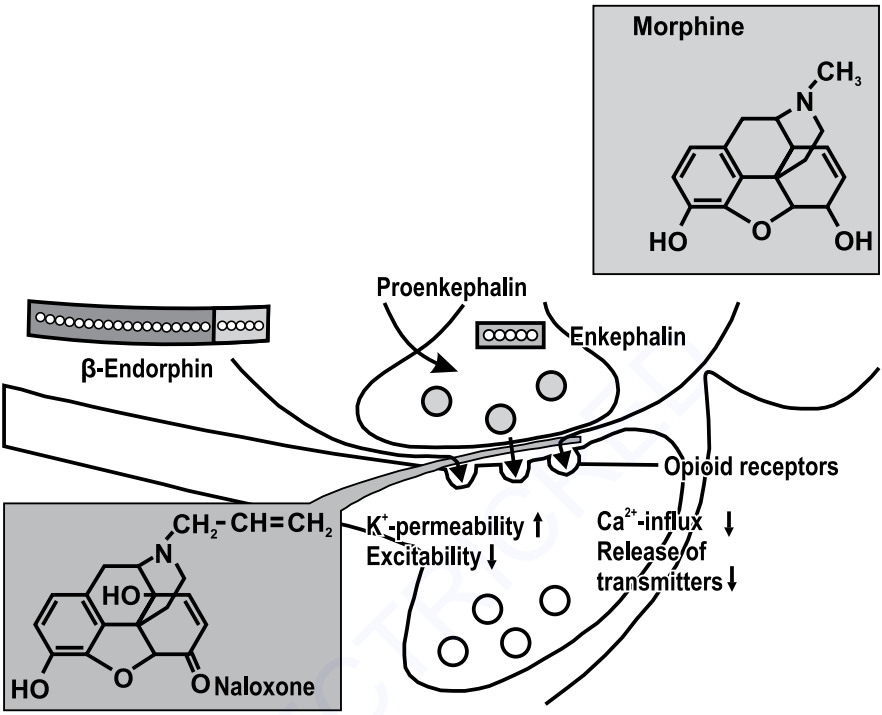

Fig. 12.3. Mechanism of action of endogenous opioids, exogenous opioids (morphine) and their antagonists (naloxone) *(by H. Lüllmann, 2000)*

conductance across the postsynaptic membrane. These events prevent the transmission of pain to the higher centers (Fig. 12.3).

To combat the severe pain, the administration of exogenous opioids (e.g., morphine) mimics the effects of endogenous opioids at the μ-opioid receptor (Fig. 12.3).

OPIOID (NARCOTIC) ANALGESICS

Analgesics are drugs reversibly and selectively inhibiting pain in the body without significant changing of consciousness.

There are two groups of analgesics:

- opioid (narcotic) analgesics
- non-opioid (non-narcotic) analgesics.

Opioid analgesics are the drugs to relieve intense pain which mimic the action of endogenous opiopeptides and may cause drug dependence.

The disparities between opioids regarding efficacy and potential for dependence reflect differing affinity and intrinsic activity profiles for the individual receptor subtypes. There are strong agonists of opioid receptors, partial agonists, and agonist-antagonists of these receptors.

Strong agonists have high affinity for μ-receptors, varying affinities for δ- and κ- receptors and low affinity for σ-receptors.

Partial agonists have low intrinsic activity.

Agonists-antagonists act as agonists on one subtype and as partial agonists or as pure antagonists on another.

The ***abuse potential*** of narcotic analgesics is determined by kinetic properties, because development of drug dependence is connected with rapid build-up of the brain concentration.

CLASSIFICATION OF OPIOID ANALGESICS AND THEIR ANTAGONISTS

A. *Strong agonists of opioid receptors:*

1. Natural compounds:
   - Morphine hydrochloride;
   - Codeine phosphate;
   - Omnopon.
2. Synthetic compounds:
   - Trimeperidine (Promedol);
   - Fentanyl.

B. *Mixed agonists-antagonists and partial agonists of opioid receptors:*

- Pentazocine;
- Buprenorphine;
- Butorphanol;
- Nalbuphine;
- Nalorphine hydrochloride.

C. *Analgesic with opioid and non-opioid mechanism of action:*

- Tramadol hydrochloride.

D. *Antagonists of opioid receptors;*

- Naloxone hydrochloride;
- Naltrexone..

MORPHINE

Morphine is an alkaloid of opium. ***Opium*** is dried juice from unripe semen capsules of poppy (*Papaver somniferum*) (Fig. 12.4). It contains more than 20 alkaloids. Among them there are phenanthrene derivatives (morphine, codeine) and isoquinoline derivatives (papaverine).

Morphine is a phenanthrene derivative (Fig. 12.5).

Fig. 12.4. *Papaver somniferum* containing morphine

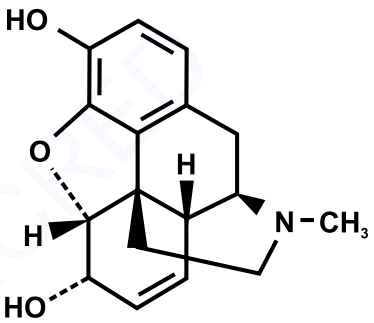

Fig. 12.5. Chemical structure of morphine

Pharmacokinetics

- is administered orally, SC, IM, IV, epidurally, intrathecally in the spinal cord
- penetrates the blood-brain barrier;
- is metabolized in the liver by conjugation with the glucuronic acid;
- is the inhibitor of the liver enzymes;
- is excreted by gastric epithelium and absorbed once more;
- finally is excreted with urine;
- begins to act in 10–20 min after the injection or 20–30 min after the oral administration;
- acts during 3–5 hrs.

Mechanism of action

- morphine stimulates all the types of opioid receptors;
- it has high affinity for μ-receptors and some action for other opioid receptors (Fig. 12.3);

- in such a way it suppresses neurotransmission in the nociceptive system that results in the rising of pain threshold in the spinal cord and altering of the brain perception of pain.

Pharmacodynamics

- analgesia (a decrease in all the kinds of pain; changes in the perception of pain – sensation of pain is not unpleasant);
- euphoria (sense of well being), then sleep;
- sedation;
- potentiation of other drugs inhibiting CNS;
- the inhibition of the respiratory center resulting in respiratory depression;
- the inhibition of the tussive center resulting in a decrease of cough;
- the inhibition of the vomiting center;
- the inhibition of the thermoregulation center in hypothalamus;
- the stimulation of the *n. vagus* center resulting in bradycardia;
- the stimulation of trigger zone of the emetic reflex that leads to vomiting in some patients after the 1st administration of morphine;
- the stimulation of the *n. oculomotorius* center resulting in miosis;
- the stimulation of vasopressin production;
- the dilation of peripheral veins;
- an increase in the tone of sphincters in the GI tract, biliary and urinary pathways;
- an increase in the tone of bronchi.

Indications

- traumatic shock;
- myocardial infarction (together with atropine);
- colic (together with atropine);
- pain associated with cancer;
- pain after surgeries;
- pre-anesthetic medication;
- pulmonary edema;
- cough dangerous for life (the danger of pulmonary bleeding or pneumothorax).

Side effects

1. Depression of respiration
2. Sleeping
3. Euphoria

Contraindications

1. Insufficience of respiration
2. Cranial trauma
3. Acute abdomen

4. Vomiting
5. Hypotension
6. Elevation of intracranial pressure
7. Constipation
8. Tolerance (to the respiratory depressant, analgesic, euphoric and sedative effects)
9. Drug dependence
10. Changes in effects of other drugs acting on the CNS

4. Cachexia
5. Children till 3 (due to the higher sensitivity of the respiratory center to morphine in such patients)
6. Elderly patients after 65 years old (due to an increased sensitivity of the respiratory center to morphine)

Acute poisoning with morphine

Signs:

– the state of sleep, unconsciousness;
– the presence of reflexes;
– normal muscular tone;
– miosis;
– bradycardia;
– Cheyne – Stokes breath;
– the retention of urination;
– spasm of the intestine and bowel.

Emergency help:

– gastric lavage by 0.5% solution of potassium permanganate;
– Naloxone, IV (an antagonist of narcotic analgesics);
– Atropine (for a decrease in the vagal action of morphine).

Opiate abuse

Opiate abuse is physical and psychical dependence on morphine (or other opioid analgesic). In opiate abuse, "smark" is self administered by an injection to achieve a faster peak concentration in the brain and an intense psychic effect.

A quick abolishing of narcotic substance causes ***abstinence*** (insomnia, nausea, vomiting, spastic pains in the abdomen, joint pains). Abstinence results from a back-cross decrease in the synthesis of endogenous ligands of opioid receptors during a long-term use of exogenous opioids.

Compositions of naltrexone with buprenorphine as well as antibodies to morphine are used to treat opiate abuse.

PECULIARITIES OF OTHER PREPARATIONS

OMNOPON

- is a mixture of opium alkaloids;
- contains 50% of morphine and 50% of codeine, papaverine, thebaine and other alkaloids;
- is administered orally, SC;
- is less active than morphine;
- does not cause spasms in the GI tract.

CODEINE

- is an opium alkaloid; is taken orally;
- is less potent analgesic than morphine; is an active inhibitor of the tussive center at doses that do not cause analgesia; potentiates the action of sedative drugs and analgesics; produces less euphoria, less respiratory suppression, and less disturbances of the GI tract functions; has lower abuse potential;
- is used as antitussive and as an ingredient of combined analgesic or sedative drugs;
- may cause suppression of respiration, constipation, tolerance, drug dependence.

TRIMEPERIDINE (PROMEDOL)

- is a synthetic preparation with a structure unrelated to morphine;
- is administered orally, SC, IM, IV; begins to act in 10 min after the IV administration and acts during 3–4 hrs;
- yields morphine in 2–4 times on analgesic activity; causes less inhibition of the respiratory center, less stimulation of the *n. vagus* and emetic centers; has spasmolytic action on the GI tract; stimulates uterus contractions without negative influence on the fetus;
- is indicated in acute severe pains, premedication, myocardial infarction, colic and labor.

FENTANYL

- is a synthetic preparation with a structure unrelated to morphine;
- is administered IV, IM; action begins 1–3 min after the administration and lasts 15–30 min;

- exceeds morphine in 100–400 times; when combined with droperidol, it produces dissociative anesthesia;
- is used for neuroleptanalgesia, premedication, analgesia in myocardial infarction and colic;
- may cause such side effects as suppression of respiration, motor excitement, rigidity of muscles of the chest and extremities, hypotension, bradycardia, an increase in blood pressure in the small cycle of blood circulation;
- is contraindicated to patients with lung diseases as well as in obstetrics.

PENTAZOCINE

- is a synthetic preparation;
- is administered orally, SC, IM, IV, or rectally; acts during 3–4 hrs;
- is an agonist-antagonist of opioid receptors. It acts as an agonist on κ-receptors and as a weak antagonist at μ- and δ-receptors. It also binds to σ- receptors that results in dysphoria;
- is less potent than morphine (analgesia is mainly due to the activation of receptors in the spinal cord);
- produces less inhibition of respiration, less spasm of smooth muscles in the GI tract; less euphoria and drug dependence;
- is used to relieve moderate pain; may be used in children and for analgesia in labor;
- in high dose causes such side effects as nausea, vomiting, vertigo, sweating, hyperemia of skin, suppression of respiration, dysphoria, abstinence in opiate abusers, tachycardia, an increase in BP (IV), an increase in intracranial pressure, a decrease in the activity of the gut;
- is contraindicated in diseases of the liver and kidney, cranial trauma, prone to seizures, pregnancy and opiate abuse;
- is not used with morphine and other agonists of opioid receptors, because may block their analgesic effects.

BUTORPHANOL

- is a strong analgesic for parenteral use;
- belongs to the group of antagonists-agonists of opiate receptors (an agonist κ- and antagonist of μ-opiate receptors);
- by onset and duration of action it is close to morphine, but is effective in smaller doses than morphine;
- compared with morphine has a lesser ability to cause physical dependence, less often causes constipation.

NALBUPHINE

- is a semi-synthetic opioid of the phenanthrene series;
- behaves as a moderate-efficacy partial agonist (or mixed agonist-antagonist) of the μ-opioid receptor and as a high-efficacy partial agonist of the κ-opioid receptor;
- has limited ability to depress respiratory function;
- the most frequent side effect is sedation; other reactions are feeling sweaty, nausea, vomiting, dizziness, vertigo, dry mouth, and headache.

NALORPHINE

- is a synthetic preparation with a structure related to morphine;
- is administered IV, IM, SC;
- is an agonist-antagonist of opioid receptors; is a weak narcotic analgesic and competitor of morphine in the binding to receptors;
- decreases the main and side effects of morphine;
- is used in acute poisoning with morphine and other narcotic analgesics;
- is not used as narcotic analgesic, because may cause psychic excitement, anxiety and hallucination;
- in higher dose may cause nausea, vomiting, headache, miosis, drowsiness and psychic excitement;
- is not used in morphine abused patients due to its ability to provoke withdrawal syndrome.

BUPRENORPHINE

- is a synthetic preparation;
- is administered orally and parenterally and has a long duration of action;
- is a partial agonist of μ-receptors;
- is suitable to control of chronic severe pains;
- is used in combined preparations to treat opiate abuse;
- may cause respiratory depression, a decrease in BP, nausea and dizziness;
- intoxication with buprenorphine cannot be reversed with antagonists, because the drug dissociates very slowly from the opioid receptors and competitive occupacy of the receptors cannot be achieved as fast as the clinical situation demands.

TRAMADOL

- is a synthetic preparation;
- is administered orally, IV, IM, rectally; acts during 3–6 hrs;
- has a mixed mechanism of action (opioid + non-opioid). It is a weak agonist of μ-receptors and is partially antagonized by naloxone. It inhibits the reuptake of norepinephrine and serotonin that leads to the reinforcement of spinal inhibition of pain impulses;
- is less potent than morphine; does not influence respiration and gastrointestinal functions, rarely causes drug dependence;
- is indicated for the control of intermediate and severe acute and chronic pains;
- causes such side effects as headache, vertigo, dormancy, sweating, lowering of BP, tachycardia, dry mouth, allergy and seizures (in overdose).

NALOXONE

- is a synthetic preparation;
- is administered IV, IM; has a rapid start of action and half-life of 1–1.5 hrs;
- is a non-selective antagonist of opioid receptors (it is a competitive antagonist at μ-, κ- and δ-receptors, with 10-fold higher affinity for μ-receptors (Fig. 12.3);
- abolishs effects of opioid analgesics including effects of agonist-antagonists; reverses the coma and respiratory depression in opioid overdose; does not produces pharmacological effects in normal individual, but provokes a withdrawal syndrome in morphine abusers;
- is used in acute poisoning with narcotic analgesics and acute alcohol poisoning.

NALTREXONE

- is a non-selective antagonist of opioid receptors similar to naloxone;
- is metabolically more stable than naloxone and is taken orally; has a long duration of action (to 48 hrs);
- is used in opiate-dependence maintenance programs and in the treatment of chronic alcoholism.

MEDICAL CANNABINOIDS

There are several reasons to include cannabinoids in this chapter together with opoid analgesics. There is an endogenous cannabinoid system in the body, just as there is an endogenous opioid system. Both of these systems are involved in the regulation of pain perception. Cannabis as an paternal substance containing exogenous cannabinoids, like opium, has abuse potential and is an illicit drug. Medicinal forms of cannabinoids can be used, among other things, to relieve certain types of chronic pain, that, however, is not so evidence based as the use of opioid analgesics.

Endocannabinoid system

The ***endocannabinoid system*** is a biological system composed of endocannabinoids and, ***cannabinoid receptors,*** that are expressed throughout the CNS and peripheral nervous system. Two primary cannabinoid receptors have been identified: ***CB1*** and ***CB2***. CB1 receptors are found in nervous system, as well as in peripheral organs and tissues, and are the main target of the endogenous partial agonist, ***anandamide***. Endocannabinoid ***2-arachidonoylglycerol*** acts as a full agonist at both cannabinoid receptors. The endocannabinoid system is involved in regulating physiological and cognitive processes, pain sensation, appetite, mood, and memory, various activity of immune system, and in mediating the pharmacological effects of cannabis

Cannabis as psychoactive substance

Cannabis, also known as marijuana, is a psychoactive drug from the Cannabis plant used primarily for medical or recreational purposes. The main psychoactive component of cannabis is Δ^{9}***-tetrahydrocannabinol*** (THC) is one of the 65 other cannabinoids in the plant. It is an agonist of cannabinoid receptors. Other important constituent of Cannabis is ***cannabidiol (CBD),*** working as an antagonist of cannabinoid receptors.

Cannabis has mental and physical effects. It causes a "high", or stoned feeling and other effects, including a general change in thought and perception, difficulty concentrating, impaired short-term memory, altered sense of time, impaired body movement, relaxation and an increase in appetite. At high doses, mental effects sometimes include psychosis, delusions, hallucinations, paranoia, anxiety and panic. Its physical effects include tachycardia, difficulty breathing, nausea. Long-term adverse effects may include addiction, decreased mental ability, chronic coughing, and susceptibility to respiratory infections, and risk of psychosis,

Cannabis is the most commonly used illegal drug both in the world though it is also legal in some jurisdictions. *The possession, use, and cultivation of cannabis is illegal in most countries of the world. Medical use of cannabis and cannabinoids, requiring the approval of a physician, has been legalized in a greater number of countries.*

Cannabinoids in medicine

Medical cannabinoids are cannabis extracts or synthetic analogues of cannabis constituents used in clinic for the treatment of chronic pain and some other conditions and diseases.

Peculiarities of preparations

Nabiximols (Sativex) is a medicine containing cannabidiol (CBD) and THC in equal proportions, is administerd as a mouth spray, was approved to treat central neuropathic pain in multiple sclerosis and for cancer-related pain. moderate to severe spasticity due to multiple sclerosis. It is well tolerated. The most common adverse effects are dizziness, drowsiness, and disorientation;

Dronabinol (Marinol, Syndros), is a specific form of tetrahydrocannabinol, the principal psychoactive constituent, found in cannabis. It is used as an appetite stimulant in patients with HIV/AIDS and cancer, antiemetic for the treatment of chemotherapy-induced nausea and vomiting, sleep apnea reliever, Dronabinol has a low risk of physical or mental dependence. A mild overdose of the drug presents drowsiness, cotton-mouth, euphoria, and tachycardia; a severe overdose – lethargy, slurred speech, decreased motor coordination, and postural hypotension.

Epidiolex is an orally administered cannabidiol solution. The oral bioavailability of CBD is approximately 6%, while its bioavailability via inhalation is 11 to 45%. The elimination half-life is 18–32 hrs. It is metabolized in the liver and intestines. Cannabidiol has low affinity for the cannabinoid CB1 and CB2 receptors, although it acts as an antagonist of both these receptors. It is an allosteric modulator of the μ- and δ-opioid receptors and can interact with some other receptors in the CNS. CBD is used in two rare forms of epilepsy (Lennox – Gastaut syndrome and Dravet syndrome). It has been proposed as a potential treatment for chronic pain, post-herpetic neuralgia, opiate addiction, Parkinson's disease and depression, but evidence was low. There is some evidence of the benefits of this preparation for people with chemotherapy-induced nausea and vomiting or muscle spasticity in multiple sclerosis. CBD does not appear to have any psychotropic effects such as those caused marijuana.

Nabilone (Cesamet) is a synthetic cannabinoid. It is taken orally, is completely absorbed in the gut, binds to plasma proteins and is metabolized by cytochrome

P450 enzymes in the liver. Nabilone is used as an antiemetic and as an adjunct analgesic for chronic pain (neuropathic pain, fibromyalgia, and pain in multiple sclerosis). Side effects of nabilone include: dizziness/vertigo, euphoria, drowsiness, dry mouth, ataxia, sleep disturbance, dysphoria, headache, nausea, disorientation, depersonalization, and asthenia.

TESTS FOR SELF-CONTROL

1. The incorrect statement about morphine is only:
A. It is an antagonist of opioid receptors
B. It is the most effective by parenteral administration
C. It causes euphoria and sedation
D. It causes respiratory depression
E. Its effects are antagonized by naloxone.

2. The side effects of opioid analgesics include all, except:
A. The inhibition of respiration
B. Stimulation of antidiuretic hormone release
C. Drug dependence
D. Tolerance
E. The suppression of hemopoiesis.

3. Pentazocine is:
A. An agonist-antagonist of opioid receptors
B. A less potent analgesic than morphine
C. The most potent in its ability to cause drug dependence
D. Agent caused dysphoria
E. The antagonist of opioid receptors used in acute poisoning with morphine.

4 Naloxone is used in acute poisoning with opioid analgetics due to:
A. Agonism to opioid receptors
B. Competitive antagonism with opioid agonists
C. The rapid onset of action
D. The long duration of action
E. The ability to cause abstinence in morphine abusers.

5. A man was taken to the emergency department with numerous traumas of the chest and head. A surgeon proposed to inject morphine to relieve patient's condition, but the anesthesiologist rejected the proposition of his colleague. Why is morphine contraindicated in this case?
A. It increases intracranial pressure

B. It stimulates the vagal center
C. It decreases intraocular pressure
D. It causes miosis
E. It depresses a center of the cough reflex.

Answers

1 – A; 2 – E; 3 – A, B, D; 4 – B, C; 5 – A.

Chapter 13 NON-OPIOID ANALGESICS

PROSTAGLANDINS

Origin and synthesis

Prostaglandins (Pg) are the derivatives of the arachidonic acid. Relative substances are thromboxane, prostacyclin, and leukotrienes. The arachidonic acid is a regular constituent of cell membrane phospolipids; it is released by phospolipase A_2 and forms the substrate of cyclooxygenases (COX) and lipoxygenases (Fig. 13.1).

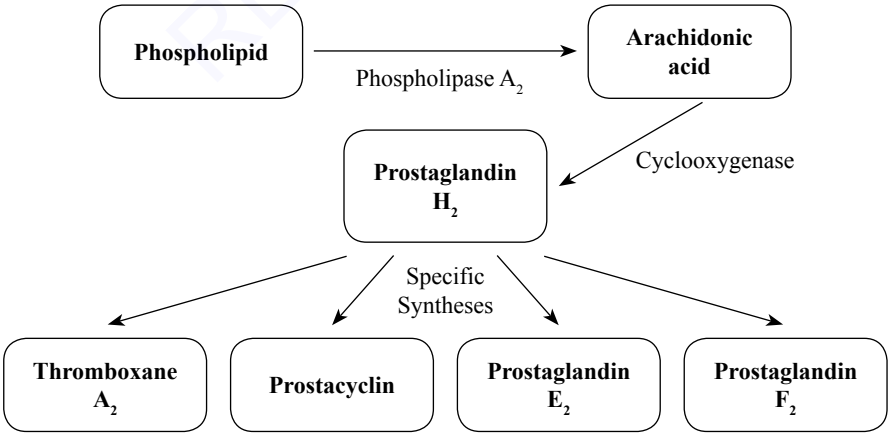

Fig. 13.1. Synthesis of prostaglandins *(http://www.picsearch.com)*

COX is the enzyme responsible for the formation of Pg. There are two isozymes: COX-1 and COX-2. COX-1 is constitutive; COX-2 is induced in the process of inflammation (Fig. 13.2).

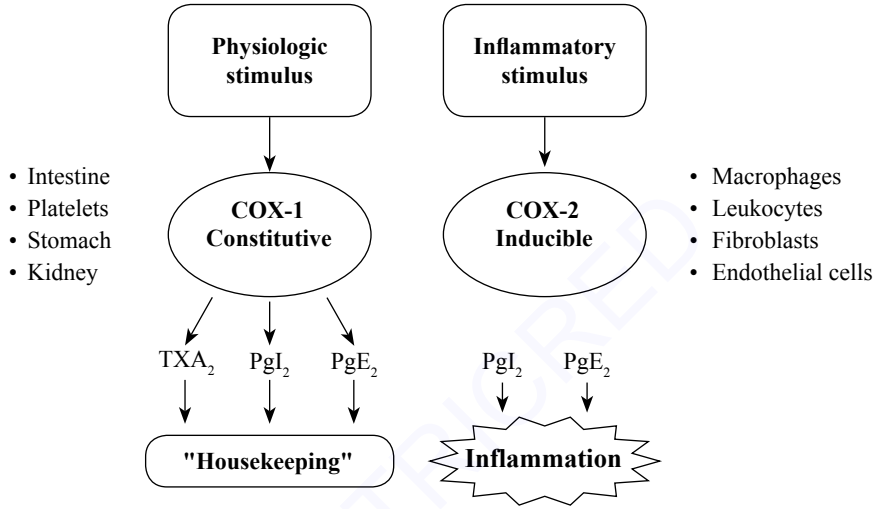

Fig. 13.2. Peculiarities of COX-1 and COX-2 *(http://www.picsearch.com)*

Biological effects

- Pg are the regulators of inflammation;
- they increase pain sensation: pain receptors become more sensitive to inflammatory mediators, such as bradykinin and serotonin (Fig. 13.3);
- Pg rise the set point of hypothalamic thermoregulatory neurons and increase the body temperature (Fig. 13.3);
- PgE_2, PgI_2 produce the dilation of arterioles, $PgF_{2\alpha}$ – venoconstriction (Fig. 13.3);
- Pg promote the production of gastric mucus and reduce the formation of gastric acid;
- they stimulate labor contractions and regulate menstruation (Fig. 13.3);
- PgE_2, PgI_2 produce the dilation of bronchi, $PgF_{2\alpha}$ causes the constriction of bronchi;
- Pg regulate the renal blood flow;
- thromboxane A_2 and prostacyclin regulate platelet aggregation and vascular diameter.

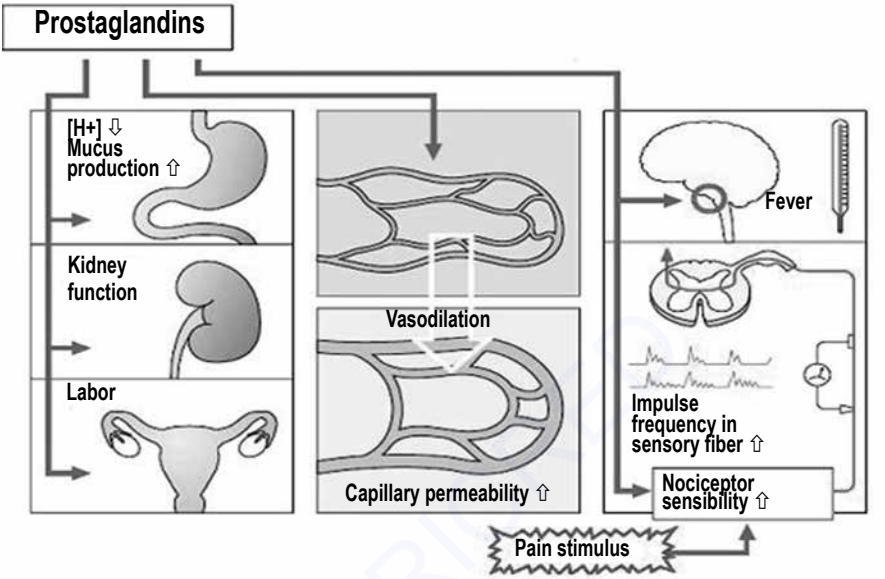

Fig. 13.3. Biological effects of prostaglandins *(by H. Lüllmann, 2000)*

NON-OPIOID ANALGESICS

Non-opioid analgesics are drugs for a decrease of intermediate and weak pain, especially resulting from inflammation.

They always have:

- analgesic action;
- anti-inflammatory action;
- antipyretic action.

Preparations with the prevalence of anti-inflammatory activity are named ***non-steroidal anti-inflammatory drugs (NSAIDs)*** (Fig. 13.4). Structurally they can be grouped into salicylates, carbonic acids, or enolic acids. Their main effects are similar and the choice between NSAIDs is dictated by their pharmacokinetics and side effects.

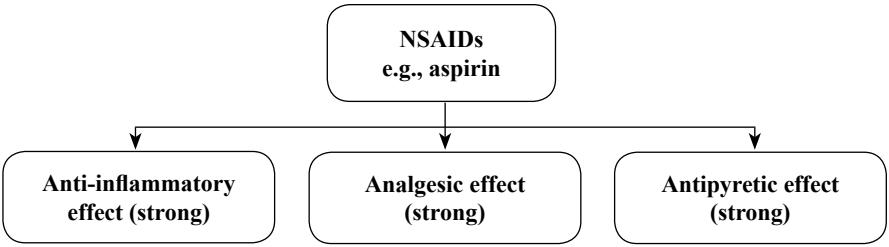

Fig. 13.4. Expression of effects of NSAIDs

Drugs with the prevalence of analgesic and antipyretic activity are named ***analgesics-antipyretics*** (Fig. 13.5).

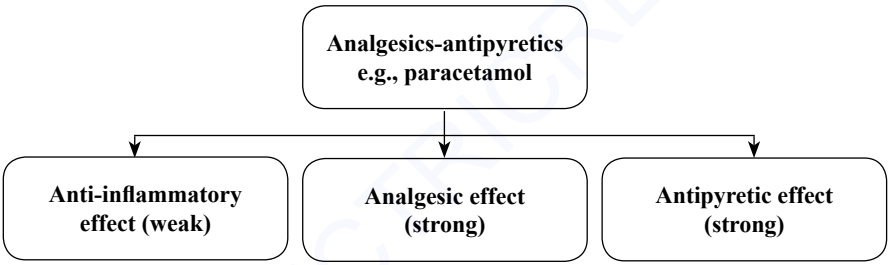

Fig. 13.5. Expression of effects of analgesics-antipyretics

CLASSIFICATION

According to the chemical structure

1. Salicylates:
   – Acetylsalicylic acid (Aspirin).
2. Pyrazoles:
   – Metamizole (Analgin);
   – Phenylbutazone (Butadione).
3. Fenamates:
   – Mefenamic acid.
4. Indolacetic acid derivatives:
   – Indomethacin.
5. Phenylacetic acid derivatives:
   – Diclofenac-sodium.

6. Propionic acid derivatives:
   – Ibuprofen.
7. Para-aminophenol derivatives:
   – Paracetamol (Acetaminophen).
8. Oxicams:
   – Piroxicam;
   – Meloxicam (Movalis).
9. Coxibs:
   – Celecoxib.

According to the mode of action

A. *Non-selective inhibitors of COX-1 and COX-2:*

1. Mainly with peripheral action:
   – Acetylsalicylic acid;
   – Phenylbutazone;
   – Metamizole;
   – Mefenamic acid;
   – Indomethacin;
   – Diclofenac-sodium;
   – Ibuprofen;
   – Piroxicam.
2. Mainly with central action:
   – Paracetamol.

B. *Selective inhibitors of COX-2:*

– Meloxicam;
– Celecoxib.

Mechanism of anti-inflammatory action

Inhibition of COX by non-opioid analgesics leads to a decrease in the synthesis of prostaglandins (PgE_2) (Fig, 13.6). That results in a decrease of the permeability of blood vessels in the site of inflammation, inhibition of hyaluronidase activity, stabilization of lysosomal membranes, and a decrease in lysosomal enzymes release. The inhibition of energy processes in the area of inflammation and the inhibition of leukocytes activity are also observed. All the listed events lead to a decrease in the exudation stage of inflammation. Some most active preparations (e.g., indomethacin) inhibit fibroblasts' activity and decrease the proliferation stage of inflammation.

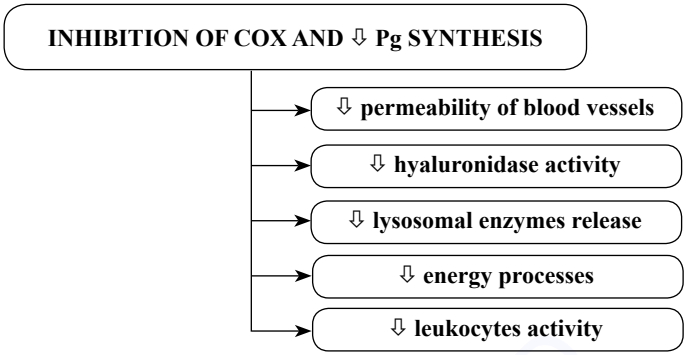

Fig. 13.6. Mechanism of anti-inflammatory action of non-opioid analgesics

Mechanism of antipyretic action

A set point of the body temperature is programmed in the hypothalamic thermoregulatory center. A stable body temperature is due to the balance between heat production and heat output. Pyrogens elevate the set point of the hypothalamic temperature controller. The body responds by restricting a heat loss and elevating heat production that results in the fever.

Non-opioid analgesics inhibit COX and decrease the synthesis of PgE_2 in the hypothalamus. In such a way they decrease the sensitivity of the hypothalamus to pyrogens, increase heat output and lower high body temperature without the action on the normal temperature (Fig. 13.7).

Mechanism of analgesic action

Inhibition of COX by non-opioid analgesics leads to a decrease in the synthesis of prostaglandins. That results in a decrease of the sensitivity of nociceptors to inflammatory mediators and an increase of the pain threshold. Such events cause a decrease in the transmission of pain impulses in the CNS and relief of pain.

Mechanism of antiplatelet action

Some non-narcotic analgesics (e.g., acetylsalicylic acid) may cause the inhibition of COX-1 in the blood platelets and a decrease in thromboxane A_2 synthesis. That results in the inhibition of platelet aggregation and adhesion, normalization of blood viscosity and prevention of thrombus formation.

In higher doses non-narcotic analgesics also inhibit prostacyclin synthesis.

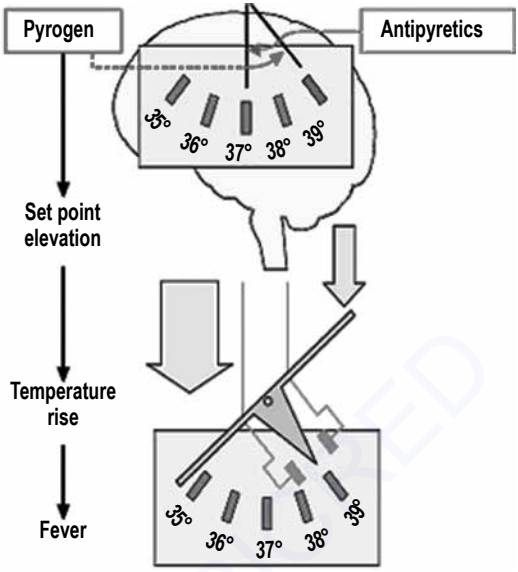

Fig. 13.7. Mechanism of antipyretic action of non-opioid analgesics *(by H. Lüllmann, 2000)*

Some other mechanisms of action

In high concentrations NSAIDs influence nitric oxide-dependent processes, inhibit 5-lipoxygenase, and reduce the production of leukotrienes. They activate PPAR connecting with colorectal carcinogenesis and act on apoptosis signalling.

ACETYLSALICYLIC ACID (ASPIRIN)

Acetylsalicylic acid is salicylate, a weak organic acid (Fig. 13.8).

Pharmacokinetics

- is taken orally, sometimes IM, IV (Acelysin);
- is absorbed in the stomach and small intestine by passive diffusion (absorption is increased by acidic pH in the stomach);
- binds to albumins in the blood plasma;
- crosses the blood-brain barrier and placenta;
- displays maximal concentration in blood in 2 hrs after the administration;
- concentrates in the adrenal glands, liver, heart and lungs;

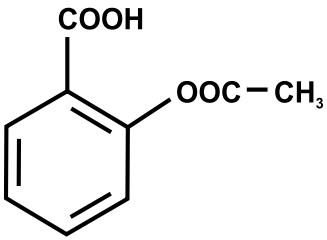

Fig. 13.8. Chemical structure of acetylsalicylic acid

- at normal low doses, is hydrolyzed to salicylate and the acetic acid by esterases present in the tissues and blood (Fig. 13.9);
- is metabolized in the liver where salicylate is converted to water-soluble conjugates;
- is excreted with urine (alkalic pH increases the excretion of aspirin and its metabolites);
- acts during 4–6 hrs; has a duration of antiplatelet action of 7 days;
- at normal low dose of 600 mg/day, has a half-life of 3.5 hrs; at anti-inflammatory doses (> 4 g/day), has a half-life of 15 hrs or more due to the saturation of hepatic metabolic pathway.

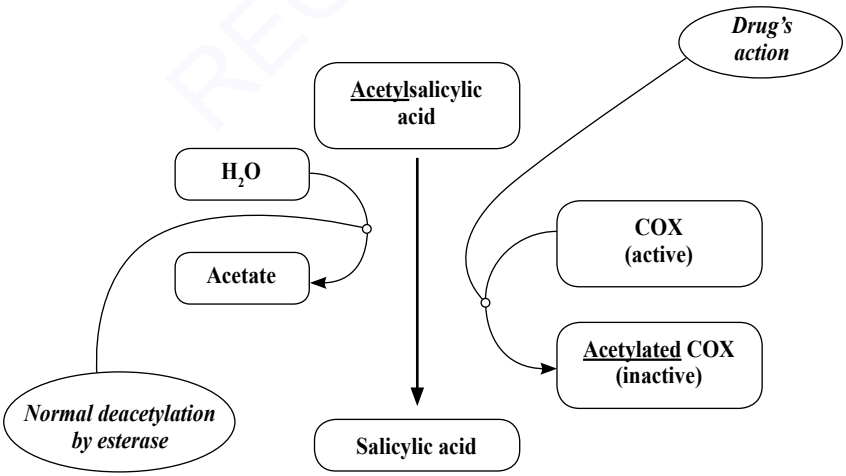

Fig. 13.9. Acetylation of COX by acetylsalicylic acid

Mechanism of action

- aspirin is a non-selective inhibitor of COX-1 and COX-2 in peripheral tissues and in the CNS;
- it irreversibly acetylates and thus inactivates COX (Fig. 13.9). All other non-opioid analgesics are reversible COX inhibitors.
- both main effects of aspirin and its group-specific side-effects results from the disturbances in Pg synthesis (Fig. 13.10).

Pharmacodynamics

- an anti-inflammatory action (a decrease in exudation);
- an antipyretic action (a decrease in high body temperature);
- an analgesic action (a decrease in intermediate and weak pain);
- an antiplatelet action (an irreversible decrease in platelet aggregation);
- an anti-gout action (an increase in output of urates);
- the stimulation of respiration (at therapeutic doses, aspirin increases alveolar ventilation; at high doses, it works directly on the respiratory center resulting in hyperventilation and respiratory alkalosis);

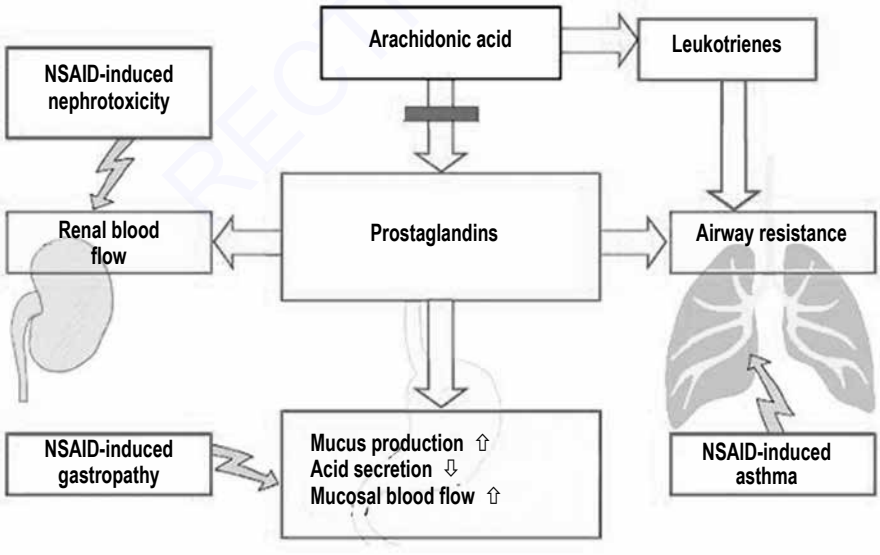

Fig. 13.10. Group-specific side effects of aspirin and other NSAIDs
(by H. Lüllmann, 2000)

- the dilation of blood vessels (in higher doses);
- the stimulation of synthesis of glucocorticoids (in higher doses);
- an increase in the secretion and excretion of bile;
- changes in pH of blood (in higher doses);
- hypoglycemia (in higher doses).

Indications

- rheumatism;
- fever;
- arthritis;
- headache, toothache, myalgia or neuralgia;
- gout;
- dysmenorrhea;
- prophylaxis of re-thrombosis, myocardial infarction, or stroke;
- thombophlebitis;
- patent ductus artriosus;
- prevention of colorectal cancer.

Side effects

1. Allergy (resulting from acetylation of albumins by aspirin)
2. Skin rash
3. Spasm of the bronchi, "aspirin asthma" (resulting from the inhibition of Pg synthesis and overproduction of leukotrienes) (Fig. 13.10)
4. Gastric ulceration (resulting from a decrease in prostacyclin synthesis in the gastric wall as well as from the irritation of the gastric mucosa) (Fig. 13.10)
5. Vertigo
6. Thrombocytopenia
7. Hypocoagulation, bleeding
8. A decrease in renal blood flow, the retention of sodium and water
9. Disturbances in normal development of pregnancy, prolonged labor, bleeding tendency in the mother and infant, a premature closure of ductus arteriosus
10. Reye's syndrome in children (hepatitis and cerebral edema)

Contraindications

1. Allergy to salicylates
2. Ulcerative disease of the stomach and duodenum
3. Ulcerative colitis
4. Bleeding
5. Bronchial asthma
6. Inhibition of hemopoiesis
7. Hepatic and renal impairment
8. Pregnancy

Concomitant administration of aspirin with many classes of drugs may produce undesirable side effects:

- Aspirin + Antacids = ⇩ aspirin's absorption;
- Aspirin + Sulfinpyrazone, probenecid = ⇩ urate excretion;
- Aspirin + Heparin, oral anticoagulants = hemorrhage;
- Aspirin + Barbiturates, thyroxine = ⇧ effects and toxicity.

PECULIARITIES OF OTHER PREPARATIONS

INDOMETHACIN

- is an indolacetic acid derivative;
- is one of the most active non-narcotic analgesics, ***belongs to NSAIDs;***
- anti-inflammation is the strongest effect: it inhibits exudation as well as proliferation;
- exceeds aspirin in anti-inflammation, analgesia, and antipyrexia;
- is administered orally, rectally, topically; displays maximal concentration in 2 hrs after the oral administration; has a half-life of 2–3 hrs; is metabolized in the liver; is excreted with urine (2/3) and with bile (1/3);
- is indicated in rheumatism, collagenosis, arthritis, gout, glomerulonephritis, trauma of joints and soft tissues, thrombophlebitis, tendovaginitis, myositis, myalgia, neuralgia (topically in the form of ointment); is also beneficial in the control of the pain associated with uveitis and postoperative ophthalmic procedures, in fever caused by Hodgkin's disease, in treating patients with ductus arteriosus;
- has such side effects as headache, vertigo, dormancy, depression, pain in the epigastric area, ulcer of the stomach, nausea, a decrease in appetite, gastrointestinal bleeding, skin rash, leukopenia, aplastic anemia, disturbances in the renal function, acute pancreatitis, hepatitis, and jaundice;
- is contraindicated in ulcerative disease, bronchial asthma, infections, pregnancy, lactation, epilepsy, Parkinson's disease, psychic disorders and anemia.

DICLOFENAC-SODIUM

- is a phenylacetyc acid dervative;
- anti-inflammation is the strongest effect;
- ***belongs to NSAIDs***, exceeds aspirin and indomethacin;
- is administered orally, IM, topically (gel, ointment);
- displays maximal concentration in plasma in 1–2 hrs after the oral administration; binds to proteins in the blood plasma (96% of preparation); has

concentration in synovial liquid which exceeds the same in blood in 5 times and half-life in synovial liquid (8 hrs) which is more durative than the same in blood (3 hrs); is excreted with urine and bile;
- has indications similar to indications of indomethacin; is approved for a long-term use in the treatment of rheumatoid arthritis, osteoarthritis, and ankylosing spondilitis;
- is less toxic than indomethacin, but may cause a loss of appetite, pain in the epigastric area, meteorism, constipation, diarrhea, rarely ulceration in the stomach, gastrointestinal bleeding, headache, drowsiness, thrombocytopenia, nasal bleeding, microhematuria, allergy, skin rash.

IBUPROFEN

- is a propionic acid derivative;
- is an active anti-inflammatory and analgesic agent, ***belongs to NSAIDs;***
- has high effectiveness for the treatment of joint diseases;
- is administered orally and applied topically (gel, ointment);
- is used for arthritis, osteoarthrosis, a joint form of rheumatism, bursitis, tendovaginitis, trauma of joints and soft tissues;
- is untoxic; has minimal influence on the gastric mucosa;
- may be used in pregnant women.

PIROXICAM

- is a preparation from oxicams;
- has a strong durative anti-inflammatory action, ***belongs to NSAIDs;***
- is taken orally once a day; has a half-life of 40–45 hrs, thus is administered once a day; is metabolized in the liver and excreted with urine in the form of glucuronides;
- is used to treat rheumatism, rheumatoid arthritis, ankylosing spondilitis, osteoarthritis, acute gout;
- may cause such side effects as gastric ulceration, skin rash, the inhibition of blood formation, toxic action on the CNS.

MEFENAMIC ACID

- is a fenamate;
- has structural similarity to salicylates; ***belongs to NSAIDs;***
- anti-inflammation and analgesia exceed those of aspirin; apyrexia is equal to that of aspirin, is the inductor of interferon;

- is used for the treatment of arthritis, arthralgia, myalgia, neuralgia, headache, toothache, fever;
- has less side effects in comparison with salicylates; may cause nausea, pain in the abdomen and diarrhea associated with the inflammation of the bowel.

METAMIZOLE (ANALGIN)

- is a pyrazole derivative (Fig. 13.11);
- ***belongs to analgesics-antipyretics***; has strong analgesic and antipyretic activity, but weak anti-inflammatory activity;
- is administered orally, IM, IV, rectally (Fig. 13.11);

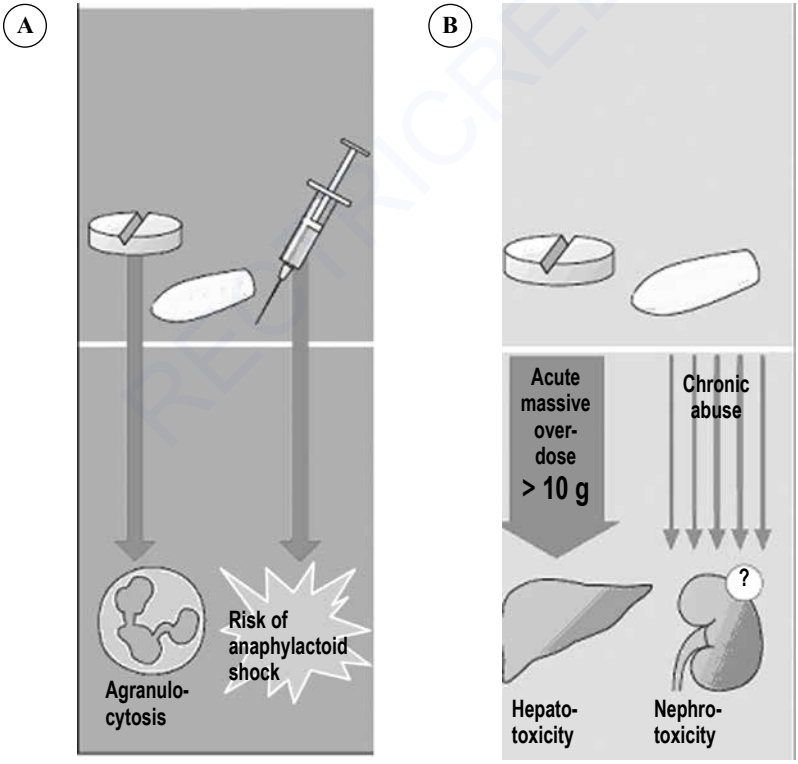

Fig. 13.11. Chemical structure, routes of administration, and side effects of analgesics-antipyretics: A – metamizole; B – paracetamol *(by H. Lüllmann, 2000)*

- begins to act in 20 min after the IM injection; acts during 3–4 hrs;
- is potentiated by antihistamines;
- is indicated in intermediate and weak somatic pains (headache, toothache, myalgia, neuralgia, arthralgia), visceral pains, control of intermediate postoperative pain, fever and dysmenorrhea;
- may cause allergy, the inhibition of hemopoiesis (agranulocytosis) (Fig. 13.11).

PARACETAMOL (ACETAMINOPHEN)

- is a para-aminophenol derivative (Fig. 13.11);
- has intermediate analgesic and antipyretic activity, a weak anti-inflammatory action, does not affect platelet aggregation ***(belongs to analgesics-antipyretics)***;
- is mainly centrally-acting preparation;
- is administered orally, rectally (Fig. 13.11);
- is metabolized in the liver to form inactive glucuronated and sulfated metabolites; is partially transformed into N-acetyl-benzoquinoneimine (a highly reactive and dangerous metabolite), which is inactivated by SH-groups of glutathione;
- is used in headache, pains in muscles and joints, the fever associated with infection and inflammatory diseases; is an analgesic-antipyretic of choice for children with viral infections or chicken pox;
- is untoxic; rarely causes disturbances in the renal function (renal tubular necrosis and hypoglycemic coma as complications of prolonged large-dose therapy); in acute overdose, may provoke hepatic necrosis due to the interaction of N-acetyl-benzoquinoneimine with hepatic proteins (should be treated by acetylcysteine, a substitute of glutathione);
- may be used in children as well as in adult patients;
- may be handed to the patient over the counter without prescription; is one of the most popular preparations in the world.

MELOXICAM (MOVALIS)

- is a drug from oxicams;
- ***is a selective inhibitor of COX-2; NSAID***; does not influence platelet aggregation and gastric mucosa;
- has mainly a peripheral action;
- is administered orally, IM;

- is absorbed in the GI tract; develops maximal concentration in 1 hr after the IM injection; displays stable concentration in the plasma in 3–5 days after the start of treatment; has concentration in synovial fluid which is more than that in the plasma; has half-elimination of 20 hrs, is excreted with urine and bile;
- is used to treat arthritis, arthrosis, spondylitis, rheumatoid arthritis;
- may cause such side effects as dyspepsia, gastric ulceration, gastrointestinal bleeding, hepatic and hematological disturbances, skin rash, headache (in 0.1–1 % of patients);
- is contraindicated to patients with hypersensitivity to NSAIDs; should be used under the physician's supervision in the cases of gastrointestinal diseases, heart failure, cirrhosis of the liver or chronic renal diseases.

CELECOXIB

- belongs to the group of coxibs;
- ***is a selective inhibitor of COX-2; NSAID***; acts in the site of inflammation;
- does not influence platelet aggregation as well as the gastric mucosa;
- is taken orally;
- is absorbed in the GI tract; develops maximal concentration in the plasma in 2–3 hrs after the administration; is bound to plasma proteins, has a half-life of 8–12 hrs; displays stable concentration in 5 days after the start of the treatment; penetrates the blood-brain barrier and placenta;
- is used in rheumatoid arthritis, osteoarthrosis;
- may cause pain in the epigastrium, dyspepsia; very rarely: gastritis, stomatitis, ulcer of the stomach, dysphagia, gastrointestinal bleeding, headache, vertigo, insomnia, depression, an increase in intracranial pressure, hypertension, tachycardia, etc.;
- is contraindicated to patients with acute gastric ulcer, hypersensitivity to NSAIDs.

AMIZON

- is a modern preparation;
- is a derivative of the isonicotinic acid;
- ***has properties of non-narcotic analgesic, direct antiviral and immune stimulating activity;***
- is taken orally 2–4 times daily; develops maximal concentration in 2–2.5 hrs after the administration: has a half-elimination from tissues of 2–3 hrs and

half-elimination from the blood of 13–14 hrs; is metabolized in the liver and excreted with urine;

- has anti-inflammatory, antipyretic, and analgesic actions resulting from the inhibition of Pg synthesis; has antiviral activity resulting from the direct influence on viruses as well as from the interferon induction; is a stimulant both of cell and humoral immunity;
- is indicated in influenza, acute viral respiratory infections, herpes, the treatment and non-specific prophylaxis of viral and bacterial infections, osteochondrosis, arthritis, neuralgia, acute and chronic inflammation in patients with surgical and gynecological pathology;
- produces such side effects as unpleasant taste, edema of nasal mucosa.

TESTS FOR SELF-CONTROL

1. The main mechanism of non-opiod analgesics action is:
A. The stimulation of prostaglandins synthesis
B. The inhibition of cyclooxygenase
C. The inhibition of monoamine oxidase
D. An increase in noradrenaline release
E. The inhibition of dopamine reuptake.

2. All the listed drugs are non-selective inhibitors of COX, except:
A. Indomethacin
B. Diclofenac sodium
C. Ibuprofen
D. Acetaminophen
E. Celecoxib.

3. Non-opioid analgesics exert the following effects:
A. An antipyretic action
B. Immunity suppression
C. An anti-inflammatory action
D. An analgesic action
E. A hypnotic action.

4. The following statements concerning paracetamol are true:
A. It is a weaker anti-inflammatory agent than aspirin
B. It reduces the fever of viral infections in children
C. It is aspirin substitute in patients with peptic ulcer

D. It disturbs hemopoiesis
E. It may cause spasm of bronchi.

5. A patient with toothache relieved his pain with the help of metamizole (analgin). Point out another useful effect of this drug that contributes to the improvement of the patient's condition:
A. A sedative effect
B. An anti-inflammatory effect
C. An antiplatelet effect
D. An antioxidative effect
E. An antimicrobial effect.

Answers:

1 – B; 2 – E; 3 – A, C, D; 4 – A, B; 5 – B.

Chapter 14 ANALEPTICS. PSYCHOMOTOR STIMULANTS

DRUGS STIMULATING CNS

Drugs stimulating CNS are preparations which increase the activity of some structures of the brain. They are divided into groups according to their site of action and main effect (Fig. 14.1).

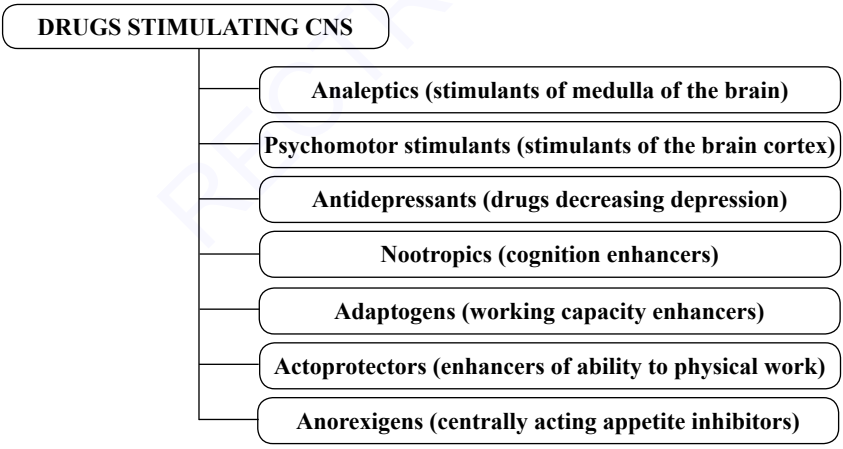

Fig. 14.1. Main groups of CNS stimulants

ANALEPTICS

Analeptics are the drugs which stimulate mainly the respiratory and vasomotor centers in medullar part of the CNS.

They always have such effects as:

- an increase in respiration resulting from the stimulation of the respiratory center;
- an increase in BP resulting from the stimulation of vasomotor center;
- a decrease in the action of drugs inhibiting CNS (an awakening effect);
- seizures (in higher doses).

CLASSIFICATION

According to the type of action

1. Direct-acting:
   – Bemegride;
   – Etimizol;
   – Strychnine nitrate;
   – Caffeine (Caffeine-sodium benzoate).
2. Indirect-acting (M-cholinomimetics):
   – Cytisine (Cytiton);
   – Lobeline.
3. Mixed-acting:
   – Camphor;
   – Sulfocamphocaine;
   – Nikethamide (Cordiamine);
   – Carbogen.

According to the mechanism of action

1. Membranetropic:
   – Camphor;
   – Sulfocamphocaine.
2. Barbituratergic:
   – Bemegride.
3. Benzodiazepinergic:
   – Nikethamide.
4. Purinergic:
   – Caffeine;
   – Etimizol.
5. Glycinergic:
   – Strychnine.

CAMPHOR

Camphor is a bicyclic ketone (Fig. 14.2), may be natural or synthetic.

Natural and synthetic camphor are isomeric forms and both have pharmacological activity. Natural camphor is contained in a camphor tree (Fig. 14.3).

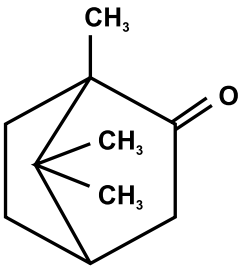

Fig. 14.2. Chemical structure of camphor

Fig. 14.3. Camphor tree containing natural camphor

Camphor is indissolved in water, but is well dissolved in oil and alcohol, has a specific aroma.

Pharmacokinetics

- is administered SC, orally, or topically;
- is absorbed in the small intestine;
- penetrates the blood-brain barrier;
- is metabolized in microsomes of the liver;
- is excreted with urine, bronchial liquid, nursing mother's milk.

Mechanism of action

- Camphor is a mixed-acting analeptic. It has a direct and indirect action;
- Direct action includes disturbances in the permeability of the neuronal membrane to Na^+. They result in an increase of Na^+ concentration in the cells that leads to the maintenance of the excitement of neurons in the medulla of brain (Fig. 14.4);
- The indirect component of camphor's mechanism of action is realized by the stimulation of chemoreceptors of *zona carotis* and a reflexive excitation of centers in the prolonged medulla (Fig. 14.4).

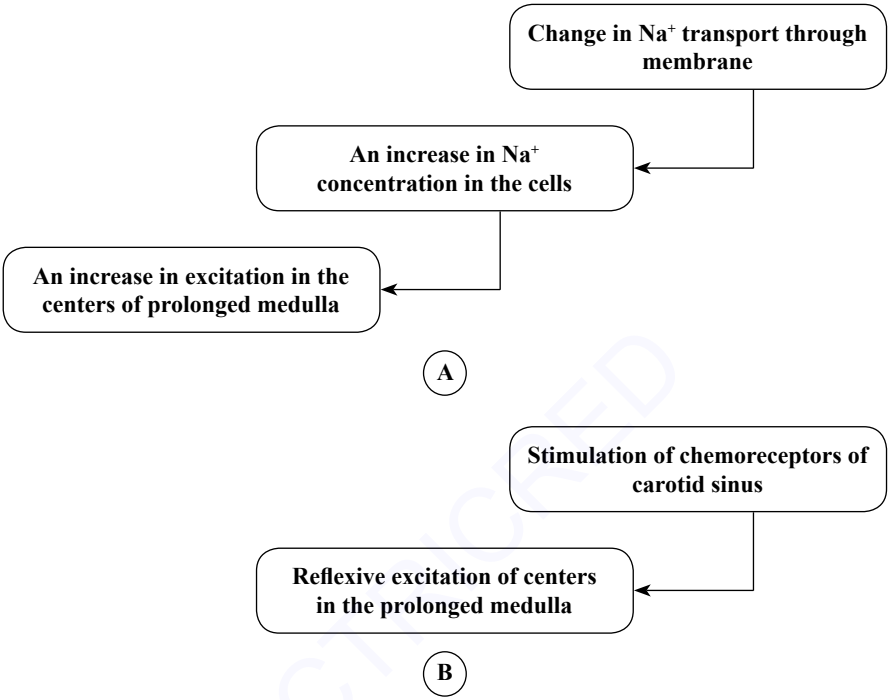

Fig. 14.4. Mechanism of camphor's action: A – direct action; B – indirect action

Pharmacodynamics

- a local action (antiseptic, irritating, trophic, whitening);
- the stimulation of the respiratory center in its moderate suppression resulting in the acceleration and deepening of breath;
- the stimulation of the vasomotor center in its suppression resulting in an increase of BP;
- an awakening action and a decrease in the effects of CNS inhibitors;
- a positive inotropic action (an increase in strength of heart contractions under the conditions of heart failure resulting from the enhance of the myocardium sensitivity to catecholamines and the intensification of metabolic processes);
- the improvement of microcirculation;
- the inhibition of platelet aggregation;
- an expectorant action resulting from excretion by bronchial glands.

Indications

- a moderate suppression of respiration caused by infections and intoxications;
- collapse, shock;
- acute and chronic heart failure;
- pneumonia;
- skin diseases, external otitis, myalgia, myositis, arthralgia, arthritis, for the prophylaxis of trophic disturbances of the skin in long lying patients (topically).

Side effects

1. Allergy
2. Seizures
3. Infiltrate in the site of injection
4. Fat embolism if the drug is administered IV or IM

Contraindications

1. Hypersensitivity to camphor
2. Epilepsy, prone to seizures
3. Should not be administered IV or IM

PECULIARITIES OF OTHER PREPARATIONS

Sulfacamphocaine is a complex compound of camphor and procaine; is water-soluble; is administered SC, IM, IV; is not applied topically; is used for the suppression of respiration, collapse, shock, overdose of drugs inhibiting CNS, heart failure; is contraindicated to patients with allergy to procaine.

Nikethamide (Cordiamine) is a commercial name of 25% solution of diethylamide of the nicotinic acid; is administered IV, IM, SC, orally; has a short action; is a mixed-acting analeptic (its direct action results from the inhibition of benzodiazepine receptors of Cl^- channels); has typical analeptic effects; improves metabolism in the heart and liver; is indicated in the suppression of respiration, collapse, shock, an overdose of CNS inhibitors, chronic heart failure (orally); may cause seizures, hyperemia of the skin, pain in the site of injection; is contraindicated to patients with epilepsy, psychic excitement and hypersensitivity to the nicotinic acid.

Bemegride is a synthetic preparation, a derivative of piperidine; is administered IV; is not bound to plasma proteins and begins to act quickly; is widely distributed in the body; is metabolized in the liver and excreted with urine; is a strong direct-acting analeptic inhibiting barbiturate receptors of Cl^- ion channels; an awakening action is the strongest effect in comparison with other effects of bemegride (by this action it is more potent than other analeptics); is indicated in acute poisonings with barbiturates, alcohol, narcotic analgesics; an overdose of general anesthetics; suppression of respiration; may cause seizures, tremor, hyperventilation and arrhythmia; is contraindicated in epilepsy, psychomotor excitement or intoxication with seizure poisonings.

Fig. 14.5. Vomiting nut containing strychnine

Etimizol is a synthetic preparation, an imidazole derivative; is administered IV, IM, and orally; has a short action; is a direct-acting analeptic inhibitinig adenosine receptors; decreases phosphodiesterase activity, thus increases cAMP concentracion in the cells; has pharmacological effects which by their strength form the line: the stimulation of the respiratory center; the stimulation of vasomotor center and awakening action; produces the stimulation of ACTH secretion resulting in anti-inflammatory and anti-allergic effects, displays cognitive enhance, the improvement of the tone of myocardium and skeletal muscles, dilates bronchi; increases surfactant synthesis in the lungs; is used in the suppression of respiration, asphyxia of newborns, the prophylaxis of lungs athelectasis during inhalation general anesthesia, bronchial asthma, pneumonia and rheumatoid arthritis; may cause dyspepsia, vertigo, restlessness, insomnia; is contraindicated in epilepsy, psychic disorders, excitement.

Strychnine is an alkaloid of vomiting nut (Fig. 14.5); is administered SC and orally; is a direct-acting drug inhibiting glycine receptors; acts mainly on the spinal cord, stimulates reflexive activity of the spinal cord; stimulates the cortex parts of analyzers, especially a vision analyzer; is used in neurological diseases accompanied by hypotonia, paralysis, paresis, asthenia, disturbances of vision resulting from encephalytis, atonia of the GI tract and urinary bladder, impotence; is used very rarely due to high toxicity: is a seizure poison (seizures caused by strychnine are treated by myorelaxants).

Carbogen is a mixture of 3–7% CO_2 and 93–97% O_2; is administered by inhalation; has a mixed action; is a physiological stimulant of the respiratory center; is used for the treatment of asphyxia, respiratory arrest, prophylaxis of athelectasis and pneumonia after inhalation general anesthesia, suppression of respiration; may cause suppression of breathing if concentrations of CO_2 will be high.

PSYCHOMOTOR STIMULANTS

Psychomotor stimulants are the drugs stimulating mainly cortical part of the CNS. They always increase mental and physical performance.

CLASSIFICATION

A. *Purinergic:*

1. Methylxantines:
   - Caffeine (Caffeine sodium benzoate);
   - Theophylline.

B. *Adrenergic:*

1. Phenilalkilamines:
   - Amphetamine.
2. Piperidine derivatives:
   - Meridile.
3. Sydnonimine derivatives:
   - Mesocarb (Sydnocarb).

CAFFEINE

Caffeine is an alkaloid. It is methylxantine (Fig. 14.6).

Caffeine is contained in coffee, tea, cola drinks, chocolate candy, and cocoa (Fig. 14.7). It is water-soluble, but salts of caffeine (caffeine sodium benzoate) are better soluble than caffeine.

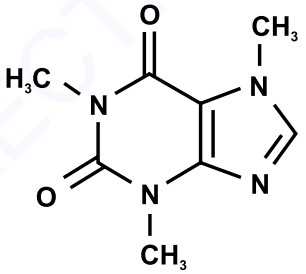

Fig. 14.6. Chemical structure of caffeine

Pharmacokinetics

- is administered orally, SC, IM, IV;
- is well absorbed in the GI tract;
- penetrates CNS and placenta;
- is metabolized in the liver;
- is excreted with urine and mother's milk;
- acts during 4 hrs; $T_{½}$ = 3.9 – 5.3 hrs, is completelly eliminated for 24 hrs.

Fig. 14.7. Plants containing caffeine: A – *Coffe arabica*; B – *Thea chinensis*

Mechanism of action

- caffeine blocks all the subtypes of adenosine receptors and decreases their inhibiting influence in the brain. In such a way it increases excitement in the brain cortex and some other areas of CNS;
- caffeine stimulates the translocation of extracellular calcium into the cells;
- it inhibits phosphodiesterase and increases cAMP concentration in the cells;
- the drug also increases the activity of phosphorilase resulting in the increase of glycogen metabolism and forming of the energy.

Pharmacodynamics

- a psychostimulant action (an increase in the excitement in the brain cortex; a decrease in the time of answer to different irritants; an increase in mental and motor activity; a decrease in fatigue and somnolence);
- an analeptic action (direct stimulation of the respiratory and vasomotor centers in the brain medulla);
- the stimulation of reflexive activity of the spinal cord;
- changes of the heart rate, which depend on the ratio between a direct action on the heart and an indirect one resulting from the stimulation of the center of *n. vagus* (as a rule, an increase in the heart rate);

- the action on blood vessels, which is the sum of the central action (vasoconstriction) and the peripheral action (vasodilation): blood vessels in the heart, lungs, kidney and skeletal muscles are dilated; blood vessels in the brain covers are dilated from the first, then – constricted (that results in a decrease of headache);
- the elevation of BP (in some individuals – lowering of BP or without changes);
- the stimulation of gastric secretion;
- a diuretic action.

Indications

- A decreased mental and physical ability to work;
- Asthenia;
- Fatigue;
- Hypotension;
- Collapse;
- The suppression of respiration;
- Diagnostics of the gastric secretory function;
- Headache (as an ingredient of combined preparations for headache).

Side effects

1. Agitation, anxiety
2. Insomnia
3. Tachycardia, arrhythmia
4. Hypertension
5. Pain in the stomach
6. Drug dependence
7. Withdrawal syndrome (lethargy, irritability, headache in users who have consumed more than 600 mg per day)

Contraindications

1. Psychomotor excitement
2. Hypertension
3. Arrhythmia
4. Atherosclerosis
5. Hyperthyroidism
6. Gastritis, ulcer of the stomach

PECULIARITIES OF OTHER METHYLATED XANTINES

Theophylline is taken orally; has a half-life about 8.5 hrs; has a cellular mechanism like caffeine; causes more CNS stimulation than caffeine; increases cardiac work and diuresis, is an active bronchodilator; is used to treat bronchial asthma, apnea and bradycardia in premature infants; is not used widely due to toxicity and questionable efficacy.

AMPHETAMINE

- is an adrenergic psychomotor stimulant, a phenylalkilamine
- is taken orally, is completely absorbed from the GI tract, metabolized in the liver, and excreted with urine, penetrates CNS, acts during 4–6 hrs
- increases the release of catecholamines into the synaptic gap, is a weak MAO inhibitor; produces the alteration of behavior which is due mainly to a release of dopamine; causes peripheral effects mediated primarily through the release of norepinephrine (Fig. 14.8)
- causes strong psychostimulation, euphoria, anorexia, a peripheral adrenomimetic action
- is indicated for an increase of mental and physical capacity to work, narcolepsy, attention deficit syndrome
- is used very rarely due to its side effects
- may cause insomnia, irritability, weakness, tremor, confusion, delirium, panic state, anorexia, hypertension, tachycardia, arrhythmia, tolerance and addition
- causes psychic and physical dependence, "amphetamine psychosis"
- the treatment of an overdose includes the acidification of urine, administration of chlorpromazine and labetalol for cardiovascular normalization.

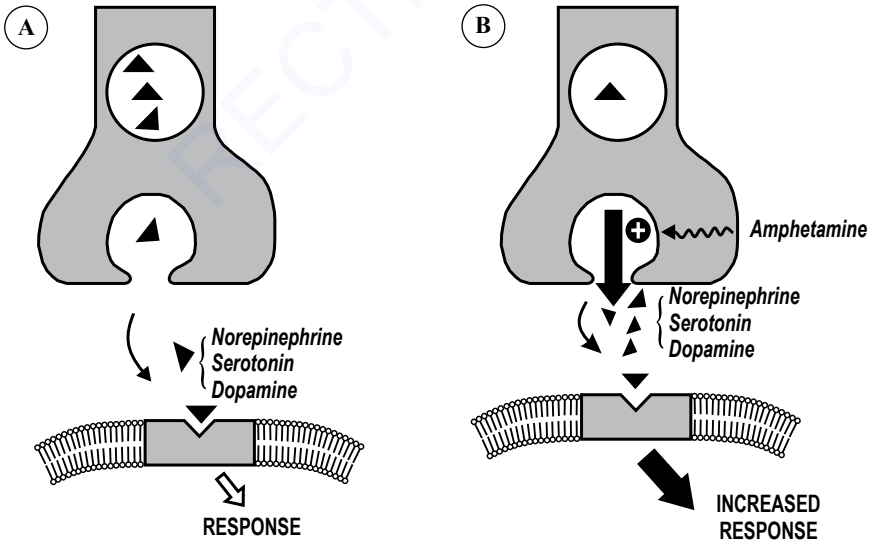

Fig. 14.8. Mechanism of amphetamine's action *(by R. Finkel et al., 2008)*

PECULIARITIES OF OTHER ADRENERGIC PSYCHOMOTOR STIMULANTS

Sydnocarb is an adrenergic psychomotor stimulant, a sydnoimine derivative; is taken orally; has a slow onset of psychomotor stimulation, does not produce euphoria, motor agitation, an increase in BP or other peripheral adrenomimetic effects; is used for the treatment of asthenia with dormancy and apathy, attention deficit in children, for a decrease in asthenia and myorelaxation caused by neuroleptics and anxiolytics; has such side effects as anxiety, anorexia, hypertension; is contraindicated to patients with agitation, arrhythmia, atherosclerosis, hypertension.

TESTS FOR SELF-CONTROL

1. Caffeine exerts all the following effects, except:
A. An increase in BP
B. Sedation
C. Psychic stimulation
D. An increase in gastric secretion
E. A decrease in fatigue.

2. Bemegride is:
A. An antagonist of adenosine receptors
B. An antagonist of barbiturate receptors
C. An agonist of barbiturate receptors
D. A psychomotor stimulant
E. A stimulant of ACTH secretion.

3. The correct statements concerning nikethamide are:
A. It is an analeptic
B. It has a mixed action
C. It suppresses respiration
D. It increases BP
E. It stimulates the respiratory center.

4. Psychomotor stimulants are used for:
A. Relief of pain
B. Asthenia
C. Attention deficit in children

D. An increase the capacity to mental and physical work
E. Insomnia.

5. For the prophylaxis of pneumonia after the inhalation general anesthesia mixed acting analeptic was used. This analeptic is administered by inhalation and includes two gaseous ingredients. What drug was most probably used?
A. Nitrous oxide
B. Cyclopropane
C. Carbogen
D. Nikethamide
E. Camphor.

Answers:

1 – B; 2 – B; 3 – A, B, D, E; 4 – B, C, D; 5 – C.

Chapter 15 ANTIDEPRESSANTS. ADAPTOGENS. NOOTROPICS. ANOREXIGENS

ANTIDEPRESSANT AGENTS

DEPRESSION

Depression is a mood altering disease, an affective disorder. It is characterized by hopelessness, despair, inability to experience pleasure in ordinary life, a loss of interest to usual activity, suppression of appetite and sleep disturbance.

There are three types of depressions: 1) reactive (or secondary); 2) endogenous; 3) manic-depressive disease.

According to ***the biogenic monoamine theory***, the development of depression results from the deficiency of monoamines (norepinephrine and serotonin) in certain areas of the brain. The pharmacological management of depression includes the regulation of adrenergic and serotoninergic processes in the CNS.

ANTIDEPRESSANTS

Antidepressants are the drugs for the treatment of depression.

CLASSIFICATION

According to the mechanism of action

A. *Inhibitors of monoamine reuptake:*

1. Non-selective inhibitors of monoamines reuptake:
   - Imipramine (Imizine);
   - Amitriptyline.

2. Selective inhibitors of serotonin reuptake:
   – Fluoxetine;
   – Sertraline.
3. Selective inhibitors of norepinephrine reuptake:
   – Maprotiline.

B. *MAO inhibitors:*

1. Non-selective (MAO-A and MAO-B):
   – Phenelzine;
   – Tranylcypromine;
   – Nialamide.
2. Selective (MAO-A):
   – Pirlindole (Pirazidol);
   – Moclobemide.

C. *Atypical antidepsessants:*

   – Trazodone;
   – Mianserin;
   – Agomelatine;
   – Ademetionine.

According to the additional action

A. *Thymoleptics* (+ a sedative effect):

   – Amitriptyline;

B. *Thymoerectics* (+ a psychostimulating effect):

   – Nialamide.

C. *Mixed acting:*

   – Imipramine;
   – Pirlindole.

IMIPRAMINE

It has a tricyclic structure (Fig. 15.1).

Pharmacokinetics

- is administrated orally or IM;
- is well absorbed in the GI tract;
- penetrates CNS;
- is metabolized in the liver and excreted with urine and bile;
- has a half-life of 4–17 hrs;
- has a latent period (a therapeutic effect develops slowly in 2–3 weeks after the start of treatment).

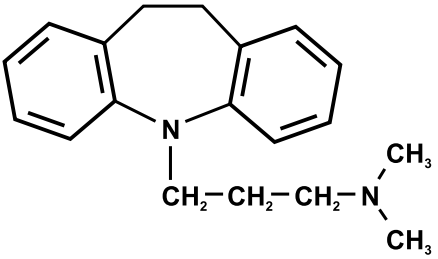

Fig. 15.1. Chemical structure of imipramine

Mechanism of action

- the mechanism of action includes the inhibition of norepinephrine reuptake resulting in the increase of adrenergic processes in the brain structures (Fig. 15.2);
- it is also connected with the inhibition of serotonin reuptake resulting in an increase of the serotonin amount in synapses that leads to an increase in serotonin inhibiting influence in the limbic system (Fig. 15.2);
- imipramine and other tricyclic antidepressants block central and peripheral M-cholinoreceptors. A sedative and antimuscarinic action is due to such blockade;
- it also blocks α-adrenergic receptors and histamine receptors.

Pharmacodynamics

- an antidepressive action;
- a thymoleptic action in the emotional sphere (a sedative or weak psychostimulant action);
- the absence of CNS stimulation or mood elevation in normal individuals;
- a peripheral M-cholinoblocking action;
- an antihistamine action.

Indications

- Severe major depression;
- Enuresis (in children older than 6 years).

Side effects

1. Excitement
2. Insomnia
3. An increase in agitation and hallucination

Contraindications

1. Psychic excitement
2. Schizophrenia
3. Glaucoma
4. Adenoma of prostate

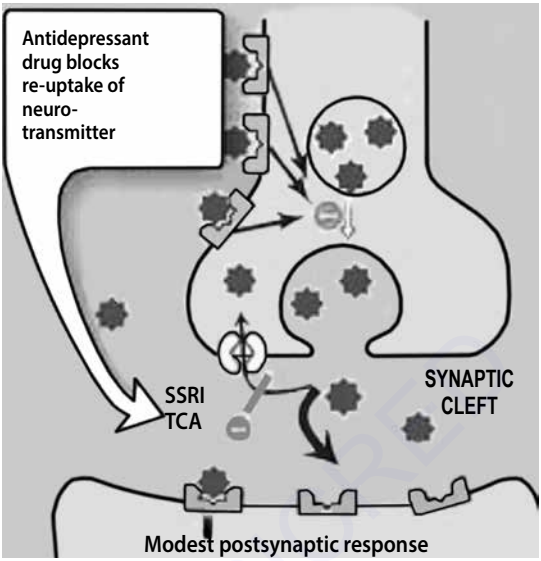

Fig. 15.2. Mechanism of action of monoamine reuptake inhibitors: TCA – tricyclic antidepressants; SSRI – selective serotonin reuptake inhibitors *(by R. Finkel et al., 2008)*

4. Headache
5. Tremor
6. Lowering of BP, orthostatic hypotension
7. Tachycardia, arrhythmia
8. Allergy
9. Changes in the blood film
10. Dry mouth
11. Disturbances of accomodation
12. An increase in intraocular pressure
13. The retention of urine
14. Constipation
15. Drug dependence
5. Atony of the urinary bladder
6. Diseases of blood
7. Diabetes mellitus
8. Tuberculosis
9. Infections
10. Severe diseases of the heart, liver, and kidney
11. Should not be taken in the evening
12. Should not be taken together or after the withdrawal of MAO-inhibitors due to the danger of elevation in the BP, rise in body temperature, convulsions, coma

PECULIARITIES OF OTHER REUPTAKE INHIBITORS

Amitriptyline has a tricyclic structure; is administered orally or IM, manifests an antidepressant action in 10–14 days after the start of treatment; is a non-selective inhibitor of the monoamines reuptake; is a thymoleptic; does not provoke agi-

tation and hallucinations, does not cause insomnia; may be taken in the evening; is indicated to patients in whom depression is accompanied by panic and anxiety; has M-cholinoblocking action and side effects resulting from the antimuscarinic effect.

Maprotiline is a tetracyclic antidepressant, an inhibitor of monoamines reuptake; inhibits the reuptake of norepinephrine relatively strongly. It is used for the treatment of depressions of all forms and severities, especially with agitation or anxiety; panic disorder, neuropathic pain, depressive phase in bipolar disorder, symptomatic relief of anxiety and tension. The side effect profile is comparable to other tricyclic antidepressants, but anticholinergic effects are less prominent.

Fluoxetine contains fluorine; is taken orally; a half-life is 1–10 days; is characterized by a latent period of 1–4 weeks; is a selective serotonin reuptake inhibitor (SSRI); possesses a psychostimulation effect; has not M-cholinoblocking and adrenobloking effects; is widely used to treat depression, neurotic bulemia, neurotic anorexia, panic disorders, some pain syndromes and premenstrual syndrome; has low toxicity, but may cause headache, nervousness, insomnia, appetite disturbances, skin rash or sexual disturbances; should not be combined with non-selective MAO inhibitors (may cause serotonin syndrome).

Sertraline is an antidepressant of SSRI class; is primarily prescribed for major depressive disorder in adult outpatients as well as obsessive-compulsive disorder, panic disorder, and social anxiety disorder in adults and children; is similar in tolerability profile to other SSRIs, including diarrhea, nausea, and sexual dysfunction, but the incidence of diarrhea is higher in comparison to other SSRIs.

NIALAMIDE

- is taken orally, has a latent period of 12–14 days;
- is a non-selective MAO inhibitor: inhibits both MAO-A and MAO-B. In such a way prevents the inactivation of monoamines within the neuron and increases the release of monoamines into the synaptic space. That is why it increases the neurotransmission in certain areas of the brain (Fig. 15.3);
- is a thymoerectic;
- increases the effects of adrenomimetics and sympathomimetics, is a reserpine antagonist;
- decreases pain syndromes;
- is used in depressions unresponsible to tricyclic antidepressants, depressions accompanied by severe anxiety, phobic states, pain syndromes, neuralgia of *n. trigeminus;*

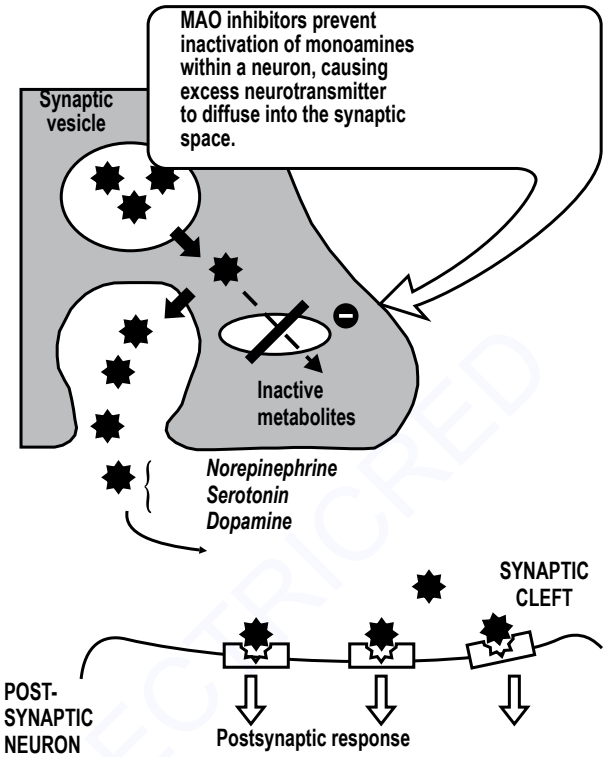

Fig. 15.3. Mechanism of action of MAO-inhibitors *(by R. Finkel et al., 2008)*

- has side effects, such as insomnia, headache, hypotension, dry mouth, constipation, a "cheese syndrome" (it occurs in patients treated with MAO inhibitors after the use of cheese, beer, and other products containing tyramine; manifests by hypertensive crisis and cerebrovascular accidents; needs IV injection of α-adrenoblocker as emergency help).

PECULIARITIES OF OTHER MAO INHIBITORS

Pirlindole has a tetracyclic structure; is a selective inhibitor of MAO-A with a reversible action; has regulatory influence on emotions: causes psychostimulation under the conditions of fatigue and dormancy as well as sedation under the conditions of anxiety; has not M-cholinoblocking properties; is indicated in depressions,

manic-depressive disease and some types of schizophrenia, has low toxicity; may be used in patients with glaucoma, adenoma of prostate or myocardial infarction.

CONCEPT ABOUT ATYPICAL ANTIDEPRESSANTS

Atypical antidepressants are modern preparations which differ from typical antidepressants by their mechanism of action. This mechanism of action is represented by the blocage of α_2-receptors and an increase in norepinephrine release, by inhibition of serotonin receptors, etc.

PECULIARITIES OF PREPARATIONS

Agomelatine is a melatoninergic antidepressant for the treatment of major depressive disorder, primarily for its favorable side effect profile without the weight gain, sexual dysfunction, and severe withdrawal associated with the most commonly used classes of antidepressants. Agomelatine is a melatonin receptor agonist and a 5-HT_{2C} receptor antagonst that disinhibits noradrenaline and dopamine release in the frontal cortex. Due to its mechanism of action, the drug is also studied for sleep regulation.

Ademetionine is a hepatoprotector with antidepressant activity. It has choleretic and cholekinetic effect, detoxification, regenerating, antioxidant, and neuroprotective properties, replenishes the deficit of S-adenosylmethionine in the body. Indications for use are chronic cholecystitis, cholangitis, toxic liver damage, chronic hepatitis, liver cirrhosis, osteoarthritis, encephalopathy associated with hepatic failure, abstinence syndrome and depression (including secondary). The drug is effective in recurrent endogenous and neurotic depressions resistant to amitriptyline. Ademetionine is considered safe for most adults, but it can worsen symptoms of bipolar disorder or Parkinson's disease.

NOOTROPIC DRUGS

Nootropic drugs (cognition enhancers) are the drugs for improving memory and ability to acquisition of new knowledge.

CLASSIFICATION

1. Pyrolidon derivatives:
   - Piracetam (Nootropil);
   - Pramiracetam.

2. GABA derivatives:
   - Aminalon;
   - Sodium hydroxibutyrate;
   - Phenibut;
   - Pantogam;
   - Picamilon.
3. Neuropeptides:
   - Sinacten-Depo;
   - Thyroliberin;
   - Melatonin;
   - Cerebrolysin.
4. Cerebrovascular drugs:
   - Vinpocetin (Cavinton);
   - Nicergoline (Sermion);
   - Pentoxyphylline;
   - Cinnarisine.
5. Pyridoxine derivatives:
   - Pyritinol (Encephabol).
6. Antioxidants:
   - Mexidol.

PIRACETAM

By its chemical structure piracetam is similar to a cyclic form of GABA (Fig. 15.4).

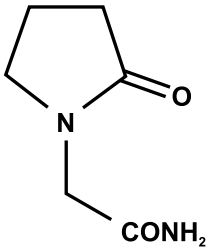

Fig. 15.4. Chemical structure of piracetam

Pharmacokinetics

- is administered orally, IM, IV;
- is well absorbed from the GI tract, has bioavailability of 90%;

- develops maximal concentration in the blood in 30 min after the administration; maximal concentration in the brain – in 1–4 hrs after the administration;
- penetrates CNS and placenta;
- does not metabolized in the organism;
- is excreted with urine;
- acts during 12 hrs.

Mechanism of action

- piracetam has a combined mechanism of action. It acts due to binding to receptors as well as due to the regulation of cell metabolism;
- the influence on cognition results from the stimulation of aspartate and glutamate receptors, $GABA_A$ and $GABA_B$ receptors;
- it increases macromolecules synthesis, stimulates glucose metabolism and the production of ATP, increases the turnover of neurotransmitters, inhibits lipid peroxidation, normalizes the structure and functions of cell membranes, decreases cortical discharge of L-proline;
- it also inhibits phosphodiesterase, increases the content of cAMP in the cells, thus dilates blood vessels in the brain and has an antiplatelet action.

Pharmacodynamics

- a nootropic action: stimulation of the higher cortical function in the delay or disturbances of their development, improving the memory, enhancing cognition, the stimulation of educational process;
- the regulation of emotional state (a weak dose-dependent psychostimulating or tranquilizing effect);
- a stress-protective action with the development of active forms of adaptation;
- an antihypoxic action (an increase in the brain stability to hypoxia);
- a cytoprotective action (an increase in the brain stability to neurotropic poisons);
- an antiseizure action in some forms of epilepsy;
- an increase in the efficacy of the treatment by neuroleptics and antidepressants, a decrease in their side effects;
- a decrease of abstinence in alcohol abused persons;
- the improvement of cerebral blood circulation;
- the reduction of blood viscosity;
- a cardioprotective action (a decrease of the myocardium lesion under the conditions of hypoxia).

Indications

A. Long-lasting treatment:

- memory disturbances with vascular, traumatic, infective, intoxication, and somatogenic genesis;
- cognition disturbances in elderly patients associated with senile dementia and Alzheimer's disease;
- cerebral circulation disturbances, cerebral atherosclerosis;
- chronic alcoholism;
- mental deficiency in children;
- cortical myoclonus epilepsy;
- sickle-cell anemia (as an additional drug).

B. Urgent therapy:

- trauma of the brain;
- edema of the brain;
- stroke;
- comatose states;
- acute intoxications with neurotropic poisons;
- abstinence in alcohol abusers;
- myocardial infarction (as an additional drug);
- hypoxia of the fetus and newborn.

C. Use in healthy persons for improving education processes, memory, and adaptation.

Side effects and contraindications

Piracetam is low toxic (an acute toxic dose is 10 g/kg of body weight). Rarely it can cause nervousness, anxiety, insomnia.

The drug has no significant contraindications.

PECULIARITIES OF OTHER PREPARATIONS

Pramiracetam is a piracetam derivative, has simiar action and indications, but is more active and is used in smaller doses.

Aminalon contains GABA; in the organism, it is metabolized, crosses through blood-brain barier and re-synthesized into GABA, interacts with $GABA_A$ and $GABA_B$ receptors; has nootropic, anticonvulsant, antihypoxic, and light antihypertesive effects; is used after the disturbunces of cerebral blood circulation, for

encephalopathy, cerebral palsy, mental retardation in children, and kinetosis; has low toxicity.

Vinpocetin (cavinton) is an alkaloid; is administered orally and IV (by IV infusion); is the inhibitor of phosphodiesterase and increases the cAMP concentration in cells; dilates cerebral blood vessels; improves cerebral circulation; has nootropic and antihypoxic actions; decreases vertigo associated with circulation disturbances; increases glucose metabolism in the brain; has an antiplatelet action; is indicated in acute and chronic disturbances of cerebral blood circulation, cerebral atherosclerosis, memory disturbances associated with cerebral ischemia, vertigo, the pathology of blood vessels in the retina and internal ear; may cause hypotension, arrhythmia, hyperemia of the face.

Pentoxiphylline by its chemical structure is similar to alkaloid theobromine; is administered orally, IV; is a phosphodiesterase inhibitor; dilates both cerebral and peripheral blood vessels of arterial type; has an antiplatelet action; has nootropic action, especially associated with the pathology of cerebral circulation; is indicated in acute and chronic disturbances of cerebral and peripheral blood circulation, ischemic stroke, diabetic angiopathia, angiopathia of ocular blood vessels; has such side effects as hypotension, weakness, vertigo, hyperemia of the skin and dyspepsia; is contraindicated to patients with myocardial infarction, bleeding, hypotension, severe atherosclerosis or pregnancy.

Nicergoline (sermion) is administered orally and IV (by IV infusion); has an α-adrenoblocking action, dilates cerebral and peripheral blood vessels, improves cerebral and peripheral circulation, thus displays a nootropic action in the CNS; has indications similar to that of pentoxiphylline; may cause hypotension, a decrease in cardiac output, vertigo, weakness, hyperemia of the skin and pain in the epigastrium.

ADAPTOGENS

Adaptogens are the drugs improving adaptation and non-specific resistance of the organism. Majority of adaptogens have a vegetable origin (Fig. 15.5).

CLASSIFICATION

1. Preparations from medicinal plants:
   - Tincture of *Ginseng;*
   - Tincture of *Schizandra;*
   - Tincture of *Aralia;*
   - Liquid extract of *Eleutherococcus*.

Fig. 15.5. Medicinal plants containing adaptogens:
A – *Panax Ginseng*, B – *Schizandra chinensis*, C – *Leuzea carthamoides*

2. Preparations from animal tissues:
   – Pantocrin (deer antler extract).

All adaptogens have the common mechanism of action and similar pharmacological properties. They are taken orally. Pantocrin may be administered IM, SC.

Mechanism of action

- mechanim of action is connected with steroidal compounds and is based on the activation of RNA synthesis, intensification of protein synthesis, stimulation of glucose metabolism and ATP synthesis, inhibition of lipid peroxidation;
- regulation of the activity of the hypophysial-adrenal system is a very important component in the adaptogens' mechanism of action. They limit the activity of this system under the conditions of acute stress or stimulate it under the conditions of chronic exhausting stress.

Pharmacodynamics

- an increase in resistance to unfavorable factors;
- the optimization of adaptation;
- a decrease in negative influence of acute and chronic stress on the organism;
- an increase in physical and mental working capacity;
- the restoration of normal daily rhythms;
- a decrease in atherogenesis;
- the stimulation of cardiovascular system, an increase in low BP;
- the normalization of decreased appetite;

- the stimulation of reproductive processes, especially in males;
- the stimulation of non-specific immunity.

Indications

- asthenia;
- hypotension;
- vegeto-vascular dystonia;
- recovery period after infections;
- atherosclerosis;
- sexual asthenia, impotence;
- stress and adaptation in healthy persons;
- physical and mental overstrain;
- non-specific prophylaxis of infections.

Side effects

1. Restlessness, nervousness, insomnia.
2. Hypertension.
3. Hyperglycemia.

Contraindications

Insomnia, hypertension, bleeding, menstruation, severe atherosclerosis or organic heart lesions. Should not be taken in the evening!

ACTOPROTECTORS

Actoprotectors are the drugs for the stimulation of working capacity without following asthenia, euphoria, or drug dependance. There is a new pharmacological group with one preparation.

BEMITHYL

- stimulates glucose metabolism and increases the synthesis of ATP and creatinphosphate;
- stimulates physical working capacity, increases the resistance to oxygen insufficiency; increases the outer temperature; improves immunity;
- is indicated in the stimulation of working capacity, asthenia, the recovery period after traumas and infections;
- has minimal side effects, but may cause headache, face hyperemia, dyspepsia, nausea, vomiting or allergy.

ANOREXIGENS

Anorexigens are the drugs decreasing appetite due to their central activity.

CLASSIFICATION

1. Catecholaminergic (stimulating CNS):
   – Amfepranone (Phepranone);
   – Chlorpheniramine (Desopimone);
   – Mazindol.
2. Serotoninergic (suppressing CNS):
   – Fenfluramine.

Mechanism of action

- the 1st group preparations increase the release and decrease the reuptake of norepinephrine and dopamine in the CNS. That's why they produce the stimulation of the saturation center resulting in a decrease of appetite and the limitation of the meal quantity;
- the 2nd group preparations decrease the concentration of serotonin in the CNS and inhibit the limbic system influence on the hunger center. In such a way they decrease appetite and limit the meal quantity.

Pharmacodynamics

- the inhibiton of appetite, limitation of meal quantity;
- a decrease in the body weight.

Indications

Severe alimentary and endocrinal obesity.

Side effects

For the 1st group: hypertension, tachycardia, arrhythmia, anxiety, insomnia, dry mouth, tolerance, drug dependence.

For the 2nd group: sleepiness, depression, euphoria, irritation of the gastric mucosa.

TESTS FOR SELF-CONTROL

1. The main mechanism by which amitriptyline increases the amount of catecholamines in the CNS synapses is:

A. An increase in catecholamines release from the presynaptic membrane
B. An increase in catecholamines synthesis in the presynaptic membrane
C. The prevention of catecholamines degradation in the synapse
D. The inhibition of the neuronal reuptake of catecholamines
E. The inhibition of MAO.

2. ll the statements concerning adaptogens are true, except:
A. They are taken orally
B. They modify the activity of hypophysial-pituitary-adrenal axis
C. They depresse immunity
D. They are used to improve non-specific resistance
E. They increase mental and physical work capacity.

3. The MAO inhibitors are:
A. Among thymoerectics
B. Not influencing the emotional sphere
C. Causing dry mouth, blurred vision
D. Causing "cheese syndrome"
E. Without dangerous side effects.

4. Piracetam is effective in the treatment of:
A. The disturbance of movement in patients with cerebral stroke
B. The retardation of mental development in children
C. The disturbances of memory after the stroke
D. Senile dementia
E. A memory impairment in alcoholics.

5. 70-year old patient has vertigo and memory disturbances on the background of atherosclerosis. He is also suffering from the disturbances of blood flow in lower extremities. Which of the listed drugs is necessary to include in the complex therapy of this patient?
A. Caffeine
B. Pentoxiphylline
C. Diazepam
D. Phenazepam
E. Amitryptiline.

Answers:

1 – D; 2 – C; 3 – A, C, D; 4 – B, C, D, E; 5 – B.

Chapter 16 INOTROPIC DRUGS

CONGESTIVE HEART FAILURE

Congestive heart failure (CHF) is a decrease in the pump function of the myocardium resulting from different causes (myocarditis, organic lesions of the heart, hypertensive disease, etc). CHF may be acute and chronic. It is accompanied by a decrease of cardiac output, the enhancing of venous pressure and lowering of arterial pressure. Such processes lead to a decrease in the renal blood flow, the stimulation of renin and aldosterone secretion, sodium and water retention in the body with the development of edema (Fig. 16.1).

INOTROPIC DRUGS

Inotropic drugs are preparations which increase the force of myocardium contraction and cardiac output without a significant increase in oxygen consumption.

They are divided into cardiac glycosides (steroidal inotropic drugs) and non-glycoside inotropic drugs (non-steroidal) (Fig. 16.2).

CARDIAC GLYCOSIDES

Origin

Cardiac glycosides are inotropic drugs from medicinal plants (Fig. 16.3). The sources of main glycosides are:

- *Digitalis purpurea* (fox gloves) for digitoxin;
- *Digitalis lanata* for digoxin;
- *Strophanthus Kombe* for strophanthin-K;

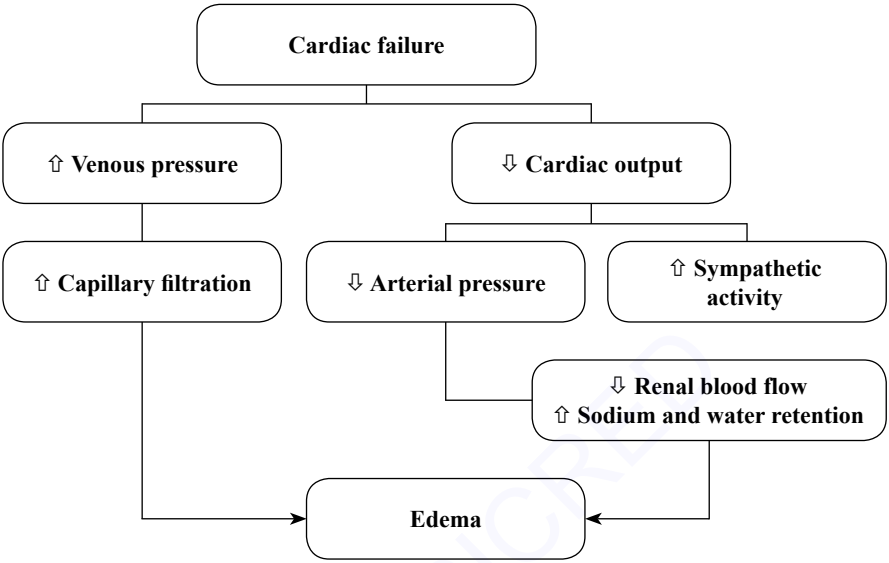

Fig. 16.1. Pathogenesis of congestive heart failure

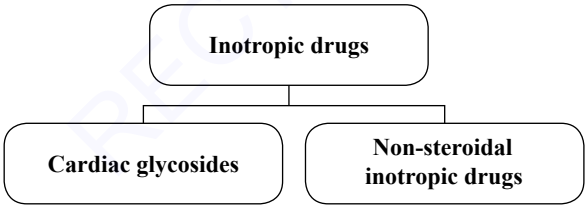

Fig. 16.2. Two groups of inotropic agents

- *Strophanthus gratus* for strophanthin G (quabain);
- *Convallaria majalis* (lily of the valley) for corglycon;
- *Adonis vernalis* for adoniside, infusion from the herb of adonis.

History of development

The modern era of the treatment with the digitalis glycosides began with the work of William Withering, who publised his famous book "An Account of the Foxglove and Some of Its Medical Uses" in 1785. Withering was aware that digi-

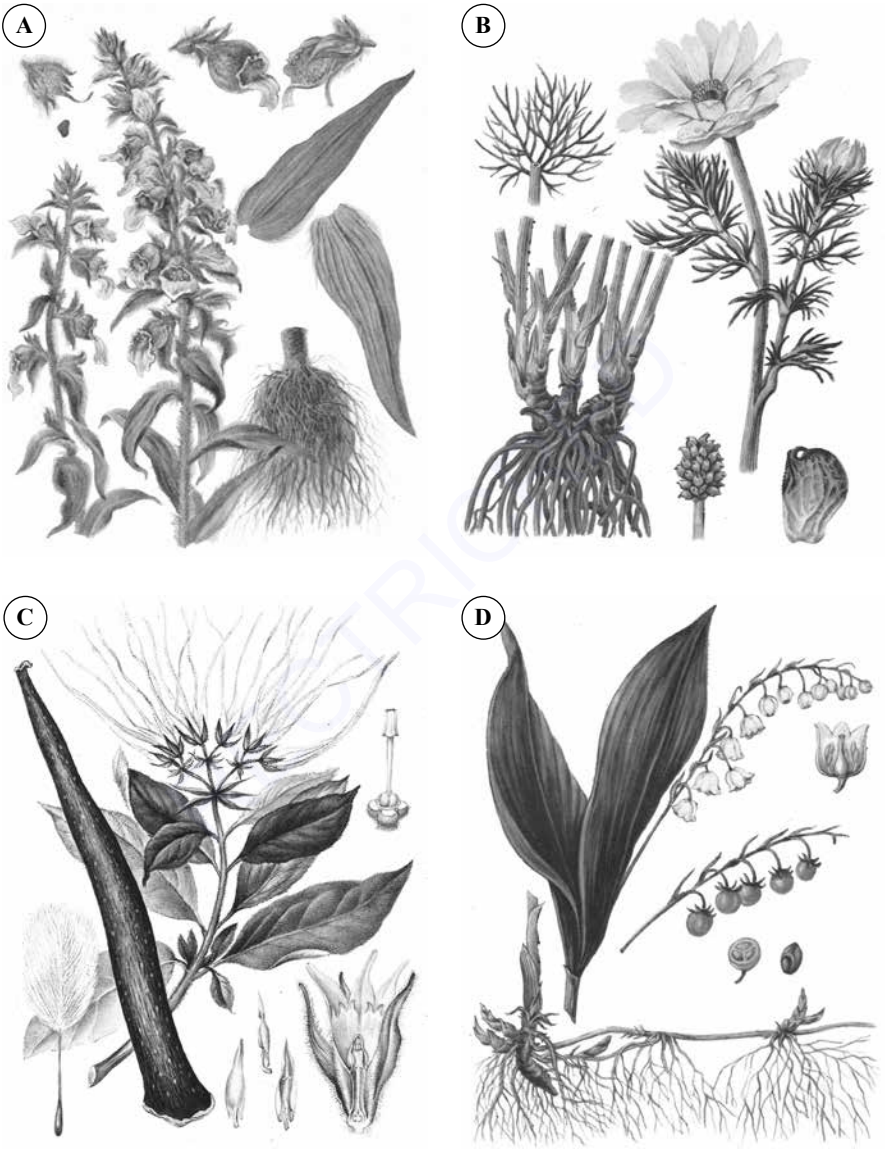

Fig. 16.3. Medicinal plants containing cardiac glycosides:
A – *Digitalis lanata*; B – *Adonis vernalis*; C – *Strophanthus combe*; D – *Convallaria majalis*

talis was only effective in certain forms of dropsy or edema, and recognized that the drug acted on the heart.

Chemical structure

All cardiac glycosides have similar structure including glycone and aglycone. This structure may be represented as follows: ***Cardiac glycoside = glycone + aglycone***. ***Glycone*** contains sugar moieties and determines pharmacokinetics. ***Aglycone*** contains a steroid structure with lactone ring and determines pharmacodynamics (Fig. 16.4).

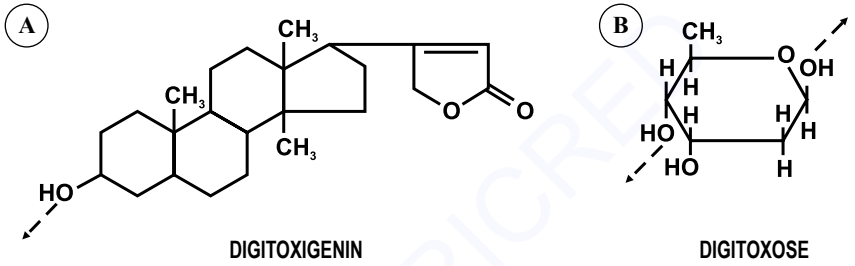

Fig. 16.4. Structural parts of cardiac glycoside digitoxin: digitoxigenin as aglycone (A) and digitoxose as glycone (B)

CLASSIFICATION

According to the origin

1. Group of *Digitalis:*
   - Digitoxin;
   - Digoxin;
   - Celanide (Lanatoside C);
   - Adoniside;
   - Infusion from the herb of *Adonidis vernalis.*
2. Group of *Strophanthus:*
   - Strophanthin-K;
   - Strophanthin-G (Quabain);
   - Corglycon;
   - Tincture of *Convallaria.*

According to the duration of action

1. Long-acting:
   - Digitoxin;

2. Intermediate-acting:
   – Digoxin;
   – Celanide.
3. Short-acting:
   – Strophanthin;
   – Corglycon.

Mechanism of action

Mechanism of positive inotropic action

Lactone ring binds to SH-groups of Na^+/K^+ ATP-ase that results in the reversible inhibition of the biological pump. Such inhibition leads to a decrease in Na^+ transport from the cell and a decrease in K^+ entry. An increase in the intracellular Na^+ content causes the accumulation of Ca^{++} in the cell (Fig. 16.5). Under the influence of high Ca^{++} concentration the interaction between actin and myosin is more active and the force of heart contractions increases.

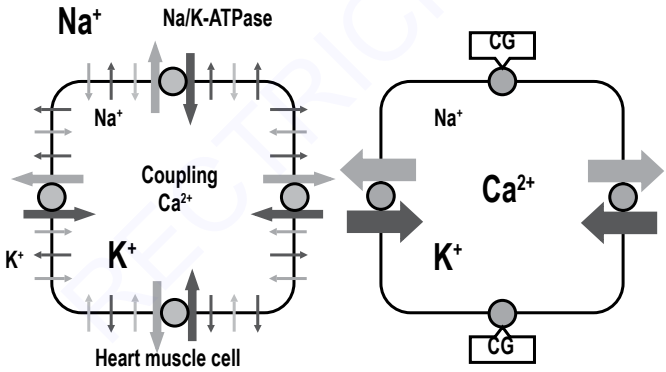

Fig. 16.5. Mechanism of cardiac glycosides' (CG) inotropic action *(by H. Lüllmann, 2000)*

Mechanism of negative chronotropic action

There are two parts in this mechanism: a vagal and an extravagal action. The vagal action is due to the reflexive and direct stimulation of the *n. vagus* center. The extravagal action is due to the direct inhibition of sinoatrial (SA) and atrioventricular (AV) nodes and hypersensitization of SA node to acetylcholine.

Pharmacodynamics

- ***positive inotropic effect*** (an increase in the force of systole, an increase in the myocardium tone);

- ***negative chronotropic effect*** (the prolongation of diastole, slowing of the heart rate);
- ***negative dromotropic effect*** (deceleration of conductivity);
- ***positive bathmotropic effect*** (an increase in myocardium excitation, manifests as extrasystoles in the overdose of cardiac glycosides);
- the improvement of blood circulation;
- a decrease in venous pressure, normalization of arterial blood pressure;
- an increase in renal blood flow, which leads to an increase in diuresis and a decrease in edema.

Phases of digitalis therapy

- the phase of digitalization is a saturation of the organism by cardiac glycosides (1–7 days). The preparation is administered in a full therapeutic dose. At the end of this phase the compensation of heart failure should be obtained;
- the phase of supporting therapy is a long treatment by an individual small dose of cardiac glycoside which is sufficient for heart compensation. Heart rate should not be less than 60 per 1 minute;
- the pre-toxic phase is the beginning of overdose. The heart rate is less than 60 beats per 1 min. The drug should be abolished;
- the toxic phase (acute intoxication).

Digitalis toxicity

Signs (Fig. 16.6):

– bradycardia, then tachycardia and arrhythmia (premature ventricular beats, fibrillation);
– an increase in the signs of heart failure;
– changes in the electrocardiogram (ECG);
– hypokalemia;
– anorexia, vomiting, nausea;
– headache, fatigue, hallucinations;
– vision disturbances (xantopsia, micropsia, macropsia).

Treatment of Digitalis intoxication:

– abolishing of cardiac glycoside;
– drugs containing potassium (potassium chloride; panangin);
– SH-group donator (dimercaprol, or unithiol);
– antiarrhythmic agents (phenytoin, lidocaine, propranolol, atropine for AV block);
– digoxin antibodies (digibind);
– glucose, vitamins preparations, oxygen inhalation.

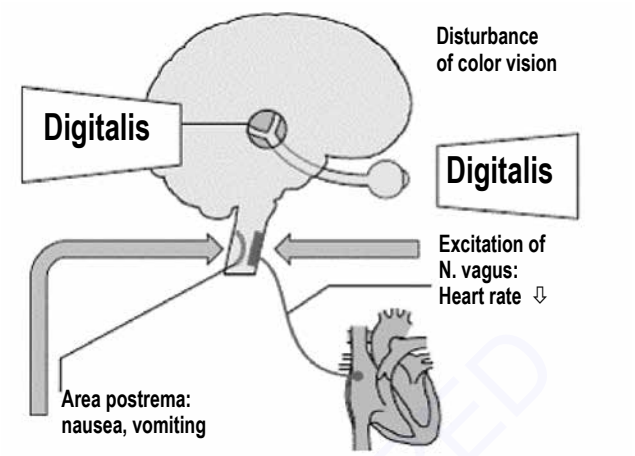

Fig. 16.6. Signs of digitalis toxicity *(by H. Lüllmann, 2000)*

Potassium preparations must be administered for the prophylaxis of digitalis toxicity.

PECULIARITIES OF PREPARATIONS

Digitoxin

- is a typical representative of the *Digitalis* group;
- is lipid-soluble, non-polar;
- is administered orally or rectally, is well absorbed in the GI tract (90–100%), binds to plasma proteins (95%), is metabolized in the liver; forms a hepatic-intestinal cycle of re-circulation, is excreted with urine and bile; begins to act slowly in 2–4 hrs after the administration; has a long durative action with a half-life of 4–7 days, stays in the organism during 21 days, accumulates;
- has a negative chronotropic effect which exceeds inotropic and other effects on its significance;
- is used in chronic heart failure of I–II B stages, supraventricular tachyarrhythmia;
- may cause hypokalemia, bradycardia, AV-block and intoxication;
- is contraindicated in poisoning with cardiac glycosides, bradycardia, AV block, acute myocardial infarction, severe aortal and mitral stenosis, potassium deficiency or childhood.

Digoxin

- is water- and lipid-soluble;
- is intermediate-acting glycoside from *Digitalis lanata;*
- may be administered orally and IV, is well absorbed in the GI tract (60–85%), binds to plasma proteins less than digitoxin (20–25%), may re-circulate, begins to act soon after the IV administration, has a half-life of 36–48 hrs, accumulates less than digitoxin;
- has less influence on AV conductivity than digitoxin;
- is used in chronic CHF, supraventicular tachyarrhythmia, acute heart failure, an attack of arrhythmia (IV);
- is less toxic, may be used in children and in patients with a non-severe AV block.

Celanide

The drug is similar to digoxin, but is absorbed worse in the GI tract and after the IV administration starts to act faster than digoxin.

Strophanthin

- is a typical preparation from *Strophanthus* group;
- is water-soluble, polar;
- is administered IV (as an exclusive case, may be administered IM together with procaine or sublingually); is not absorbed in the GI tract (only 5% of a dose), does not bind to plasma proteins, has no re-cycling, is not metabolized in the body, is excreted with urine, starts to act in 10–15 min after the administration, develops a maximal effect in 1.5–2 hrs after the administration; has a half-life of 8 hrs; stays in the organism to 24 hrs; does not accumulate;
- has a strong positive inotropic action which is the most significant among other effects;
- is used to treat acute heart failure, attack of supraventricular arrhythmia as well as for rapid digitalization;
- as a rule, does not cause intoxication.

Corglycon

The drug is similar to strophanthin, but begins to act slower.

Infusion from the herb of adonis

- is galenic preparation which contains glycosides from *Adonis vernalis;*
- is taken orally, does not accumulate;

- is weaker than all other preparations;
- has a sedative and direct diuretic action;
- is used for the treatment of light forms of CHF, cardioneurosis and neurosis (is combined with valerian and bromides);
- has low toxicity.

NON-STEROIDAL INOTROPIC DRUGS

These inotropes improve cardiac pump function by adrenergic mechanisms, the inhibition of phosphodiesterase (PDE) III, or in another way.

CLASSIFICATION

1. Adrenomimetics
   - Dobutamine (β_1-adrenergic agonist)
   - Dopamine (β_1-adrenergic agonist)
   - Isoprenaline (β_1-, β_2- adrenergic agonist)
   - Ephedrine (α-, β- adrenergic agonist)
2. Selective PDE III inhibitors
   - Amrinone
   - Milrinone
3. Calcium sensitizers
   - Levosimendan (Simdax).

DOBUTAMINE

- is a non-glycoside inotropic agent
- is similar to dopamine by its chemical structure
- is administered by IV infusion
- is a selective agonist of β_1-adrenoceptors in the heart (Fig. 16.7)
- has a positive inotropic action, improves coronary circulation, reduces peripheral resistance, redistributes blood flow in favor of the heart and lungs, increases the renal blood flow, does not act on the heart rate; does not cause hypertension
- is used in acute heart failure, cardiogenic shock
- may cause tachycardia, arrhythmia.

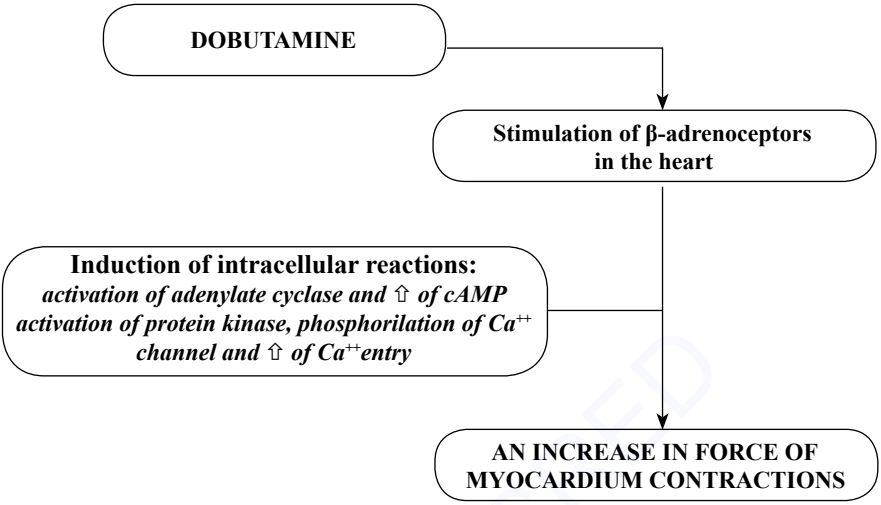

Fig. 16.7. Mechanism of dobutamine's action

LEVOSIMENDAN

- is a non-glycoside inotropic agent, calcium sensitizer;
- is administered by IV infusion; hemodynamic effects persist for at least 24 hrs and can be observed up to 9 days after discontinuation of 6 hrs infusion;
- exerts positive inotropic effect by binding to troponin C in a calcium-dependent manner; has a vasodilatory effect by opening of ATP-sensitive K^+ channels in vascular smooth muscles; combined inotropic and vasodilatory actions result in the increased force of contraction, decreased preload and afterload; has cardioprotective effect due to opening the mitochondrial ATP-sensitive K^+-channels in cardiomyocytes;
- is indicated in acutely-decompensated severe CHF if the conventional therapy is not sufficient;
- side effects include headache, hypotension, arrhythmias, myocardial ischemia, hypokalemia, and nausea.

TESTS FOR SELF-CONTROL

1. Only one inotropic drug has a non-glycoside structure:
A. Digoxin
B. Digitoxin

C. Dobutamine
D. Corglycon
E. Infusion from the herb of adonis.

2. The main effects of cardiac glycosides include all, except:
A. An increase in the strength of myocardium contractions
B. A decrease in the heart rate
C. A decrease in the conductivity of the heart
D. An increase in neurotransmission in the CNS
E. The improvement of blood circulation.

3. Digitalis toxicity is characterized by the following:
A. Disturbances of color vision
B. Hypokalemia
C. Heart block
D. Ventricular tachyarrhythmia
E. Hyponatremia.

4. Acute heart failure may be treated by:
A. Strophanthin (ampoules)
B. Corglycon (ampoules)
C. Digitoxin (rectal suppositories)
D. Digoxin (tablets)
E. Celanide (ampoules).

5. Digoxin in tablets was prescribed to a patient with chronic CHF. After 1 month of treatment a decrease in the heart rate was noted; a doctor advised to the patient to continue the treatment with a lower dose of digoxin. In spite of this, bradycardia was soon transformed into AV block. Choose the necessary drug for the abolishing of this manifestation of glycoside toxicity.
A. Potassium chloride
B. Phenytoin
C. Atropine
D. Lidocaine
E. Propranolol.

Answers:

1 – C; 2 – D; 3 – A, B, C, D; 4 – A, B, E; 5 – C.

Chapter 17 ANTIANGINAL DRUGS

ANGINA PECTORIS

Angina pectoris is one of the forms of ischemic heart disease. Two other forms are myocardial infarction and cardiosclerosis (Fig. 17.1).

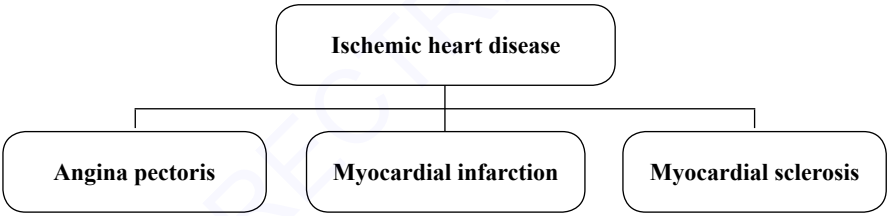

Fig. 17.1. Ischemic heart disease and its forms

Angina pectoris is characterized by a sudden, severe pressing or acute chest pain radiating to the left arm and neck. Anginal pain occurs when the oxygen supply to myocardium is insufficient for its needs. The imbalance between oxygen delivery and utilization may result from a spasm or from the obstruction of heart blood vessels (Fig. 17.2). The coronary blood flow is insufficient to meet the heart's metabolic requirements. It causes the onset of anginal pain.

ANTIANGINAL DRUGS

Antianginal drugs are preparations which delay or prevent angina attack.

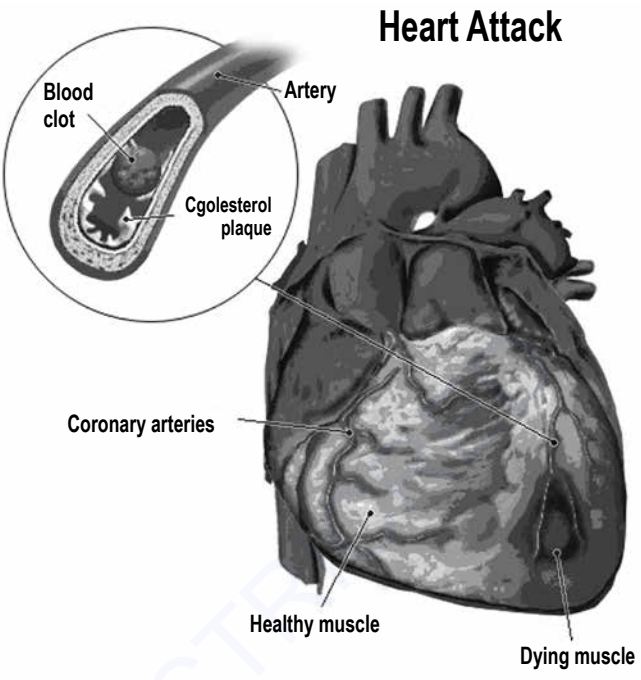

Fig. 17.2. Pathogenic factors of angina attack and myocardial infarction *(http://www.picsearch.com)*

CLASSIFICATION

A. *Drugs that decrease oxygen demand of myocardium and increase oxygen supply:*

1. Organic nitrates:
   - Nitroglycerine (glyceril trinitrate, GTN);
   - Isosorbide dinitrate;
   - Isosorbide mononitrate;
   - Sustac.
2. Calcium channel blockers:
   - Verapamil;
   - Nifedipine;
   - Amlodipine.

B. *Drugs that decrease oxygen demand of myocardium:*

1. β-adrenoblockers:
   - Propranolol;

- Metoprolol;
- Talinolol;
- Atenolol.

C. *Drugs that increase oxygen supply:*

1. Substances of myotopic action:
   - Dipyridamole;
   - Papaverine;
   - Drotaverine (No-spa).
2. Substances of the reflexive mechanism of action:
   - Validol.

D. *Drugs acting on myocardial metabolism:*

- Sodium adenosine triphosphate;
- Mildronate (Meldonium);
- Trimetazidine;
- Corvitin.

DRUGS THAT DECREASE OXYGEN DEMAND AND INCREASE OXYGEN SUPPLY

ORGANIC NITRATES

NITROGLYCERINE

The drug has a chemical structure of glyceril trinitrate (Fig. 17.3); is lipid- and alcohol-soluble.

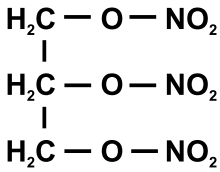

Fig. 17.3. Chemical structure of nitroglycerine

Pharmacokinetics

- is taken sublingually;
- is well absorbed from the oral cavity;
- does not undergo hepatic first-pass metabolism after the sublingual administration;

- starts to act in 15–30 sec, develops peak concentration in 3–5 min after the administration;
- is metabolized in erythrocytes and in the liver with the formation of active metabolites (mono- and dinitrates);
- finally is inactivated in the liver by conjugation;
- is excreted with urine and air;
- stays in the organism during 30–45 min.

Mechanism of action

- nitrate (NO_2) is transformed into nitrous oxide (= NO, endogenous endothelial-derived relaxation factor, EDRF);
- it binds to SH-groups of nitrate receptors;
- that results in activation of guanylate cyclase and leads to an increase in the cGMP content in cells and a decrease in the Ca^{++} entry;
- such processes lead to the dephosphorilation of the myosin light chain and relaxation of vascular smooth muscles (Fig. 17.4).

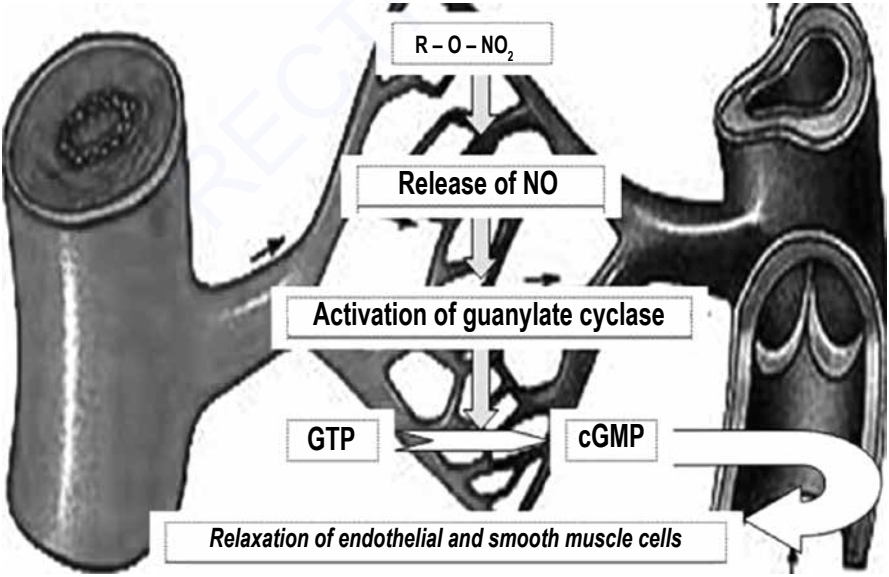

Fig. 17.4. Mechanism of nitroglycerine's action

Pharmacodynamics

- the dilation of venous vessels, pooling of blood in the veins, as a result, the redistribution of blood in the body and a decrease in preload on the myocardium;
- the dilation of arterial vessels, a decrease in total peripheral vascular resistance, as a result, a decrease in afterload on the myocardium;
- a decrease in load on the myocardium resulting in ***a decrease of oxygen demand;***
- the dilation of coronary vessels, redistribution of the coronary blood flow in favor of the area of ischemia and ***an increase in oxygen supply;***
- the inhibition of impulses from the vasomotor center;
- the relaxation of the smooth muscles of bronchi and the biliary system.

Indications

- angina pectoris attack;
- thrombosis of the central vein of the retina;
- combined therapy of hypertensive crisis;
- paroxysmal nocturnal dyspnea;
- myocardial infarction and edema of lungs (a special medicinal form of nitroglycerine for IV injections is used).

Side effects

1. Headache (as a result of the dilation of blood vessels in the brain tunics and increasing of intracranial pressure; may be diminished by the applying of validol or non-narcotic analgesics).

2. Hypotension, postural hypotension, collapse (may be treated by phenylephrine).

3. Reflex tachycardia.

4. Pain in the eyes, an increase in intraocular pressure (as a result of dilation of ocular blood vessels).

5. Flushing of the skin (as a result of the dilation of blood vessels in the skin).

6. Tolerance (as a result of the oxidizing of SH-groups of nitrate receptors; may be overcome by the provision of a daily "nitrate-free interval" and by the use of thiodrugs or antioxidants).

7. Overdose (the forming of methemoglobin, hypoxia, collapse, respiratory failure; needs the administration of methylene blue as an antidote).

Contraindications

1. Hypersensitivity.
2. Hypotension.

3. Myocardial infarction accompanied by hypotension.
4. Hypertrophic obstructive cardiomyopathy.
5. Aortic and mitral stenosis.
6. Cardiac tamponade.
7. Constrictive pericarditis.
8. An increase in intracranial pressure (trauma of the brain, hemorrhagical insult).
9. Glaucoma.

LONG-ACTING NITRATES

Sustac is tablets for the oral administration which contain microcapsules of nitroglycerine; exists in two forms: sustac-mite with a lower dose and sustac-forte with a higher dose of nitroglycerine; is slowly absorbed from the gut; begins to act in 30–60 min after the administration and acts during 4–6 hrs; is used for the prevention of an angina attack.

Isosorbide dinitrate is used in the form of tablets, spansules, spray, injections; after sublingual administration begins to act in 3–20 min and acts during 1–2 hrs; as an oral form, has an onset of action in 30–60 min and duration of action 2–10 hrs; may be administered in coronary blood vessels by special systems in clinic; is used for the prevention as well as for the termination of an angina pectoris attack.

Isosorbide mononitrate begins to act in 15–30 min and acts during 6–12 hrs; is an active metabolite of isosorbide dinitrate and has better bioavailability; is used for the prevention of an angina attack.

CALCIUM CHANNEL BLOCKERS

Calcium channel blockers (calcium antagonists) are preparations which block calcium channels of L-type and cause an antianginal, antiarrhythmic and antihypertensive action.

CLASSIFICATION

According to the chemical structure

1. Phenylalkylamines:
   – Verapamil.
2. Dihydropyridines:
   – Nifedipine (Phenigidine);
   – Amlodipine.

3. Benzodiazepines:
   – Diltiazem.

According to generations

1. The first generation:
   – Verapamil;
   – Nifedipine;
   – Diltiazem.
2. The second generation:
   – Nifedipine-retard.
3. The third generation:
   – Amlodipine.

Mechanism of action

These drugs block voltage-gated L-type calcium channels and decrease Ca^{++} entry in the cells of the myocardium and smooth muscles of the blood vessels (Fig. 17.5).

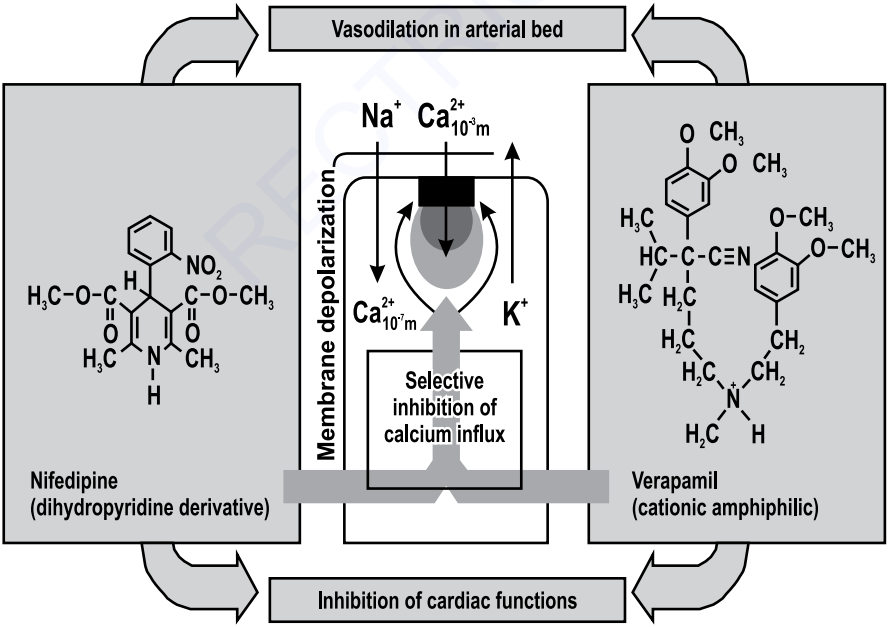

Fig. 17.5. Mechanism of action of calcium channel blockers *(by H. Lüllmann, 2000)*

Reduction of intracellular calcium concentration leads to a decrease in the activation of Ca^{++}-ATP-ase, a decrease in phosphate utilization, deceleration of slow diastole depolarization of membranes.

The result is a decrease in the contractility, excitability, and automaticity of the myocardium, relaxation of smooth muscles and dilation of blood vessels.

Pharmacodynamics

- the dilation of blood vessels, the reduction of total peripheral resistance, the redistribution of blood in the body, a decrease in the load on the myocardium resulting in ***a decrease of oxygen consumption;***
- the dilation of coronary arteries and arterioles resulting in ***an increase of oxygen supply;***
- a decrease in AV and SA node conduction, the prolongation of the effective refractory period within the AV node resulting in ***antiarrhythmic action;***
- the dilation of peripheral blood vessels resulting in a decrease of BP and an ***antihypertensive action;***
- an antiplatelet action and a decrease in blood viscosity;
- the relaxation of the smooth muscles of the uterus, bronchi, and gut.

Indications

- angina pectoris;
- hypertension;
- tachyarrhythmia.

PECULIARITIES OF PREPARATIONS

Verapamil is a calcium channel blocker from the first generation; is administered orally and IV; is well absorbed in the GI tract; develops a peak concentration in 1–2 hrs; has a half-life of 3–6 hrs; undergoes first-pass biotransformation in the liver; is excreted with urine; has a strong action on the heart rate as well as vasodilation; is used for the treatment of tachyarrhythmia, angina pectoris, hypertension, for the termination of arrhythmia paroxysm; may cause AV-block, heart failure, an increase in digitalis toxicity when it is given together with digitalis preparations.

Nifedipine is a calcium channel blocker from the first generation; is administered orally and sublingually; begins to act in 10 min after the sublingual administration; displays peak level in 30 min; has a half-life of 3–6 hrs; has strong vasodilation and weak action on the heart rate; is used for angina pectoris, especially for Prinzmetal's angina, for the control of hypertension; may cause reflexive tachycardia, hypotension, peripheral edema.

Amlodipine is a calcium channel blocker from the third generation; is taken orally; is absorbed in the GI tract more fully and slower than nifedipine; binds to plasma proteins stronger; is metabolized minimally; has long period of half-excretion; does not cause tachycardia.

DRUGS DECREASING OXYGEN DEMAND OF MYOCARDIUM

β-ADRENOBLOCKERS

These preparations block β-adrenoceptors and limit adrenergic stimulation of the heart (Fig. 17.6). In such a way, they decrease the heart rate, striking and minute volume of the myocardium. The result is a decrease in the consumption of oxygen by the myocardium that leads to the limitation of ischemia and hypoxia in the heart muscle.

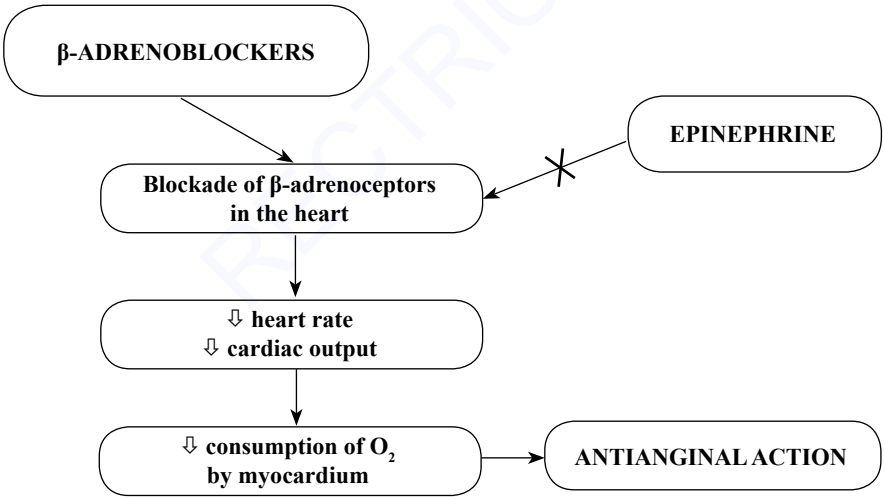

Fig. 17.6. Antianginal action of β-adrenoblockers

PECULIARITIES OF PREPARATIONS

Propanolol (Anaprilin) is administered orally, IV; is absorbed in the GI tract; binds to proteins in the blood plasma; penetrates CNS; acts during 3–4 hrs; blocks

both β_1- and β_2-adrenoceptors; decreases the heart contractility, striking and minute volume, as a result, ***decreases the consumption of oxygen*** by myocardium **(*antianginal* effect)**; decreases the excitability and conductivity of the myocardium, decreases the heart rate ***(antiarrhythmic effect)***; decreases cardiac output and renin's secretion in the kidney, thus lowers BP ***(antihypertensive effect)***; also decreases intraocular pressure; has a sedative action; is used to treat ischemic heart disease (the prevention of an angina pectoris attack, myocardial infarction), supraventricular tachyarrhythmia, hypertension, hyperthyroidism, migraine and glaucoma, has side effects, such as: bradycardia, AV block, heart failure, hypotension, worsen of peripheral blood circulation, spasm of the bronchi, gastric ulcer, hypoglycemia (when insulin is co-administered), weakness and drowsiness.

Metoprolol has a cardioselective action on β_1-receptors; is taken orally for the treatment of hypertension, angina pectoris, and arrhythmia, may be administered IV in acute cases, has less side effects than propranolol, does not produce spasm of the bronchi and the stimulation of gastric secretion, may be used in patients with bronchial asthma, ulcerative disease, and diabetes mellitus.

Talinolol has a cardioselective action on β_1-receptors, has inner sympathomimetic activity and a membrane stabilizing effect (does not inhibit the heart contractility and conductivity), has less side effects and less contraindications connected with the influence on β_2-adrenoceptors.

Atenolol is a preparation of the cardioselective action (on β_1-receptors), is similar to metopolol, but acts longer, does not penetrate CNS.

DRUGS INCREASING OXYGEN SUPPLY IN MYOCARDIUM

VALIDOL

- is a menthol derivative;
- is taken sublingually;
- has a reflexive mechanism of action: irritates sensitive nerve endings in the oral mucous membrane and initiates reflex changes in the vasomotor center activity, thus dilates coronary blood vessels, ***increases the oxygen supply*** in the myocardium and terminates an angina attack;
- is less active than nitroglycerine;
- is used for the termination of an angina pectoris attack;
- has no significant side effects; may cause glossitis if it is taken very often.

DIPYRIDAMOLE

- is administered orally or IV;
- inhibits adenosine desaminase, decreases the reuptake of adenosine by myocardiocytes and erythrocytes, increases the concentration of adenosine in plasma resulting in the dilation of coronary vessels and ***an increase in the oxygen supply;***
- produces the dilation of coronary vessels, an increase in the amount of collateral vessels in the myocardium, the improving of coronary blood flow; an increase in coronary sinus oxygen saturation, antiplatelet action;
- is used for the prevention of an angina pectoris attack (is less effective than nitrates and other drugs), for the prevention of thrombosis and re-thrombosis in patients with atherosclerosis or prosthetic cardiac valves; for the treatment of disturbances of cerebral and peripheral blood circulation;
- may cause side effects, such as hypotension, flushing of the skin, headache, dyspepsia, a syndrome of "stealing" in the myocardium (the dilation of normal coronary vessels is more intensive than that of vessels with atherosclerotic lesions and the drug redistributes coronary blood flow in favor of the normal areas of the myocardium with the worsening of blood supply in the area of ischemia) (Fig. 17.7).

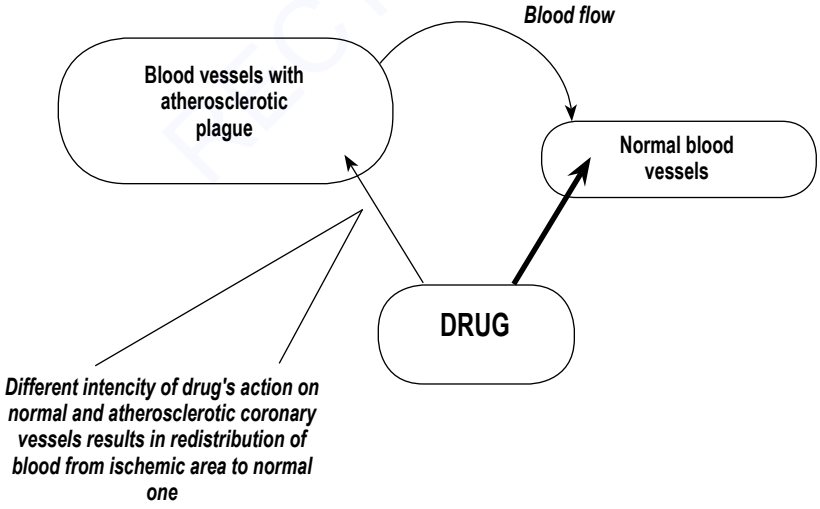

Fig. 17.7. Mechanism of "stealing" syndrome

PAPAVERINE

- is an isoquinoline derivative, an opium alkaloid
- is taken orally, IM, IV; acts about 4 hrs
- is phosophodiesterase inhibitor, increases the cAMP concentration in cells by which dilates coronary and systemic blood vessels, relaxes smooth muscles
- produces the dilation of coronary blood vessels and ***an increase in the oxygen supply***; the dilation of systemic vessels and a decrease in BP; a decrease in a spasm of smooth muscles in the gut, biliary and urinary pathways
- is used for the prevention of an angina attack (the effectiveness is low), hypertension, spasms of smooth muscles and colic
- may cause weakness, somnolence, constipation, disturbances of AV-conduction in high doses or a syndrome of "stealing".

DROTAVERINE (NO-SPA)

Drotaverine is a phosphodiesterase inhibitor. It is more potent and less toxic than papaverine, but in angina pectoris is also used rarely, because the efficacy is low.

DRUGS ACTING ON MYOCARDIUM METABOLISM

Drugs acting on metabolism in the myocardium are additional drugs in the treatment of angina pectoris.

PECULIARITIES OF PREPARATIONS

Mildronate (Meldonium) is a drug improving metabolism and energy supply of tissues, synthetic analogue of γ-butyrobetaine; inhibits γ-butyrobetaine hydroxinase, reduces the synthesis of carnitine and transport of long-chain fatty acids through the cell membranes, prevents accumulation of activated forms of non-oxidized fatty acids, restores the balance between oxygen delivery and its consumption in the cells, warns violation of ATP transport; activates glycolysis, stimulates production of nitric oxide in the vascular endothelium; pharmacological effects include reducing the mental and physical overstrain, cardioprotective action, vasodilation, activation of immunity, reducing blood glucose concentration and prevention of diabetic complications. antihypoxic and anticonvulsant effects; is used in angina pectoris, myocardial infarction, CHF, stroke and cerebrovascular insufficiency, reduced working capacity, abstinence syndrome and vascular diseases of the eye; has minimal side effects; is contraindicated to sportsmen as doping.

Trimetazidine is antiischemic metabolic agent which improves myocardial glucose utilization through the inhibition of fatty acid metabolism by blocking of g-chain 3-ketoacyl-CoA thiolase (fatty acid oxidation inhibitor): has antianginal, coronarolytic, antihypoxic, and neuroprotective effects; is used for prevention of angina attacks as well as for the treatment of cardiac ischemia; chorioretinal vascular disorders, vertigo of vascular origin, dizziness in Meniere's disease and tinnitus; has high safety and tolerability profile.

ATP-long is a complex compound of ATP and metals (sodium and magnesium); is taken orally; is well absorbed in the gut; enhances ATP content in the myocardium; limits ischemia; improves contractility; has antiarrhythmic action; is the additional drug in prophylaxis of the angina attack.

Corvitin contains bioflavonoid quercetin, which modulates the activity of enzymes involving in the degradation of phospholipids, influencing free radical processes and nitric oxide biosynthesis; has antioxidant, anti-inflammatory, antiallergic, anticancer, and cardioprotective effects, increases force and normalizes the rhythm of the heart; it is administered by IV infusion in myocardial infarction, decompensation of CHF, acute and chronic ischemic disturbances of cerebral circulation, reperfusion syndrome under the surgical treatment of obliterating atherosclerosis of the aorta and peripheral arteries.

TREATMENT OF ANGINA IN PATIENS WITH CONCOMITANT DISEASES

The choice of drugs for the treatment of angina pectoris is grounded on the form of the disease (stable, non-stable, varient) as well as on the presence of concomitant diseases (Table 17.1).

PRINCIPLES OF TREATMENT OF MYOCARDIAL INFARCTION

Myocardial infarction is a formation of the area of necrosis in the myocardium due to local ischemia resulting from the obstruction of blood vessel, most commonly by thrombus or embolus. It manifests by persistent intense cardiac pain, diaphoresis, pallor, hypotension, faintness, nausea, vomiting. Myocardial infarction may be complicated by acute heart failure and cardiogenic shock.

Main groups of preparations for the treatment of myocardial infarction and goals of their administration:

- for analgesia: narcotic analgesics, nitrous oxide;
- for a decrease in ischemia: organic nitrates (nitroglycerine), β-adrenoblockers;

Table 17.1. **Choice of drugs for angina pectoris with concomitant diseases**

Concomitant disease	*Drugs commonly used in treating angina*
None	Long-acting nitrates, β-adrenoblockers, calcium channel blockers
Recent myocardial infarction	Long-acting nitrates, β-adrenoblockers
Bronchial asthma	Long-acting nitrates, calcium channel blockers
Hypertension	Long acting nitrates*, β-adrenoblockers, calcium channel blockers
Diabetes	Long acting nitrates, calcium channel blockers
Chronic renal diseases	Long-acting nitrates, β-adrenoblockers*, calcium channel blockers*

***** – less effective drugs.

- for a decrease in arrhythmia: antiarrhythmics (lidocaine, amiodarone, polarizing solution), β-adrenoblockers;
- for the inhibition of blood coagulation: anticoagulants (heparin);
- for the lysis of thrombus: thrombolytics: (streptokinase, alteplase);
- for a decrease in acute heart failure: inotrtopic drugs (dobutamine), vasodilators.

TESTS FOR SELF-CONTROL

1. Nitroglycerine causes all the listed side effects, except:
A. The delay of AV conduction
B. Reflex tachycardia
C. Tolerance
D. Hypotension
E. Headache.

2. A calcium channel blocker for the treatment of hypertension and angina pectoris is:
A. Nitroglycerine
B. Nifedipine

C. Drotaverine
D. Papaverine.
E. Propranolol.

3. The drugs for emergency help in an angina pectoris attack are:
A. Propranolol
B. Verapamil
C. Validol
D. Isosorbide dinitrate
E. Nitroglycerine.

4. The following statements concerning antianginal drugs are true:
A. Isosorbide mononitrate is an active metabolite of isosorbide dinitrate
B. Calcium channel blockers cause a "stealing syndrome"
C. Propranolol is a long-acting nitrate
D. Validol has a reflexive mode of action
E. Dipyridamol is a coronarolytic and antiplatelet drug.

5. A patient with ischemic disease has not informed the doctor that he had had attacks of bronchospasm. A doctor prescribed a drug which has made the attacks of angina pectoris less frequent, but the attacks of bronchospasm have become more frequent. What medicine has been prescribed?
A. Atenolol
B. Propranolol
C. Verapamil
D. Diltiazem
E. Isosorbide dinitrate.

Answers:

1 – A; 2 – B; 3 – C, D, E; 4 – A, D, E; 5 – B.

Chapter 18 ANTIARRHYTHMICS

CARDIAC RHYTHM AND ITS DISORDERS

Each heart beat originates as an electrical impulse from a small area of tissue in the right atrium of the heart called the sinus node or sinoatrial node (SA-node) (Fig. 18.1). The impulse initially causes both of the atria to contract, then activates the atrioventricular (or AV) node which is normally the only electrical connection between the atria and the ventricles or main pumping chambers. The impulse then spreads through both ventricles via the His-Purkinje fibers causing a synchronized contraction of the heart muscle, and thus, the pulse.

The ***cardiac action potential*** is a specialized action potential in the heart. There are 5 phases in cardiac AP (Fig. 18.2).

The resting membrane potential is caused by the difference in ionic concentrations and conductances across the membrane of the cell during phase 4 of the AP. The normal resting membrane potential in the ventricular myocardium is about –85 to –95 mV. This potential is determined by the selective permeability of the cell membrane to various ions. The membrane is most permeable to K^+ and relatively impermeable to other ions. If the resting membrane potential becomes too positive, the cell may not be excitable, and conduction through the heart may be delayed, increasing the risk for arrhythmias.

Phase 0 is a rapid depolarization phase. This phase is due to the opening of the fast Na^+ channels causing a rapid increase in the membrane conductance to Na^+ (Table 18.1). ***Phase 1*** of the AP occurs with the inactivation of the fast Na^+ channels. The transient net outward current causing the small downward deflection of the AP is due to the movement of K^+ and Cl^- ions. ***Phase 2*** (the "plateau" phase) of the cardiac AP is sustained by a balance between the inward movement of Ca^{++} through L-type calcium channels and the outward movement of K^+ through the

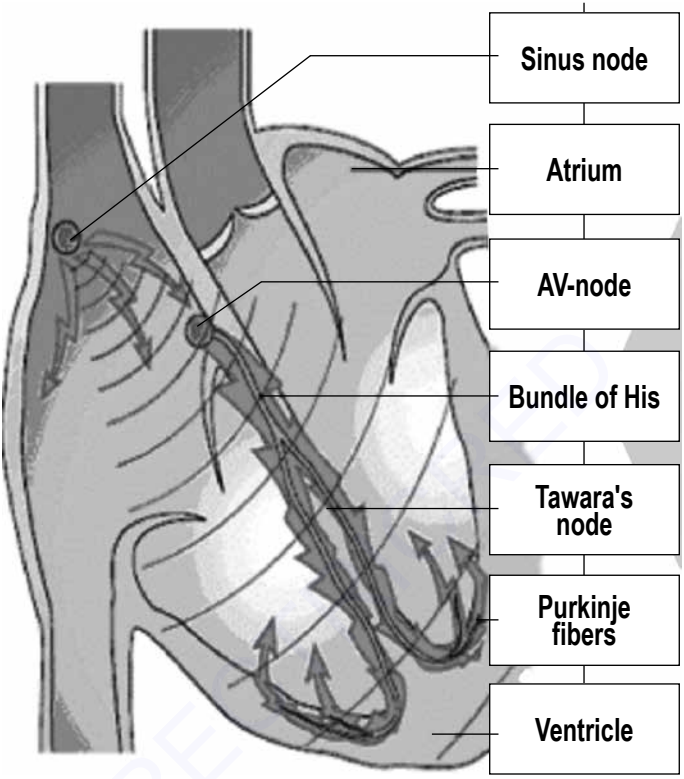

Fig. 18.1. Electrical conduction system of the heart *(http://www.picsearch.com)*

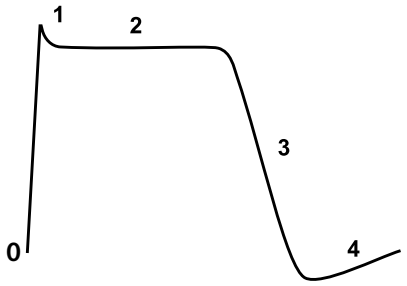

Fig. 18.2. Cardiac action potential (Phases 0–4)

Table 18.1. **Ionic currents and states of Na^+channels during cardiac action potential**

Phase of action potential	***Ionic currents***	***States of Na^+-channels***
Phase 0	Fast Na^+ entry	Open (active)
Phase 1	K^+ and Cl^- movement	Closed, opening impossible (inactivated)
Phase 2	Slow Ca^{++} entry, outward K^+ movement	Closed, opening impossible (inactivated)
Phase 3	K^+ efflux	Closed, partly can be activated
Phase 4		Closed, opening possible

slow delayed rectifier potassium channels. During ***Phase 3*** (the "rapid repolarization" phase) of the AP, the L-type Ca^{++}-channels close, while the slow delayed rectifier K^+-channels are still open. The delayed rectifier K^+-channels close when the membrane potential is restored to about -80 to -85 mV. ***Phase 4*** is slow spontaneous depolarization during diastole caused by an inward positive current of Na^+ and Ca^{++}.

Cardiac arrhythmia *(also* ***dysrhythmia)*** is a term for any from a large and heterogeneous group of conditions in which there is abnormal electrical activity in the heart. They may occur due to the disturbances of impulse formation, disturbances of impulse conduction, or both.

Any part of the heart that initiates an impulse without waiting for the SA-node is called an ***ectopic focus.*** Premature beat caused by an impulse from the ectopic focus is named ***extrasystole***.

Re-entry arrhythmias occur when an electrical impulse recurrently travels in a tight circle within the heart, rather than moving from one end of the heart to the other and then stopping. Re-entry circuits are responsible for atrial flutter, most paroxysmal supraventricular tachycardias, and dangerous ventricular tachycardia.

When an entire chamber of the heart is involved in a multiple micro-reentry circuits, and therefore quivering with chaotic electrical impulses, it is said to be in ***fibrillation***.

There are many kinds of heart arrhythmias. The heart beat may be too fast or too slow, and may be regular or irregular. Some arrhythmias are life-threatening medical emergencies that can result in a cardiac arrest and sudden death. They are divided into ***tachyarrhythmias*** with the heart rate of more than 80 beats per min and ***bradyarrhythmias*** when the rate is less than 60 beats per min. According to the site of initiation arrhythmias may by atrial and ventricular. Paroxismal atrial tachyarrhythmia, atrial flutter, ventricular flutter, atrial fibrillation, extrasystolia,

ventricular fibrillation belong to tachyarrhythmias. Bradycardia is often associated with AV-block.

Restoration of the heart rate may be achieved by pharmacotherapy or cardioversion (an electrical shock).

ANTIARRHYTHMIC DRUGS

Antiarrhythmics are a group of pharmaceuticals that are used to suppress fast rhythms of the heart (cardiac arrhythmias), such as atrial fibrillation, atrial flutter, ventricular tachycardia, and ventricular fibrillation.

VAUGHAN WILLIAMS ANTIARRHYTHMICS CLASSIFICATION

The ***Vaughan Williams classification*** is one of the most widely used classification schemes for antiarrhythmic agents. ***Antiarrhythmics designed for the treatment of tachyarrythmias are classified on the base of their electrophysiological effects***. They are represented by 4 classes. Class I drugs exert their effect by the inhibition of Na^+-channels: subclass IA-blocks Na^+-channels which are in the open state; subclass IB – both in activated and inactivated states; subclass IC includes the most potent agents with a more significant action on the open channels. Class II drugs increase the refractory period of the AV-node. Drugs of the class III block K^+-channels resulting in the prolongation of repolarization (Phase 1 and 3). Class IV blocks Ca^{++} slow inward movements during Phase 2, thus increasing the duration of the refractory period.

This scheme classifies a drug based on the primary mechanism of its antiarrhythmic effect. However, its dependence on primary mechanism is one of the limitations of this classification, since many antiarrhythmic agents have multiple action mechanisms. Another limitation is a lack of consideration within the classification system for the effects of drug metabolites. A historical limitation was that drugs, such as digoxin and adenosine – important antiarrhythmic agents – had no place at all in the Vaughan Williams classification system. This has since been rectified by the inclusion of class V.

CLASSIFICATION

A. *Class I. Membrane-stabilizing agents (Na^+ channel blockers):*

1. Subclass IA:
   - Quinidine;

- Procainamide;
- Disopyramide.

2. Subclass IB:
   - Lidocaine;
   - Phenytoin;
   - Mexiletine.
3. Subclass IC:
   - Propafenone;
   - Flecainide;
   - Ethacyzin.

B. *Class II. β-adrenoblockers:*
- Propranolol;
- Metoprolol.

C. *Class III. K^+-channel blockers:*
- Amiodarone;
- Dronedarone;
- Bretylium;
- Sotalol.

D. *Class IV. Ca^{++}-channel blockers (agents that affect the AV-node):*
- Verapamil;
- Diltiazem.

E. *Class V. Agents of other or unknown mechanisms:*
1. Cardiac glycosides:
   - Digitoxin;
   - Digoxin.
2. Potassium preparations:
   - Panangin.
3. Magnesium preparations:
   – Rythmocor;
   – Magnesium orotate:
4. Adenosine.

CLASS I. MEMBRANE-STABILIZING AGENTS SUBCLASS IA

Mechanism of action

- class IA-agents block the fast Na^+-channels and inhibit Na^+ influx;
- blocking of these channels depresses the Phase 0 depolarization, which prolongs the AP duration by slowing conduction (Fig. 18.3);

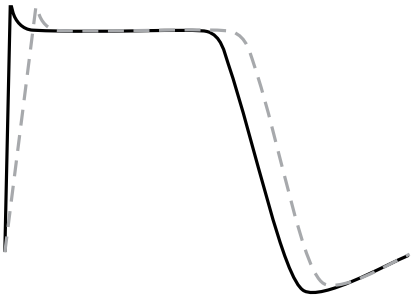

Fig. 18.3. Effect of class IA antiarrhythmic agents on cardiac action potential

- agents in this class also cause decreased conductivity and increased refractoriness.

Indications

- supraventricular tachycardia;
- ventricular tachycardia;
- symptomatic ventricular premature beats;
- the prevention of ventricular fibrillation.

PECULIARITIES OF PREPARATIONS

Qiunidine is an alkaloid, isomeric form of quinine; is taken orally, has the duration of action of 6–8 hrs; inhibits excitability, automaticity, and conductivity in the atria, AV node, bundle of His and Purkinje fibers, inhibits ectopic arrhythmias, ventricular arrhythmias caused by increased normal automaticity, prevents re-entry arrhythmias, decreases the contractility of the myocardium, has M-cholinoblocking properties and can induce tachycardia in normal individuals; is used in the treatment of atrial, AV-junctional, and ventricular arrhythmias, is applied to maintain the sinus rhythm after the direct current cardioversion; may cause the deformation of the QRS complex, some kinds of ventricular tachyarrhythmia, heart block, asystole, heart failure, hypotension, weakness, headache, vision disturbances, spastic pain in the abdomen, nausea, vomiting, diarrhea, hemolytic anemia (as a manifestation of idiosyncrasy), thrombocytopenia, skin rash or itch; is contraindicated to patients with hypersensitivity, AV-block, poisoning with cardiac glycosides, serious disturbances of ventricular conduction, hypotension, hypokalemia and pregnancy.

Procainamide is a procaine derivative; is administered orally, IM, IV, has a half-life of 2–3 hrs, is acetylated in the liver to N-acetylprocainamide which has

properties of class III drug; is not toxic, does not inhibit contractility; may cause side effects, such as AV-block, reversible lupus erythematosus-like syndrome, nausea, vomiting, seizures, asystole, and the induction of ventricular arrhythmias (in overdose). Procainamide can be used in the treatment of atrial fibrillation in the setting of Wolff – Parkinson – White (WPW) syndrome, and in the treatment of a wide complex of hemodynamically stable tachycardias. While procainamide and quinidine may be used in the conversion of atrial fibrillation to the normal sinus rhythm, they should only be used together with an AV-node blocking agent.

Disopyramide is similar to quinidine; is administered orally and parenterally (IV); increases the refractory period in atria, inhibits conduction in the bundle of His, produces a negative inotropic effect (which is greater than the effect of quinidine and procainamide), has M-cholinoblocking properties; is used in atrial and ventricular premature beats, supraventricular tachyarrhythmia, is more effective in the treatment of ventricular arrhythmia; may cause worsening of arrhythmia, heart failure, hypotension, dry mouth, blurred vision, retention of urination, headache and allergic reactions; is contraindicated in AV-block, denominated bradycardia, heart failure or cardiogenic shock.

SUBCLASS IB

Mechanism of action

- class IB antiarrhythmic agents are Na^+-channel blockers;
- they increase membranes permeability for the influx of K^+ and decrease the permeability for K^+ efflux;
- class IB agents have fast onset and offset kinetics, meaning that they have a little or no effect at slower heart rates, and more effects at faster heart rates;
- class IB-agents shorten the AP duration and reduce refractoriness (Fig. 18.4).

Indications

- ventricular tachycardia;
- symptomatic premature ventricular beats;
- the prevention of ventricular fibrillation.

PECULIARITIES OF PREPARATIONS

Lidocaine is a local anesthetic; is administered IV, IM, by IV infusion, is widely distributed in the body tissues, is metabolized in the liver, is excreted with urine, acts during 6–8 hrs; blocks Na^+-channels, increases K^+ efflux, accelerates repolarization, inhibits Phase 2, inhibits Phase 4 in Purkinje fibers, that's why decreases

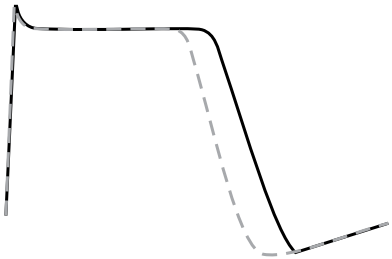

Fig. 18.4. Effect of class IB antiarrhythmic agents on the cardiac action potential

their automaticity, decreases the re-entry; unlike quinidine, lidocaine suppresses arrhythmias caused by abnormal automaticity, does not influence the atria; is more effective in ventricular tachyarrhythmia; is the drug of choice for the emergency treatment of cardiac arrhythmias; may cause vertigo, disturbances of consciousness, seizures, suppression of respiration, nausea, vomiting, hypotension, collapse, bradycardia, arrhythmia, asystole, shock and allergy; is contraindicated in hypersensitivity, epilepsy, AV-block, bradycardia and weakness of the SA-node.

Mexiletine is a stable preparation; is taken orally; is used for the chronic treatment of ventricular arrhythmias associated with previous myocardial infarction; may cause nausea, vomiting, nistagmus, blurred vision.

Phenytoin is an antiepileptic drug; is administered orally and IV; in the myocardium it decreases K^+ loss caused by cardiac glycosides, inhibits premature beats in acute poisoning by cardiac glycosides, improves blood circulation in the heart, lowers BP; is used in acute poisoning with cardiac glycosides, heart surgeries or arrhythmias of central origin.

SUBCLASS IC

Mechanism of action

- class IC antiarrhythmic agents markedly depress the Phase 0 repolarization (Fig. 18.5);
- they decrease conductivity, but have a minimal effect on the AP duration;
- of the sodium channel blocking antiarrhythmic agents (the class I antiarrhythmic agents), the class IC-agents have the most potent Na^+-channel blocking effects.

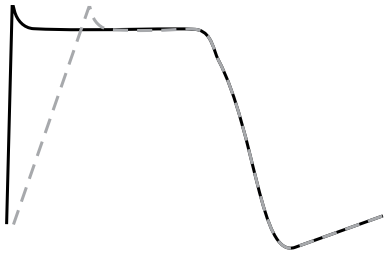

Fig. 18.5. Effect of class IC antiarrhythmic agents on cardiac action potential

Indications

- life-threatening ventricular tachycardia or ventricular fibrillation;
- refractory supraventricular tachycardia (atrial fibrillation).

PECULIARITIES OF PREPARATIONS

Propafenone is administered orally, IV; has membrane-stabilizing properties, is β-adrenoblocker and calcium antagonist, decreases automaticity, inhibits the conduction of excitement in the AV-node, bundle of His and Purkinje fibers; is used in ventricular tachyarrhythmia if other remedies are ineffective; may cause postural hypotension.

Flecainide is taken orally, undergoes minimal biotransformation, and has a half-life of 16–20 hrs; suppresses Phase 0 upstroke in Purkinje and myocardial fibers, causes the slowing of conduction in all cardiac tissues with a minor effect on the duration of AP and refractoriness, reduces automaticity; is used in treating refractory ventricular arrhythmias, is particularly useful in suppressing of premature ventricular contractions; may cause dizziness, blurred vision, headache, nausea, aggravation of CHF and induction of some kinds of dangerous ventricular arrhythmias.

Ethacyzin is an antiarrhythmic drug class IC for oral administration with prolonged action; increases the duration of refractory periods of the atria and AV-node, slows the rate of an increase in AP in the atrial and ventricular fibers of Purkinje, suppresses sinoatrial conduction; has negative inotropic effect, local anesthetic and spasmolytic activity; is indicated in the ventricular and supraventricular extrasystoles, paroxysms of fibrillation and atrial flutter, ventricular and supraventricular tachycardia, including the syndrome of premature ventricular excitation; may cause such side effects as sinus node block, AV-blockade, violation of intraventricular conduction, decreased myocardial contractility and coronary blood flow,

secondary arrhythmia. dizziness, headache, drowsiness; diplopia, paresis of accommodation, nausea, pain in the epigastric area.

CLASS II. β-ADRENOBLOCKERS

Mechanism of antiarrhythmic action

- β-adrenoblockers block β_1-adrenoceptors, prevent the action of catecholamines on the myocardium.
- These drugs diminish Phase 4 depolarization.
- As a result, they prolong the refractory period and decrease conductivity.
- They act by slowing conduction through the AV-node.
- They depress automaticity.
- Thus β-adrenoblockers decrease the heart rate and contractility.

Indications

Tachyarrhythmia caused by increased sympathetic activity
Atrial flutter and fibrillation
AV nodal re-entrant tachycardia.

Side effects

1. AV block
2. Bradycardia
3. Worsening in CHF.

A complete pharmacological characteristics of β-adrenoblockers is presented in Chapter 8.

CLASS III. K^+-CHANNEL BLOCKERS

Mechanism of acion

- Class III agents predominantly block the K^+ channels, thereby prolonging repolarization (Fig. 18.6).
- Since these agents do not affect the Na^+-channel, conduction velocity is not decreased.
- The prolongation of the AP duration and refractory period, combined with the maintenance of normal conduction velocity, prevents re-entrant arrhythmias.
- Class III antiarrhythmic agents exhibit reverse use dependent prolongation of the AP duration. This means that the refractoriness of the ventricu-

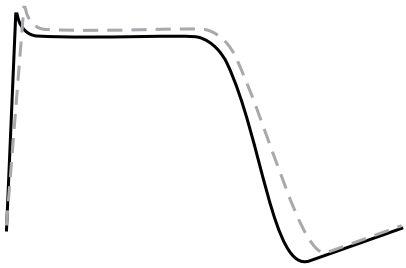

Fig. 18.6. Effect of class III antiarrhythmic agents on cardiac action potential

lar myocyte increases at lower heart rates. This increases the susceptibility of the myocardium to early after-depolarizations at low heart rates. Antiarrhythmic agents that exhibit reverse use-dependence are more efficacious at preventing a tachyarrhythmia that converting someone into normal sinus rhythm. Because of the reverse use-dependence of class III agents, at low heart rates class III antiarrhythmic agents may paradoxically be more arrhythmogenic.

PECULIARITIES OF PREPARATIONS

Amiodarone is a benzofuran derivative, contains iodine and is related structurally to thyroxine; is administered orally or IV; binds to plasma proteins (95% of the drug), is metabolized in the liver (main metabolite is desethylamiodarone which strengthens the antiarrhythmic action of the drug), is excreted with bile, has a half-life of 20–100 days; displays complex effects showing class I, II, III, and IV actions, blocks K^+-channels, blocks Ca^{++} and Na^+-channels; modifies the condition of α- and β-adrenoceptors as well as glucagons receptors (non-competitive antagonism); increases the duration of AP and the refractory period in the ventricular and atrial muscle; has an antiarrhythmic action; produces systemic and coronary vasodilation resulting in antianginal action; is used for the treatment of ventricular arrhythmia, ventricular fibrillation in patients of the risk group, supraventricular tachyarrhythmias, angina pectoris; myocardial infarction, for the prevention of sudden coronary death; may cause side effects, such as pulmonary fibrosis (reversible), bradycardia, AV-block, phototoxicity, corneal microdeposits and blurred vision, hyper- and hypothyroidism, ataxia, tremor, myopathy and neuropathy, anorexia, nausea, vomiting; is contraindicated in patients with sinus bradycardia, AV block, syndrome of sinus node weakness, diseases of the thyroid gland, pulmonary

fibrosis, hypersensitivity to iodine, pregnancy, lactation. The course of treatment must have a provision of two days "drug-free interval" every week.

Dronedarone is an antiarrhythmic indicated to use in adult patients in a stable clinical condition, who have previously suffered or are having atrial fibrillation; has chemical structure similar to amiodarone, but without iodine and with lower lipophilicity; is multichannel blocker of K^+-, Na^+-, and Ca^{++}-channels, is non-competitive antagonist of adrenergic receptors; reduces BP and myocardium contractility, has vasodilating action that is more pronounced in the coronary arteries; can cause CHF, bradycardia, dysgeusia, liver lesions, diarrhea, vomiting, nausea, abdominal pain, dyspepsia, dermatitis and asthenia; provokes risk of cardiovascular death after the long usage.

Bretylium tosilate is administered IV, IM, is excreted unchanged with urine; has a potent antiarrhythmic effect in ventricular arrhythmias; increases the duration of the refractory period in Purkinje fibers, has a sympatholytic action, decreases BP; is used for ventricular fibrillation, mainly in the acute period of myocardial infarction or in the resistance to electrical defibrillation; may cause severe postural hypotension, transitory tachycardia and ectopic beats, nausea, vomiting; is contraindicated in pheochromocytoma, acute disorders of brain blood circulation, hypotension, collapse, severe renal failure, aortal stenosis, pulmonary hypertension, pregnancy and lactation.

Sotalol is a β-adrenoblocker and antiarhythmic of class III; is administered orally and IV; is effective in many cases of supraventricular tachyarrhythmia, especially in atrial fibrillation, supraventricular tachycardia, the WPW syndrome, ventricular tachycardia; is more effective than class I drugs in preventing of arrhythmia recurrence and in decreasing of mortality in patients with sustained ventricular tachycardia; has side effects connected with β-adrenoblocking properties (bradycardia, worsening in CHF).

CLASS IV. Ca^{++}-CHANNEL BLOCKERS

Mechanism of antiarrhythmic action

- Ca^{++}-channel blockers block calcium channels of L-type;
- they inhibit Ca^{++} entry into the cells of the conductive system in the heart;
- result is the inhibition of automaticity and re-entry;
- they do not act on the conductivity.

Indications

Supraventricular tachyarrhythmia
Fibrillation of atria, atrial flutter

Paroxismal tachycardia.

Common properties of Ca^{++}-channel blockers and peculiarities of some preparations are described in Chapter 17.

CLASS V. AGENTS OF OTHER OR UNKNOWN MECHANISMS

CARDIAC GLYCOSIDES

Cardiac glycosides (e.g., digoxin) shorten the refractory period in atrial and ventricular myocardial cells while prolonging the effective refractory period and diminishing conduction velocity in Purkinje fibers.

They are used to control the ventricular response rate in atrial fibrillation and flutter.

Other pharmacological properties of cardiac glycosides are described in Chapter 16.

POTASSIUM AND MAGNESIUM PREPARATIONS

Potassium preparations (e.g., ***Panangin***) increase the speed of spontaneous depolarization in SA- and AV-nodes as well as in all conduction system, thus inhibits the automaticity. They also normalize Phase 0. These drugs are used to treat tachyarrhythmias, especially caused by hypokalemia.

Magnesium preparations ***(Magnesium orotete)*** and combined drugs containing magnesium and potassium ***(Rythmocor)*** also can be used.

ADENOSINE

Adenosine is a nucleoside which is administered IV and have a very rapid and short action, is uptaken by red blood cells. It stimulates A_1-adenosine receptors in the SA-node. In high doses, adenosine decreases conduction velocity, prolongs the refractory period, and decreases the automaticity in AV-node. It is the drug of choice for abolishing acute supraventricular tachycardia. Adenosine is not toxic, but may cause flushing, chest pain and hypotension.

DRUGS FOR BRADYARRHYTHMIA AND AV BLOCK

CLASSIFICATION

1. M-cholinoblockers:
   – Atropine.
2. Adrenomimetics:
   – Isoprenaline;
   – Ephedrine.

PECULIARITIES OF PREPARATIONS

Atropine is a non-selective M-cholinoblocker, has a dose-dependent action on the heart rate. At low doses, the predominant effect is a decreased heart rate (bradycardia) due to blockade of M_1-receptors on the inhibitory pre-junctional neurons. With higher doses of atropine, the cardiac receptors on the SA-node are blocked, and the cardiac rate increases (tachycardia).

Isoprenaline is a non-selective β-adrenergic agonist, stimulates β_1-adrenoceptors in the heart and increases the heart rate.

Ephedrine is an indirect-acting adrenomimetic, has a presynaptic action, stimulates norepinephrine release and its action on adrenergic receptors in the heart, in such a way increases the cardiac rate and causes tachycardia.

All these drugs are described as autonomics in Chapters 6, 7.

TESTS FOR SELF-CONTROL

1. All of the following correctly characterizes the drugs, except:
A. Procainamide blocks Na^+-channels
B. Amiodarone blocks K^+-channels
C. Verapamil blocks Ca^{++}-channels
D. Bretylium blocks K^+-channels
E. Quinidine blocks Ca^{++}-channels.

2. Incorrect statement concerning lidocaine is:
A. It is administered parenteraly
B. It is class IA antiarrhythmic
C. It is metabolized in the liver
D. It shortens an action potential
E. It is the drug of choice in ventricular fibrillation.

3. The drugs for the maintenance of the cardiac rhythm after the cardioversion are:
A. Quinidine
B. Adenosine
C. Digoxin
D. Procainamide
E. Disopyramide.

4. Adenosine:
A. Is given only IV
B. Has the shortest duration of action
C. Is class III antiarrhythmic
D. Stimulates A_1-adenosine receptors
E. Is used for the termination of acute supraventricular tachyarrhytmia.

5. To maintain the normal sinus rhythm, a patient with atrial fibrillation was prescribed with antiarrhythmic drug containing iodine. This drug has very long duration of action and may cause reversible pulmonary fibrosis and corneal microdeposits. What preparation was prescribed?
A. Procainamide
B. Propranolol
C. Sotalol
D. Amiodarone
E. Mexiletine.

Answers

1 – E; 2 – B; 3 – A, D, E; 4 – A, B, D, E; 5 – D.

Chapter 19 ANTIHYPERTENSIVE DRUGS. HYPERTENSIVE AGENTS

HYPERTENSION

Hypertension is a sustained diastolic blood pressure greater than 90 mm Hg accompanied by an elevated systolic blood pressure (more than 140 mm Hg).

Chronic hypertension leads to:

- congestive heart failure;
- myocardial infarction;
- renal damage;
- cerebrovascular accidents.

Arterial blood pressure is the sum of cardiac output and peripheral resistance. Cardiac output depends on the heart rate and contractility. Peripheral resistance depends on the blood vessels tone and the volume of circulating blood.

Regulation of blood pressure level

Increased sympathetic activity leads to the activation of β_1-adrenoceptors in the heart and results in the enhance of cardiac output. It also causes stimulation of α_1-adrenoceptors and an increase in peripheral resistance.

The renin-angiotensin system takes part in the regulation of vasoconstriction and volume of blood. The activation of this system is caused by the stimulation of angiotensin receptors by angiotensin II. It leads to vasoconstriction, an increase in vascular peripheral resistance, retention of sodium and water. These processes results in the enhance of BP and an increase in the load on the myocardium.

Main links of pathogenesis of hypertension

Hypertension is a result of disregulation in the cardiovascular system and water-electrolytes balance. Its development is connected with:

- disturbances in the ratio between inhibition and stimulation in the cortex of the brain;
- changes in activity of the vasomotor center;
- activation of sympathetic stimulation of the heart and blood vessels;
- changes in the blood vessels wall;
- the activation of renin-angiotensin system;
- an increase in the blood volume.

ANTIHYPERTENSIVE DRUGS

Antihypertensive drugs are drugs for the treatment of hypertension.
Treatment strategies:

- mild hypertension can be controlled with one drug;
- severe hypertension must be treated with a combination of drugs;
- drugs for the combined therapy of hypertension are selected to minimize the side effects of the combined regimen;
- ***"first-line" drugs are diuretics, β-adrenoblockers, inhibitors of angiotensin converting enzyme (ACE), calcium channel blockers, α-adrenoblockers.***

CLASSIFICATION

A. *Neurotropic agents:*

1. Drugs decreasing vasomotor center activity (centrally-acting α_2-adrenomimetics and imidazoline receptor agonists):
   - Clonidine (Clopheline);
   - Methyldopa;
   - Moxonidine.
2. Anti-adrenergic drugs:

a) α-Adrenoblockers:
   - Prazosin;
   - Doxazosin.

b) β-adrenoblockers:
   - Propranolol (Anaprilin);
   - Metoprolol;
   - Atenolol;
   - Bisoprolol.

c) α,β-adrenoblockers:
   - Labetolol;

- Carvedilol.

d) Adrenergic neuron blocking agents (sympatholytics):
   - Reserpine;
   - Guanethidine (Octadine).

3. M-cholinoblocker:
   - Platyphylline.
4. N-cholinoblockers (ganglionic blockers):
   - Hexamethonium;
   - Pentamine.

B. *Myotropic vasodilators:*

1. Ca^{++} channel blockers:
   - Nifedipine;
   - Verapamil;
   - Amlodipine;
   - Diltiazem;
2. Magnesium salts:
   - Magnesium sulfate.
3. Phosphodiesterase inhibitors:
   - Papaverine;
   - Drotaverine (No-Spa);
   - Bendazole (Dibazol).
4. Potasium channel openers:
   - Appressin;
   - Minoxidil;
   - Diazoxide.
5. Other vasodilators:
   - Sodium nitroprusside.

C. *Drugs acting on renin-angiotensin system:*

1. ACE inhibitors:
   - Captopril;
   - Enalapril;
   - Lisinopril;
   - Fosinopril.
2. Angiotensin II receptor antagonists:
   - Losartan;
   - Temisartan.
3. Renin inhibitors:
   - Aliskiren.

D. *Diuretics:*

– Hydrochlorothiazide;
– Furosemide.

DRUGS DECREASING VASOMOTOR CENTER ACTIVITY

CLONIDINE

Pharmacokinetics

- is administered sublingually, orally, IV, IM;
- is completely absorbed in the GI tract;
- after the IV or sublingual administration, begins to act in 5–10 min, after oral administration – in 30–60 min;
- penetrates CNS;
- is metabolized in the liver and excreted with urine;
- acts during 2–12 hrs.

Mechanism of action

- the drug stimulates α_2-adrenoceptors in the CNS;
- the stimulation of presynaptic α_2-adrenoceptors and imidazoline receptors I_1 in the adrenergic sinapses of the vasomotor center results in the inhibition of the norepinephrine release into the synaptic gap and a decrease in sympathetic impulsation to peripheral blood vessels;
- that leads to the dilation of blood vessels, lowering of BP, and slow heart rate.

Pharmacodynamics

- a decrease in BP (antihypertensive action);
- a decrease in the heart rate and cardiac output;
- a decrease in renin activity;
- sedation;
- a decrease in pain;
- a decrease in the intraocular pressure;
- the potentiation of other drugs inhibiting CNS.

Indications

- acute hypertension (hypertension crisis);
- chronic hypertension;

- glaucoma (eye drops);
- migraine;
- pain syndromes;
- chronic alcoholism;
- the potentiation of general anesthesia.

Side effects

1. Weakness, somnolence
2. Hypotension, postural hypotension
3. Transitory elevation of BP after the IV or sublingual administration (resulting from the stimulation of peripheral adrenoceptors)
4. Constriction of blood vessels in the brain
5. Dry mouth
6. Inhibition of gastric secretion
7. Constipation
8. Retention of sodium and water
9. Changes in glucose level in the blood
10. Abolishing syndrome

Contraindications

1. Severe atherosclerosis
2. Job needed a quick reaction
3. Should not be given together with alcohol and psychotropic drugs

METHYLDOPA

- is taken orally, is well absorbed in the GI tract, penetrates CNS, starts to act slowly;
- is similar to norepinephrine by the chemical structure, that's why acts as "a false neurotransmitter" in the CNS: stimulates α_2-adrenocepotors and decreases the norepinephrine release in synapses of the vasomotor center; by this mechanism it decreases activity of the vasomotor center, inhibits sympathetic impulsation to blood vessels, dilates blood vessels and lowers BP (is a centrally acting sympatholytic);
- has an antihypertensive action, improves cerebral blood flow, increases lactation;
- is used for the treatment of hypertension;
- has side effects which are similar to the same of clonidine, also may cause muscular and joint pains, a rise in the body temperature, skin rash and galactorrhea;
- is contraindicated to patients suffering from depression, Parkinson's disease, liver diseases.

MOXONIDINE

- is a selective agonist of the imidazoline receptor I_1 in the medulla of brain; therefore causes a decrease in sympathetic nervous system activity and a decrease in BP;
- It lowers BP, promotes sodium excretion, improves condition of patients with insulin resistance syndrome and prevents renal and cardiac complications of hypertension;
- is a second-line antihypertensive drug for the treatment of mild to moderate essential hypertension;
- may cause dry mouth, headache, fatigue, dizziness, intermittent facial edema, nausea, sleep disturbances, asthenia, vasodilation, and skin reactions.

ANTI-ADRENERGIC DRUGS

α-ADRENOBLOCKERS

Prazosin and ***doxazosin*** selectively block α_1-adrenoceptors, dilate blood vessels, reduce peripheral vascular resistance and decrease BP. They are taken orally for the treatment of mild to moderate chronic hypertension.

β-ADRENOBLOCKERS

β-adrenoblockers (propranolol, metoprolol, etc) are the "first-line" preparations for chronic hypertension. They are taken orally to control hypertension. A full effect develops in several weeks.

Mechanism of antihypertensive action

- β-adrenoblockers lower BP due to blockage of β_1-adrenoreceptors in the heart and a decrease in cardiac output;
- they also block β_1-adrenoreceptors in the kidney and inhibit renin secretion resulting in a decrease of peripheral resistance and blood volume (Fig. 19.1);
- action on cardiac output develops quickly and leads to a decrease in systolic pressure;
- action on renin-angiotensin system develops in few days and leads to a decrease of diastolic pressure and stable lowering of BP.

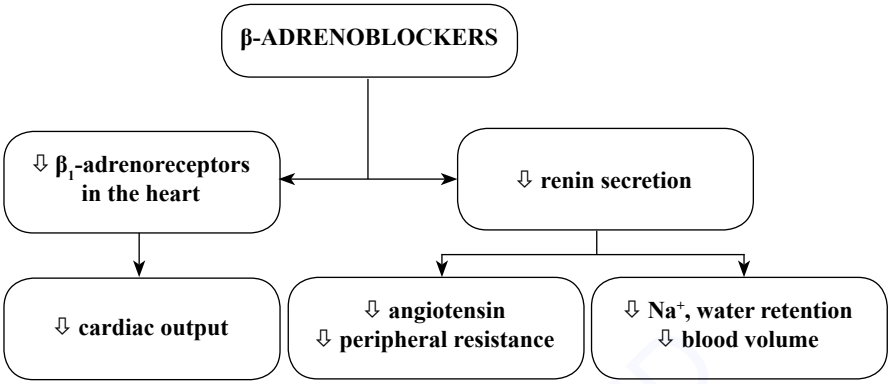

Fig. 19.1. Mechanism of antihypertensive action of β-adrenoblockers

α,β-ADRENOBLOCKERS

Labetalol and ***carvedilol*** act both on α- and β-adrenoceptors, but action on β-receptors is more significant. They produce lowering BP mediated by the blockade of β-adrenoceptors and vasodilation due to blockade of α-adrenoceptors.

SYMPATHOLYTICS

Reserpine acts in the peripheral tissues as well as in the CNS (a sedative and neuroleptic action); is used for mild forms of hypertension; produces sodium and water retention; is combined with thiazide diuretics; may cause disturbances of sleep, depression, and side effects connected with a prevanence of PANS.

Guanethidine is a potent peripherally acting sympatholytic; is used for severe forms of hypertension; begins to act slowly (in 2–4 days after the start of treatment); may cause postural hypotension, and side effects connected with PANS prevalence in the body (bradycardia, spasm of the bronchi, increased activity of the gut).

Adrenoblockers and sympatholytics belong to autonomics and are described in detail in Chapter 8. Cholinergic drugs for the managment of acute and chronic hypertesion are characterized in Chapter 6.

MYOTROPIC VASODILATORS

CALCIUM CHANNEL BLOCKERS

Calcium channel blockers (nifedipine, verapamil, amlodipine) have an antihypertensive action resulting from the dilation of blood vessels and a decrease in peripheral vascular resistance. They are suitable for chronic use in hypertension of any severity. The choice of calcium channel blockers is grounded on the effect of the drug on cardiac pacemakers and contractility as well as on the coexisting diseases (angina pectoris, bronchial asthma, peripheral vascular diseases).

Detail description of these agents is represented in Chapter 17.

MAGNESIUM SALTS

MAGNESIUM SULFATE

- is administered IV, IM (after the oral administration acts as a laxative);
- is an antagonist of calcium ions in the cells;
- has a sedative, hypnotic and narcosis action, the inhibition of the vasomotor center; an antiseizure action, the dilation of blood vessels, and a decrease in BP; an antiarrhythmic action, the dehydratation of tissues, a diuretic action, a decrease in the intracranial pressure; a spasmolytic action is an antidote in acute poisonings with compounds of calcium;
- is used in hypertensive emergency, chronic hypertension, seizures attack, edema of the brain, tachyarrhythmia, myocardial infarction, toxicosis of pregnancy, an overdose of calcium preparations;
- may cause side effects, such as pain and infiltrate in the site of administration (IM), suppression of respiration (IV). If the suppression of respiration is occurred, calcium chloride (IV) and carbogen (inhalation) should be used.

PHOSPHODIESTERASE INHIBITORS

BENDAZOLE (DIBAZOL)

- a synthetic preparation, an imidazole derivative;
- is administered IM, IV, orally; acts during 4–6 hrs;
- inhibits PDE III and increases the amount of cAMP in the cells, that's why produces the relaxation of smooth muscles and dilation of blood vessels;
- has antihypertensive and spasmolytic actions; stimulates functions of the spinal cord; is an interferon inductor;

- is indicated in hypertensive emergency, mild hypertension, spasms of blood vessels, spasms of smooth muscles in the gut, colic, neurological diseases with lesions of the spinal cord and for non-specific prophylaxis of viral infections;
- is combined with papaverine to elevate antihypertensive activity.

POTASSIUM CHANNEL OPENERS

APPRESSIN (HYDRALAZIN)

- is administered orally, IM, IV; begins to act slowly (even after IV administration); is well absorbed in the GI tract; is metabolized in the liver by acetylation; the speed of acetylation in one patient differs from that in another (rapid and slow acetylation); is excreted with urine and feces; acts during 4–12 hrs;
- activates K^+-channels, causes hyperpolarization and the blockage of Ca^{++}-channels, relaxes arteriolar smooth muscles and dilates arteriolar vessels; as a result, decreases peripheral vascular resistance and decreases BP;
- displays an antihypertensive action, increases the heart rate and cardiac output (resulting from reflexes as well as from a direct action on β-adrenoceptors in the heart); elevates pressure in the lung artery; increases renin secretion;
- is used to treat moderate and severe hypertension, CHF;
- is combined with β-adrenoblockers and diuretics;
- causes side effects, such as weakness, headache, tachycardia, worsen in angina, flushing of the skin, sweating, reversible lupus-like syndrome, retention of water and salts.

DIAZOXIDE

- is administered orally, IV; begins to act in 2–5 min after the IV administration; has the duration of action from 2–4 hrs (IV) to 12 hrs (orally);
- is K^+-channel opener, arteriolar vasodilator;
- produces a decrease in BP; a reflexive increase in the heart rate; a decrease in the tone of smooth muscles in the gut and uterus; the inhibition of insulin secretion, a decrease in renal filtration and ureic acid excretion;
- is used to treat hypertensive emergency and chronic hypertension;
- may cause tachycardia, worsening in angina pectoris and diabetes, uricosemia, constipation.

MINOXIDIL

- is a K^+-channel opener, arteriolar vasodilator;
- is more potent than hydralazin;
- is used for severe hypertension, renal failure, alopecia (as ointment);
- may cause hyrsutism as a side effect.

OTHER VASODILATORS

SODIUM NITROPRUSSIDE

- is administered by IV infusion; begins to act within 1 min; stops to act in 5 min after the end of IV infusion;
- contains group NO binding to Fe, that's why the mechanism of action is the same as the mechanism of nitroglycerine; exceeds nitroglycerine's potency in 1000 times; is an arteriolar and venous vasodilator;
- decreases BP; decreases the load on the myocardium; increases cardiac output under the conditions of heart failure; increases the secretion of renin;
- is used in hypertensive emergency, acute heart failure, edema of the lungs, controlled hypotension in surgeries;
- may cause hypotension, nausea, headache, sweating, restlessness and retrosternal pain.

DRUGS ACTING ON RENIN-ANGIOTENSIN SYSTEM

ACE INHIBITORS

Mechanism of action

ACE inhibitors block ACE and disturb the transformation of angiotensin I into angiotensin II.

The result is a decrease of output of the sympathetic nervous system, vasodilation, a decrease in sodium and water retention, enhance in the bradykinin level in blood (Fig. 19.2).

Pharmacodynamics

- vasodilation caused by diminishing of angiotensin II contens and an increase in the bradykinin level in blood;

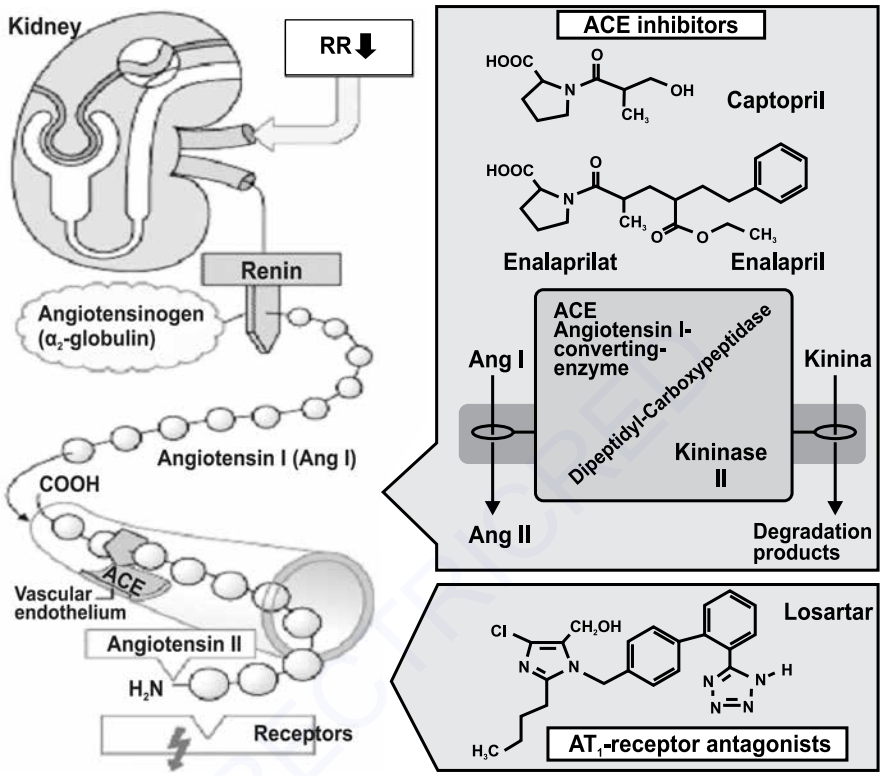

Fig. 19.2. Renin-angiotensin system and mechanism of action of ACE inhibitors and angiotensin II-receptor inhibitors *(by H. Üllmann, 2000)*

- a decrease in the blood volume resulting from the inhibition of the secretion of aldosterone and reducing of its action on sodium and water excretion;
- a decrease in BP resulting from the vasodilation and a decrease of blood volume;
- a decrease in the load on the myocardium;
- an increase in cardiac output under the conditions of heart failure;
- a decrease in oxygen demand of the myocardium;
- the reduction of pressure in blood vessels of the lungs;
- the retention of potassium in the organism.

Indications

- hypertension;
- chronic CHF;
- myocardial infarction.

Side effects

1. Dry cough, spasm of the bronchi (resulting from an increase in the bradykinin level).
2. Skin rash.
3. Fever.
4. Hypotension.
5. Hyperkalemia.
6. Disturbance in the renal function.
7. Altered taste (dysgeusia).

PECULIARITIES OF PREPARATIONS

Captopril is taken orally; reaches peak blood level in 60 min; has the duration of action of 6–8 hrs; is eliminated from the body within 24 hrs; the initial dose can be increased in 1- to 2-week intervals.

Enalapril is more potent than captopril; has the duration of action which is twice as long as that of captopril; is taken orally once or twice a day.

Lisinopril is an active metabolite of enalapril; is absorbed slowly and has a slow onset of action; is taken orally once a day.

Fosinopril is administered as a prodrug and is converted *in vivo* to the active form fosinoprilat; unlike other ACE inhibitors that are primarily excreted by the kidneys, is eliminated from the body by both renal and hepatic pathways, thus it may be used in patients with renal failure; has the highest lipophilicity and the best penetration into tissues, so it is reliable for a long time control BP level during the day and exerts a pronounced organoprotective effect.

ANTAGONISTS OF ANGIOTENSIN RECEPTORS

LOSARTAN

- is taken orally and acts during 6–8 hrs;
- blocks angiotensin II receptors of AT_1-type, dilates blood vessels, decreases BP and load on the myocardium;
- is used for the monotherapy of hypertension and CHF;has less side effects than ACE inhibitors, does not cause dry cough and spasm of the bronchi.

Telmisartan also is an antagonist of AT_1-angiotensin receptors, is slightly more effective than losartan in lowering BP; has better bioavailability and prevalence of hepatic clearance as compared to losartan; displays the longest half-life (24 hrs) between other sartans.

RENIN INHIBITORS

ALISKIREN

- is the first member of the new class of orally active direct renin inhibitors;
- by inhibiting renin, it blocks the conversion of angiotensinogen to angiotensin I, which results in a reduction in angiotensin II concentrations; suppresses the effects of renin and leads to reduction in the plasma renin activity;
- can be used either as monotherapy or in a combination with other antihypertensive agents; combination therapy with angiotensin receptor blockers may provide additional BP-lowering effect compared with the monotherapy;
- is well tolerated; side effects are fatigue, headache, dizziness, diarrhea, nasopharyngitis, and back pain.

DIURETICS

All the oral diuretics are effective in the treatment of hypertension, but thiazides (***hydrochlorothiazide, dichlothiazide***) have found the widest use. They act on the cell basal membrane in proximal tubules and decrease the reabsorption of sodium and chlorides. As a result, they increase sodium, chlorides, potassium and water excretion with urine, decrease the volume of blood and edema of blood vessel wall that leads to a decrease in peripheral resistance and lowering of BP.

Furosemide is a loop diuretic which is used parenterally in hypertensive emergency.

Potassium-sparring diuretics may also be used to treat hypertension. They act in distal tubules, increase excretion of sodium and water, cause the retention of potassium in the body.

DRUGS FOR HYPERTENSION EMERGENCY

For parenteral administration:

– sodium nitroprusside (by IV infusion in severe hypertensive crisis);
– labetalol;
– pentamine;
– furosemide;

– magnesium sulfate;
– bendazole and papaverine;
– diazoxide.

For sublingual administration:

– clonidine;
– nifedipine;
– captopril.

HYPERTENSIVE DRUGS

To treat acute hypotension (collapse, shock) it is used ***α-adrenomimetics*** (noradrenaline, phenylephrine), ***α, β-adrenomimetics*** (adrenaline, ephedrine), ***analeptics*** (camphor, nikethamide).

To treat chronic hypotension it is used ***phenylephrine*** (in the form of tablets), ***analeptics*** (caffeine), ***adaptogens***.

All the listed preparations are described in detail in Chapters 7, 14, 15.

TESTS FOR SELF-CONTROL

1. In hypertensive emergency the drugs of the first choice are:
A. Clonidine + furosemide
B. Metyldopa + dichlothiazide
C. Reserpine + dichlothiazide
D. Guanethidine + dichlothiazide
E. Strophanthin + furosemide.

2. Only one of following drugs is a potent vasodilator realizing its effects through the –NO group:
A. Papaverine
B. Drotaverine (No-spa)
C. Sodium nitropusside
D. Prazosin
E. Captopril.

3. An antihypertensive action of β-adrenoblockers is due to:
A. A decrease of cardiac output
B. The inhibition of the conductivity in the heart
C. A decrease of the oxygen demand in the myocardium

D. A decrease of the renin synthesis in the kidney
E. A decrease of intraocular pressure.

4. The correct statements concerning antihypertensive drugs are:
A. Clonidine is an inhibitor of the vasomotor center activity
B. Diazoxide is a K^+-channel opener, arteriolar vasodilator
C. Guanethidine is a sympatholytic for hypertensive emergency
D. Lisinopril is an active metabolite of enalapril
E. Diuretics are not combined with other antihypertensive drugs.

5. Hypertensive patient was treated with a drug that decreases the vascular tone. His treatment was complicated by persistent dry cough. Which drug was most probably used?
A. Papaverine
B. Phentolamine
C. Captopril
D. Prazosin
E. Clonidine.

Answers

1 – A; 2 – C; 3 – A, D; 4 – A, B, D; 5 – C.

Chapter 20 ANTIATHEROSCLEROTIC DRUGS

ATHEROSCLEROSIS

Atheroscleosis is a chronic disease of arteries which results in the forming of an atheromatous plaque. The atheromatous plaque develops in such stages as the infiltration of the blood vessels wall by cholesterol, local forming of fibrin, development of connective tissue and its calcinosis (Fig. 20.1). The atheromathous plaque causes disturbances in blood flow complicated by myocardial infarction, ischemic insult, aneurism of the aorta, and gangrene of extremities.

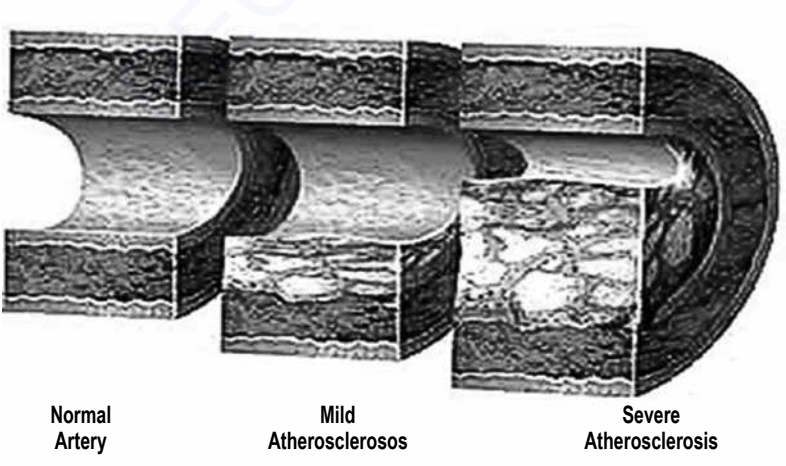

Fig. 20.1. Atheromathous plaque in the blood vessel *(http://www.picsearch.com)*

Main links of pathogenesis

There are four main links in the development of atherosclerosis:
- hyperlipoproteinemia;
- an increase in free radical lipid peroxidation;
- hypercoagulation of blood;
- lesions of endothelium.

Hyperlipoproteinemia

The main classes of lipoproteins are:
– chylomicrones (Chy);
– low density lipoproteins (LDL);
– very low density lipoproteins (VLDL);
– high density lipoproteins (HDL).

Chy, LDL, VLDL are atherogenic lipoproteins. HDL are antiatherogenic lipoproteins. According to laboratory findingds, there are 5 types of hyperlipoproteinemia. Hyperlipoproteinemia of type II–IV leads to the development of atherosclerosis.

Lipid peroxidation

Lipid peroxidation is non-enzymic oxidation initiated by free radicals of oxygen. It destroys cell membranes and leads to the forming of lipid peroxides. An increase in lipid peroxidation and the inhibition of antioxidant protection result in the injuries of the blood vessels wall. Oxidized lipids are taken by macrophages which are transformed into foam cells (components of the atheromathous plaque).

Hypercoagulation of blood

An increase in platelet aggregation and adhesion leads to an increase in blood coagulation and to the sedimentation of fibrin on the site of injured inthima of arteries that is a prediction of the atheromatous plaque.

Endothelium lesions

Normal endothelium has no gaps through which atherogenous lipoproteins and cholesterol can enter the blood vessels wall. The contraction of endothelial cells caused by bradykinin leads to the forming of such gaps and opens the way to cholesterol infiltration of the wall of arteries.

Principles of pharmacotherapy of atherosclerosis

There are the following basic principles of pharmacotherapy of atherosclerosis:
- an early beginning of the treatment;
- a long-durative treatment;
- courses of treatment in the periods of worsening of the disease caused by the season deficit of antioxidants, stress, etc.;

- the choice of preparations according to a leading clinic-laboratory syndrome;
- the oral administration of drugs and their minimal toxicity under the conditions of long-lasting therapy;
- the laboratory control of the effectiveness of treatment.

ANTIATHEROSCLEROTIC DRUGS

Antiatherosclerotic drugs are drugs for the treatment of atherosclerosis. They protect arteries from atherosclerosis and are angioprotectors (Fig. 20.2).

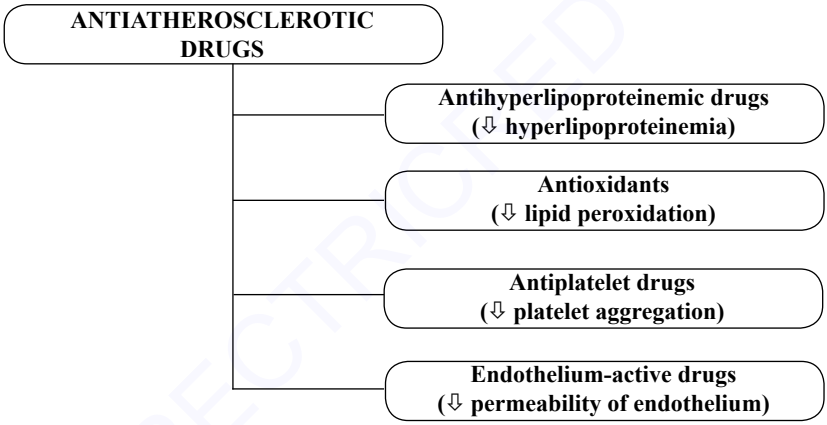

Fig. 20.2. Main groups of antiatherosclerotic drugs

ANTIHYPERLIPOPROTEINEMIC DRUGS

Antihyperlipoproteinemic drugs are preparations for a decrease of blood plasma level of atherogenous lipoproteins and cholesterol.

CLASSIFICATION

1. Drugs interfering with intestinal absorption of cholesterol:
   – Cholestyramine;
   – Ezetimibe.
2. Inhibitors of de novo cholesterol synthesis:
   – Fenofibrate;

– Lovastatin;
– Simvastatin;
– Atorvastatin;
– Rosuvastatin;
– Nicotinic acid (niacin).

3. Drugs increasing cholesterol catabolism:
– Essentuale;
– Lipostabil.

CHOLESTYRAMINE

- is a synthetic preparation (resin);
- is taken orally in a day dose of 10.0–20.0.
- is a bile acids sequestrant: binds to bile acids in the intestine, forms insoluble compounds which are excreted with feces. A loss of bile acids leads to an increase in the conversion of cholesterol into bile acids in the liver and a compensatory increase in hepatic LDL receptors. That results in the enhanced capture of LDL and cholesterol from the blood plasma and reduction in the plasma LDL and cholesterol level (Fig. 20.3);

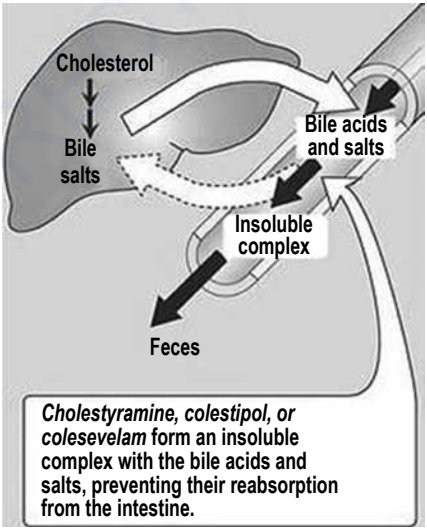

Fig. 20.3. Mechanism of cholestyramine's action *(by R. Finkel et al., 2008)*

- is indicated in atherosclerosis with hyperlipoproteinemia of II–IV types, cholestasis, and elevated plasma bile acids;
- causes side effects, such as dyspepsia, constipation, a decrease in the absorption of fat-soluble vitamins and other drugs.

EZETIMIBE

- is cholesterol-lowering agent, taken orally once a day;
- blocks specific cholesterol transporter in the gastrointestinal epithelial cells (Niemann-Pick C1-Like1 protein);
- acts by decreasing cholesterol absorption in the small intestine, is a selective inhibitor of cholesterol absorption;
- is used alone when other hypolipidemic medications are not tolerated, or together with statins when its use alone does not control cholesterol;
- may cause headache, diarrhea, myalgia, hyperfermentemia, hypersensitivity reactions, and myopathy.

LOVASTATIN

- belongs to statins; is a structural analog of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) (metabolite in cholesterol biosynthesis), natural compound from *Aspergillus terreus;*
- is taken orally once a day (in the evening); is a prodrug (transforms into the active form in the blood);
- inhibits HMG CoA reductase and blocks the hepatic synthesis of cholesterol on the stage of mevalonic acid, increases the expression of hepatic LDL receptors and activates receptor-mediated clearance of LDL (Fig. 20.4);
- decreases plasma levels of LDL, LDL-cholesterol, VLDL-cholesterol; elevates plasma level of HDL-cholesterol;
- is used to treat atherosclerosis with hyperlipoproteinemia of IIa-IIb type, atherosclerosis at a high risk of myocardial infarction; secondary hyperlipidemia resulting from diabetes mellitus or a nephrotic syndrome;
- may cause an increase in serum level of hepatic transaminases, dyspepsia, diarrhea, myopathy, renal failure.

PECULIARITIES OF OTHER STATINS

Simvastatin is a semisynthetic preparation; has pharmacokinetics similar to lovastatin's one; can be prescribed at a normal or moderately elevated baseline

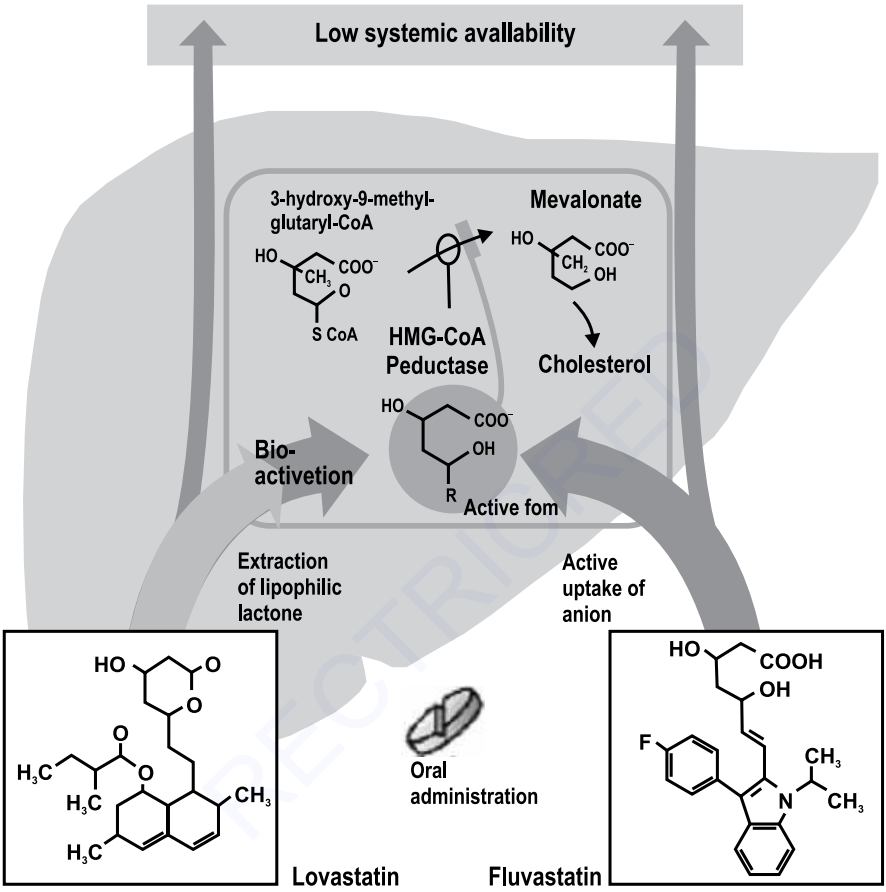

Fig. 20.4. The influence of statins on cholesterol synthesis *(by H. Üllmann, 2000)*

level of common cholesterol and LDL-cholesterol; is stronger than lovastatin, but less potent than atorvastatin and rosuvastatin.

Atorvastatin is a synthetic preparation; has a greater bioavailability and half-life than lovastatin; is stronger than simvastatin and lovastatin; has more potent effect than simvastatin in reducing of common cholesterol, LDL-cholesterol and triglycerides, may be given to wider range of patients, especially with acute coronary syndrome and diabetes mellitus.

Rosuvastatin is a synthetic drug; is not metabolized by the P-450 system and does not form active metabolites; has the greatest bioavailability and half-life between other statins; is distinguished by rapid onset of effect (after 1 week of the treatment) and the most pronounced action on LDL-cholesterol, and HDL-cholesterol.

FENOFIBRATE

- is a fibric acid derivative;
- is taken orally 2–3 times daily;
- has a complex mechanism of action:
  1) is an agonist of the nuclear transcription regulator of the genes coding enzymes of lipid metabolism;
  2) is a stimulant of peroxysome proliferator-activated receptor-α (PPAR-α);
  3) is an activator of lipoprotein lipase and increases the hydrolysis of triglycerides;
  4) is an inhibitor of hepatic synthesis of VLDL.
- reduces the plasma level of Chy, VLDL, and triglycerides, lowers VLDL-cholesterol, LDL-cholesterol and increases HDL-cholesterol (less than triglycerides); also reduces plasma fibrinogen; activates fibrinolysis; inhibits inflammation in the vascular wall;
- is indicated in atherosclerosis with the hyperlipoproteinemia of III or V type;
- may cause dyspepsia, myositis, myopathy, cholelithiasis, cholecystitis and arrhythmia.

NICOTINIC ACID (NIACIN)

- is a water-soluble vitamin, but an antiatherosclerotic action is not due to vitamin activity;
- is taken orally in higher doses (3.0 per day);
- inhibits lipolysis in the fat tissue and hepatic triglyceride esterification; promotes the activity of lipoprotein lipase;
- reduces VLDL and triglycerides levels; elevates the level of HDL; inhibits platelet aggregation, increases fibrinolysis, and dilates blood vessels;
- is used in atherosclerosis with hyperlipidemia, especially of type V type;
- may cause a flush syndrome, peptic ulcer of the stomach, hepatic lesions, glucose intolerance and hyperuricemia.

ESSENTIALE

- contains essential phospholipids, which regulate the metabolism of lipoproteins, transferring neutral lipids and cholesterol to oxidation sites, mainly by increasing the ability of HDL to bind to cholesterol;
- has normalizing effect on the metabolism of lipids and proteins; on the detoxification function of the liver; on the restoration and stabilization of the liver cellular structure, reduces the lithogenic index and stabilizes bile;
- is used in atherosclerosis (orally) and more often in chronic hepatitis; cirrhosis of the liver, toxic liver lesions (by IV infusion and orally);
- side effects are minimal (gastrointestinal disturbances, diarrhea).

LIPOSTABIL

- is a combined preparation containing essential phospholipids, vitamins, AMP, and hydroxyethyltheophylline;
- is taken orally, may be administered IV under the conditions of hepatic diseases or fat embolism;
- has the mechanism of action similar to the mechanism of essentiale, but acts stronger, protects hepatic cells, can dissolve fat embols;
- is used in atherosclerosis with hyperlipoproteinemia, liver diseases and fat embolism.

ANTIOXIDANTS

Antioxidants are natural or synthetic substances which inhibit free radical lipid peroxidation.

CLASSIFICATION

1. Direct-acting antioxidants:
   - α-Tocopherol acetate;
   - Ascorbic acid;
   - Rutin;
   - Probucol.
2. Indirect-acting antioxidants:
   - Glutaminic acid;
   - Methionine;
   - Cysteine.

Mechanism of antihyperlipoproteinemic action

Direct-acting antioxidants inhibit oxidation of cholesterol resulting in a decrease of the ingestion of the oxidized cholesterol laden LDL by macrophages. That's why they inhibit the conversion of macrophages into foam cells which are the basis for plaque formation (Fig. 20.5).

Indirect-acting antioxidants do not interact with free radicals and peroxides. They are needed for the synthesis of glutathion (natural direct antioxidant which supports the activity of the ascorbic acid and takes part in detoxification processes in the liver). In this process, the glutaminic acid takes out the carbon chain, methyonine is a donator of methyl group and cysteine is a donator of the SH-group.

Indications

Antioxidants are used for the treatment of atherosclerosis accompanied by enhanced lipid peroxidation. Their effectiveness is increased if antioxidant preparations are used in a combination.

PECULIARITIES OF PREPARATIONS

α-Tocopherol acetate is a fat-soluble vitamin; is taken orally to treat atherosclerosis; is the most active low-weight antioxidant in the organism; is located in

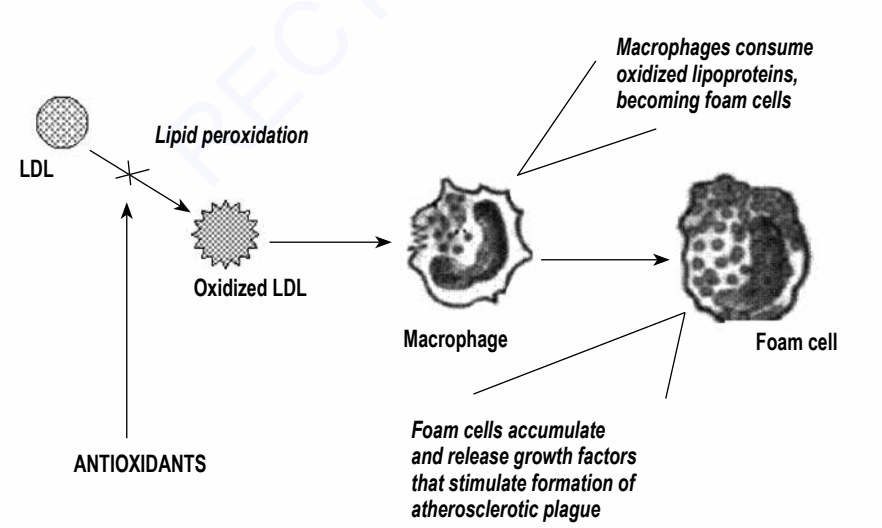

Fig. 20.5. Mechanism of antioxidants action in atherosclerosis

membrane lipids; neutralizes all kinds of free radicals and peroxides; decreases LDL-cholesterol, inhibits the destruction of elastic fibers in the vascular wall and forming of atheromathous plaque; decreases platelet aggregation.

Ascorbic acid is a water-soluble vitamin; is taken orally for the treatment of atherosclerosis; is an active low weight antioxidant which acts in the hydrophylic phase of membranes; it neutralizes free radicals and peroxides as well as supports the activity of tocopherol; takes part in cholesterol synthesis in the liver; inhibits the destruction of vascular wall and forming of atheromathous plaque, normalizes contents of lipoproteins and cholesterol in the blood plasma.

Detail description of antioxidants is represented in Chapter 27.

ANTIPLATELET DRUGS

Aspirin and low doses of ***heparin*** (IM or by inhalation) are used for the treatment of atherosclerosis accompanied by hypercoagulation of the blood.

Pharmacological properties of antiplatelets are described in detail in Chapter 22.

ENDOTHELIUM-ACTIVE DRUGS

PARMIDIN (PRODECTIN)

- is taken orally 2–3 times daily;
- is an antagonist of bradykinin. It decreases the influence of bradykinin on endothelial cells and in such a way decreases contractions of endothelial cells. The absence of gaps between endothelial cells makes impossible the transport of LDL-cholesterol into the vascular wall and decreases the infiltration of blood vessels wall by cholesterol (Fig. 20.6);
- decreases the permeability of the blood vessels wall, stimulates endothelium regeneration, inhibits inflammation, has an antiplatelet action;
- is used to treat atherosclerosis (especially of peripheral vessels or without any significant changes in laboratory analyses), diabetic angiopathy, thrombosis of veins in the retina, endarteritis obliterans and trophic ulcer of the lower extremities;
- may cause headache, dyspepsia and skin rash.

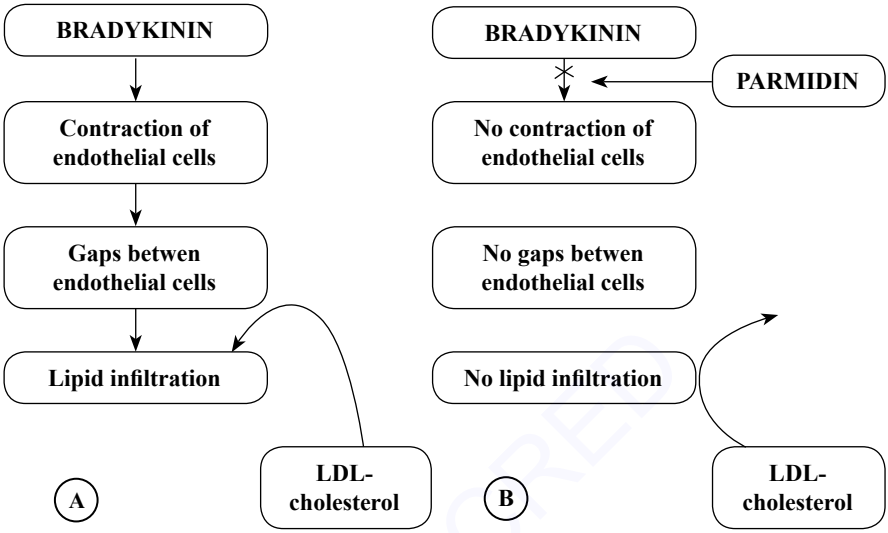

Fig. 20.6. Mechanism of parmidin's action:
A – without parmidin; B – under the influence of parmidin

TESTS FOR SELF-CONTROL

1. Cholestyramine lowers the level of cholesterol by:
A. Sequestering bile acids in the intestine
B. The prevention of bile acids reabsorption
C. An increase of VLDL excretion
D. The inhibition of lipid peroxidation
E. The activation of lipoprotein lipase.

2. The following statements concerning antioxidants are correct, except:
A. They inhibit free radical lipid peroxidation
B. They inhibit the oxidation of cholesterol and its uptake by macrophages
C. They slow the development of atherosclerosis
D. They inhibit the synthesis of cholesterol at the stage of the mevalonic acid
E. Direct-acting antioxidants are natural and synthetic substances.

3. The drugs inhibiting de novo cholesterol synthesis are:
A. Lovastatin

B. Parmidin
C. Fenofibrate
D. Cholestyramine
E. α-tocopherol acetate.

4. Fibrates decrease the lipoproteins level in the blood plasma by:
A. The activation of lipoprotein lipase
B. Lowering of circulating triglycerids
C. The prevention of cholesterol absorption from the gut
D. The alteration of LDL composition
E. All the above listed.

5. A 60-year old patient visited her doctor for routine examination. Blood sampling revealed an elevated level of VLDL and triglycerides in the blood plasma. Due to this antiatherosclerotic drug was prescribed. This drug belongs to vitamin preparations and in higher dose enhances lipoprotein lipase synthesis and decreases the level of triglycerides in blood. It also dilates blood vessels and increases fibrinolysis. What drug was prescribed?
A. Nicotinic acid
B. Ascorbic acid
C. Lovastatin
D. Fenofibrate
E. Cholestyramine.

Answers

1 – A; 2 – D; 3 – A, C; 4 – A, B, D; 5 – A.

Chapter 21 DRUGS ACTING ON HEMOPOIESIS (HEMATINICS)

HEMOPOIESIS

Hemopoiesis is a production of blood cells from undifferentiated stem cells. It is located in the bone marrow and divided into erythropoiesis and leukopoiesis.

Erythropoiesis is a production of erythrocytes in the bone marrow. The development of erythrocytes is accompanied by the reduction of nuclei and saturation by hemoblobin.

Pathology of erythropoiesis displays as anemia or polycytemia.

Anemia is a blood disorder characterized by the reduction of erythrocytes count, hemoglobin, and hematocrit, although not all three findings may be present.

Types of anemia:

- hypochromic iron-deficiency anemia (Fig. 21.1);
- hyperchromic megaloblastic anemia (Fig. 21.1);
- hemolytic anemia;
- aplastic anemia.

Polycytemia is a disease with highly increased red blood cells mass and hemoglobin concentration caused by the pathological proliferation of erythroid cells in the bone marrow.

Leukopoiesis is a production of lymphocytes and granulocytes.

Pathology of leukopoiesis is manifested as leukopenia or leukemia.

Leukopenia is a decrease in the amount of leukocytes in the blood resulting from the inhibition of their forming in the bone marrow.

Leukemia (leukosis) is a cancer of blood characterized by the malignant proliferation of white blood cells precursors in the bone marrow resulting in the increase of the leukocytes amount.

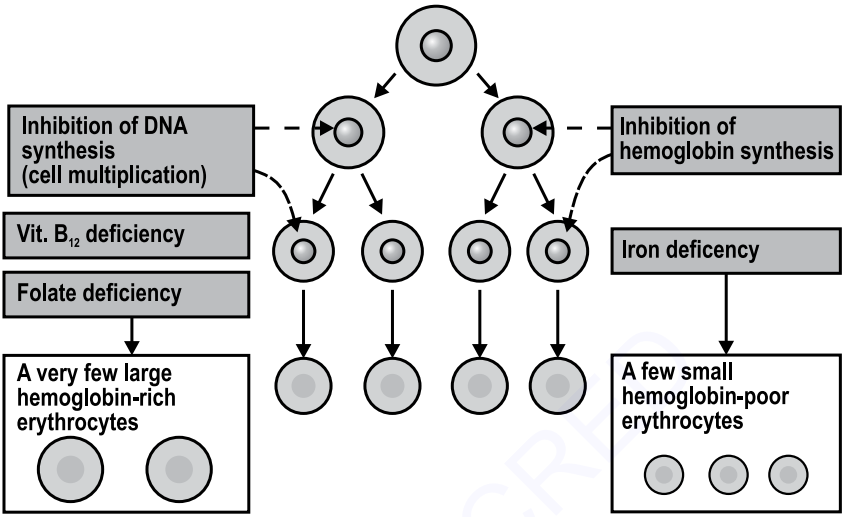

Fig. 21.1. Pathology of erythropoiesis *(by H. Lüllmann, 2000)*

DRUGS ACTING ON HEMOPOIESIS

Drugs acting on hemopoiesis (hematinics) are divided into agents acting on erythropoiesis and agents acting on leukopoiesis. Stimulants and inhibitors are represented in each group.

DRUGS ACTING ON ERYTHROPOIESIS

CLASSIFICATION

A. *Erythropoiesis stimulants:*

1. Drugs used in hypochromic iron-deficiency anemia:

a) iron preparations:
   - Ferrous sulfate;
   - Tardyferon;
   - Ferrum-lek.

b) cobalt preparations:
   - Coamid.

c) combined preparations:
   - Fercovenum;

- Ferroplex;
- Haemostimulinum.

d) adjuvant hematinics:
- Erythropoetin (Epoetin α);
- Recormon (Epoetin β).

2. Drugs used in hyperchromic megaloblastic anemia:
- Cyanocobalamin;
- Folic acid.

B. *Erythropoiesis inhibitors:*
- Sodium phosphate containing P^{32};
- Imiphos.

DRUGS USED IN HYPOCHROMIC IRON-DEFICIENCY ANEMIA

FERROUS SULFATE

It is a salt containing Fe^{++}.

Pharmacokinetics

- is taken orally;
- is transformed into the ionic form with the participation of HCL in the stomach; is absorbed in the intestine (Fe^{++} binds to apoferritin and in the form of ferritin crosses intestinal epithelium) (Fig. 21.2);
- absorption in the GI tract is 10–20% of a dose and increases under the conditions of anemia;
- Fe^{++} absorption is stimulated by vitamin C and glucose and inhibited by calcium, antacids, tetracycline, andchloramphenicol;
- Fe^{++} binds to transferrin in the blood plasma and is transported in this complex;
- concentrates in the bone marrow and depo tissues (the liver and spleen);
- is excreted with urine, feces, epithelial cells, and menstrual blood in women.

Mechanism of action

- participates in the formation of hemoglobin in the erythrocytes;
- takes part in the formation of myoglobin in the muscles;
- participates in the synthesis of some enzymes (cytochrome oxidase and others).

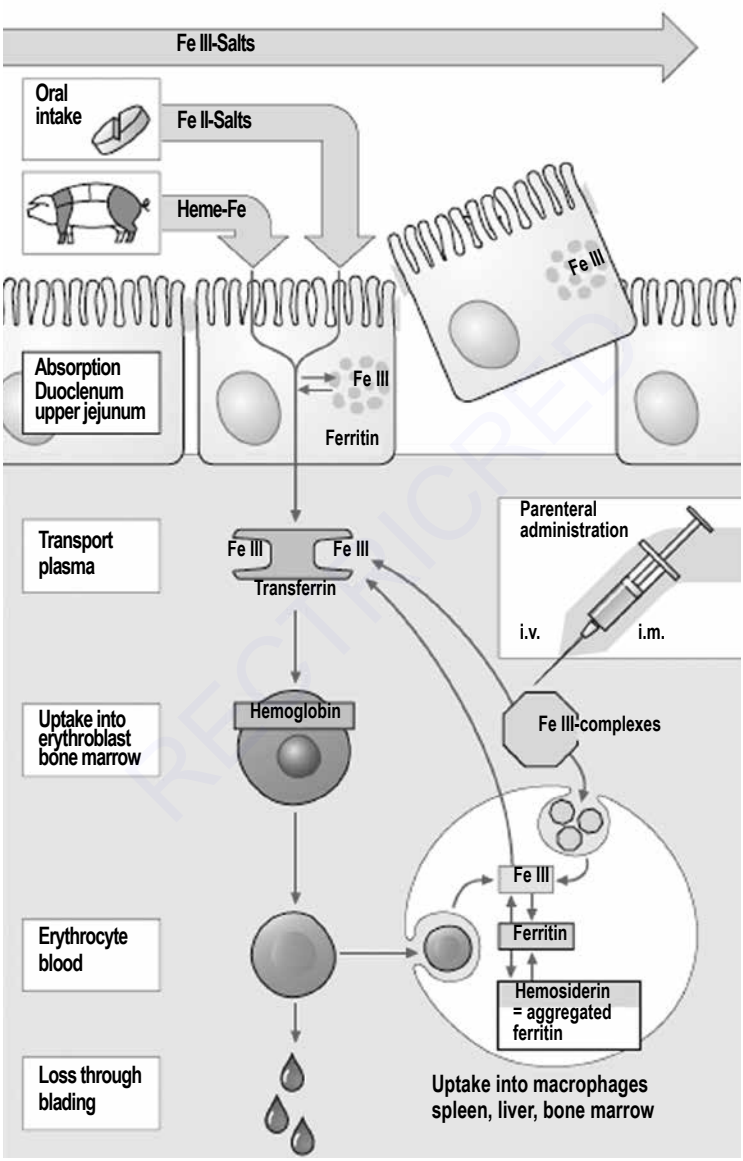

Fig. 21.2. Pharmacokinetics of iron *(by H. Lüllmann, 2000)*

Pharmacodynamics

- an increase in the amount of red blood cells;
- an increase in the saturation of erythrocytes by hemoglobin;
- the reduction of symptoms of anemia (weakness, paleness, tachycardia, etc) which begins in 5–7 days after the start of treatment.

Indications

- hypochromic anemia of various etiology (anemia from an acute and chronic blood loss, alimentary iron deficiency, pregnancy, etc).

Depot-preparation of ferrous sulfate (dragee or coated tablets) is used as preparation ***Tardyferon***.

Side effects

1. Dyspepsia
2. Constipation (resulting from the binding of iron with H_2S in the intestine and bowels)
3. Teeth darkness (resulting from the binding of iron to H_2S in the oral cavity and forming of black compound FeS)
4. Black color of feces imitating intestinal bleeding
5. Hemosiderosis
6. Allergy

Contraindications

1. Hemolytic anemia
2. Hemosiderosis, hemochromatosis

Acute poisoning with ferrous compounds

***Signs*:**

– the irritation and necrosis of the gastric mucosa;
– lesions of the liver and brain;
– collapse, coma.

Emergency help:

– lavage of the stomach with 1% solution of sodium bicarbonate;
– albumin solution (orally);
– **Desferal** ***(Desferrioxamine)*** (IV and into the stomach) as an antidote. The drug acts by binding free iron in the bloodstream and enhancing its elimination in the urine. By removing excess iron, the agent reduces the damage of organs and tissues. Desferal also is used to treat hemochromatosis, a disease of iron accumulation. Acquired hemochromatosis is common in patients with certain types of chronic anemia (e.g., thalassemia and myelodysplastic syndrome) who require many blood transfusions.

PECULIARITIES OF OTHER PREPARATIONS

Ferrum-lek is a compound of iron with maltose or saccharose; is made in two forms: the 1st form – for IM administration (maltose-containing); the 2nd one – for IV administration (saccharose-containing); is used for anemia resulting from iron malabsorption or for severe anemia; may cause nausea, vomiting, allergic reactions and hypotension (rarely).

Coamid contains cobalt; is administered IM, IV; accumulates in the bone marrow; increases the synthesis of erythropoietin, promotes the including of iron into hemoglobin; is the additional remedy in the treatment of hypochromic anemia, is used together with iron preparations.

Fercovenum is a combined preparation containing ferrous saccharate and cobalt gluconate; is administered only IV in a dose which is calculated according to color index and the patient's body weight; is used for severe hypochromic anemia (hemoglobin level may be restored during the 1st day of the treatment) and for anemia on the ground of iron malabsorption; may cause side effects, such as face hyperemia, retrosternal pain, hypotension, a shock-like reaction.

Ferroplex is a combined preparation in the form of dragee which contains ferrous sulfate and vitamin C.

Haemostimulinum is in the form of tablets; contains ferrous lactate and copper sulfate; stimulates erythropoiesis as well as the synthesis of oxido-reductases needed for normal function of the CNS.

Epoetin β is a glycoprotein, natural factor stimulating mitosis and proliferation of erythroid cells; is administered SC or IV; has a half-elimination of 4–12 hrs after IV injection and 12–28 hrs after SC administration; is used for the treatment of hypochromic anemia in patients with renal failure, for the prevention and treatment of anemia resulting from the cancer chemotherapy, anemia accompaning myelomic disease, before autohemotransfusion, and for the prevention of anemia in premature newborns; may cause side effects, such as hypertension, hypercoagulation of blood, skin rash and allergy; is contraindicated in hypersensitivity, hypertension, myocardial infarction, prone to thrombus formation.

DRUGS USED IN HYPERCHROMIC MEGALOBLASTIC ANEMIA

The folic acid and cyanocobalamin (vitamin B_{12}) are necessary for the normal formation of red and white blood cells. The deficit of cyanocobalamin or the folic acid results from dietary factors, poor absorption, or therapy with folate antagonists (metotrexate, sulfa drugs or trimethoprim). It leads to the development

of ***megaloblastic anemia*** (also known as malignant, pernicious, Addison-Birmer's anemia). Megaloblastic anemia is characterized by the presence of megaloblasts in the blood, hyperchromic condition, CNC disturbances, and glossitis.

CYANOCOBALAMIN

- is a water-soluble vitamin;
- is taken orally, is administered IM, IV; binds to an intrinsic Castle factor in the stomach and is absorbed in the intestine by endocytosis; concentrates in the liver;
- is biotransformed to cobalamin, cofactor of the folic acid reductase (Fig. 21.3), takes part in the synthesis of purine and pyrimidine nucleotides and transforms megaloblastic hemopoiesis into normoblastic one, normalizes the blood film (the count and qualities of erythrocytes, leukocytes, and thrombocytes);
- takes part in the synthesis of myelin and acetylcholine, decreases neurological disturbances connected with megaloblastic anemia;
- takes part in the function of the epithelium and decreases disturbances in the tongue mucosa (Hunter's glossitis);
- is indicated in hypercromic megaloblastic anemia, hypoplastic anemia, radiation sickness, neurological diseases, liver diseases, dystrophy in children and glossitis;
- may cause allergy, hypercoagulation, tachycardia, pain in the heart, worsen in angina pectoris;
- is contraindicated to patients with hypersensitivity, thrombosis and thromboembolism.

FOLIC ACID

- is a water-soluble vitamin;
- is taken orally; is absorbed in the small intestine and deposited in the liver (Fig. 21.3);
- takes part in the synthesis of purine and pyrimidine nucleotides, amino acids and proteins;
- is an additional remedy in the treatment of hyperchomic megaloblastic anemia; is used together with cyanocobalamin; is also indicated in chronic gastroenteritis, sprue, in pregnancy for the prophylaxis of neurological pathology of the fetus and newborn.

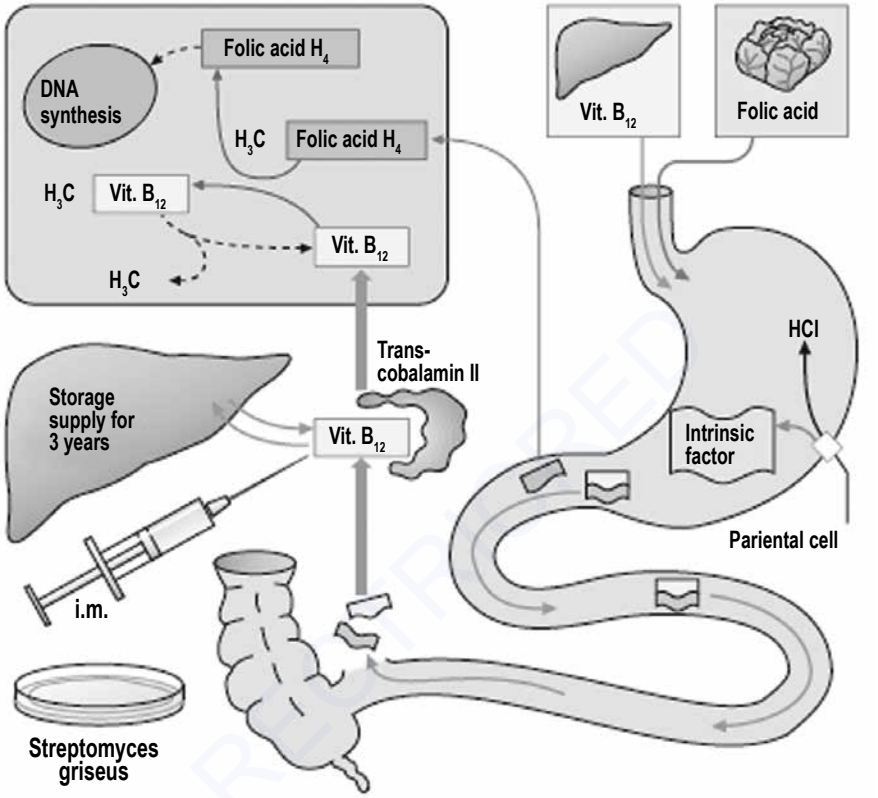

Fig. 21.3. Absorption and storage of folates and cyanocobalamin
(by H. Lüllmann, 2000)

ERHYTHROPOIESIS INHIBITORS

Sodium phosphate with radioactive phosphor is administered IV in special clinic; is absorbed by erythoblasts and kill them due to radiation, that's why inhibits red blood cells forming, decreases the amount of erythrocytes and viscosity of the blood, improves the condition of patient suffering from polycytemia.

Imiphos is an anticancer drug; interacts with DNA and inhibits production of red blood cells in the bone marrow and in such a way improves the condition of the patient with polycytemia.

DRUGS ACTING ON LEUKOPOIESIS

CLASSIFICATION

A. *Leukopoiesis stimulants:*

1. Nucleic acid derivatives:
   – Sodium nucleinate.
2. Pyrimidine derivatives:
   – Methyluracil;
   – Pentoxilum.
3. Colony stimulating factors:
   – Filgrastim;
   – Molgrastim;
   – Lenograstim.

B. *Leukopoiesis inhibitors and anticancer drugs:*

1. Alkylating agents:
   – Mechlorethamide (Embichin);
   – Cyclophosphamide;
   – Dopan;
   – Myelosan;
   – Chlorbutin (Leukeran);
   – Sarcolysine.
2. Antimetabolites:
   – Methotrexate;
   – Mercaptopurine;
   – Phtoruracil.
3. Anticancer antibiotics:
   – Actinomycin (Dactinomycin);
   – Rubomycin.
4. Alkaloids:
   – Vinblastine;
   – Vincristine;
   – Demecolcine (Colchamine);
   – Paclitaxel.
5. Enzymes:
   – L-asparaginase.
6. Steroid hormones:
   – Prednisolone;
   – Gonadal hormones and their antagonists (Fosfestrol, Tamoxifen, etc.).

7. Monoclonal antibodies:
   – Rituxan (Rituximab);
   – Zevalin (Y^{90}-Ibritumomab);
   – Mylotarg (Gemtuzumab);
   – Erbitux (Cetuximab).

LEUKOPOIESIS STIMULANTS

METHYLURACIL

- is a pyrimidine derivative;
- is administered orally, rectally, or applied topically (as ointment); is well absorbed in the GI tract and completely metabolized in the body; acts during 4–6 hrs;
- is a substrate for the synthesis of nucleic acids;
- stimulates leukopoiesis and increases the amount of white blood cells; stimulates phagocytosis and immunity; improves tissues regeneration; accelerates the development and ending of inflammation;
- is indicated in leukopenia, wounds and bone fractures with poor regeneration, ulcers, burns, gastric ulcer, chronic inflammations with slow recovering, radiation sickness, suppressed immunity and paradontitis;
- may cause dyspepsia, allergy;
- is contraindicated in severe disturbances of leukopoiesis, aplastic anemia, leukemia and cancer.

PECULIARITIES OF OTHER PREPARATIONS

Pentoxylum acts similar to methyluracil, but irritates the skin and mucous membranes; is not applied rectally or topically.

Sodium nucleinate is produced by hydrolysis of nucleic acids; may be administered parenteraly; causes allergic reactions.

Molgrastim is a glycoprotein, natural colony stimulating factor which stimulates the proliferation and differetiation of granulocytes precursors in the bone marrow; is administered IV for the treatment of agranulocytosis.

Lenograstim is a recombinant human granulocyte colony-stimulating factor, stimulates the proliferation and differentiation of progenitor cells of the neutrophilic series, causes an increase of neutrophils count in the blood, increases the functional activity of neutrophils; is used for prevention and treatment of neutropenia caused by chemotherapeutic antitumor agents, bone marrow transplantation,

or aplastic diseases of the hematopoietic system; can cause pain in the muscles and bones, enlarged spleen, thrombocytopenia, anemia, epistaxis, dysuria, headache, diarrhea, and fever as side effects.

LEUKOPOIESIS INHIBITORS AND ANTICANCER DRUGS

Leukopoiesis inhibitors are drugs for the treatment of leukemia and cancer. They inhibit functions of DNA at different stages of a cell cycle and are cytostatics. These drugs are immunity depressants. They are also used in collagenosis and autoimmune diseases.

MAIN GROUPS OF LEUKOPOIESIS INHIBITORS

Mechanism of action and clinical use

Antimetabolites (methotrexate, 6-mercaptopurine) are structural analogues of natural compounds and block enzymes participating in the synthesis of nucleic acids (Fig. 21.4). Their maximal cytotoxic effects are S-phase specific. Methotrexate is used to treat acute lymphocytic leukemia, Burkitt's lymphoma, chorioncarcinoma, breast cancer, head and neck carcinomas. 6-mercaptopurine is used in the maintenance of remission of acute lymphoblastic leukemia.

Alkylating agents (chlorbutin, dopan, myelosan, etc) are biotransformed in anions interacting with nucleophylic centers of DNA (Fig. 21.5). As a result, they

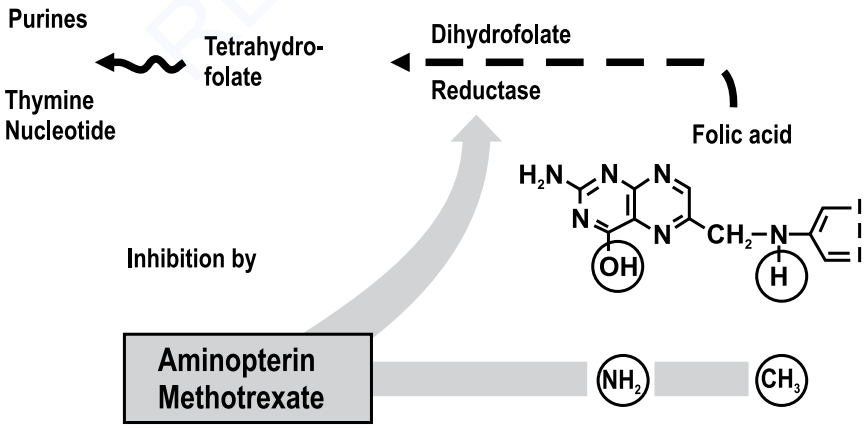

Fig. 21.4. Mechanism of action of methotrexate *(by H. Lüllmann, 2000)*

inhibit the reduplication of DNA and m-RNA synthesis that is lethal for tumor cells. They are used to treat lymphatic and solid cancer. Alkylating agents are highly toxic for all rapidly divided cells. They are mutagenic and cancerogenic (may cause secondary malignancy).

Antibiotics (dactinomycin, rubomycin, etc) inhibit the reduplication of DNA by the mechanism of intercalation (Fig. 21.5). Effects are maximal in the S and G_2 phases (cell-cycle specific agents). They are used for the treatment of acute lymphocytic leukemia, lymphomas, sarcomas, and a variety of carcinomas.

Enzyme (L-asparaginase) destructs amino acid asparagine. L-aspraginase hydrolyzes blood asparagine and thus deprives the tumor cells of this nutrient required for protein synthesis. It is used to treat childhood acute lymphocytic leukemia in combination with vincristine and prednisolone.

Alkaloids (vinblastine, vincristine, etc.) are "mytotic" poisons; they block mytosis on the stage of metaphase (cycle-specific agents).Vinca alkaloids are microtubule inhibitors (Fig. 21.6). Vincristine is used in the treatment of acute lymphoblastic leukemia in children, lymphomas, Wilm's tumor, soft tissue sarcomas.

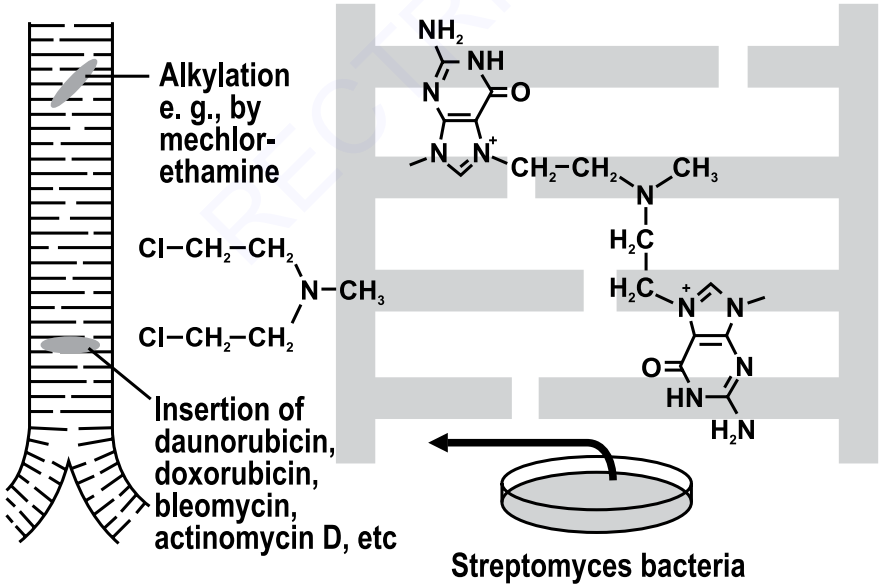

Fig. 21.5. Mechanism of action of alkylating agents and antitumor antibiotics *(by H. Lüllmann, 2000)*

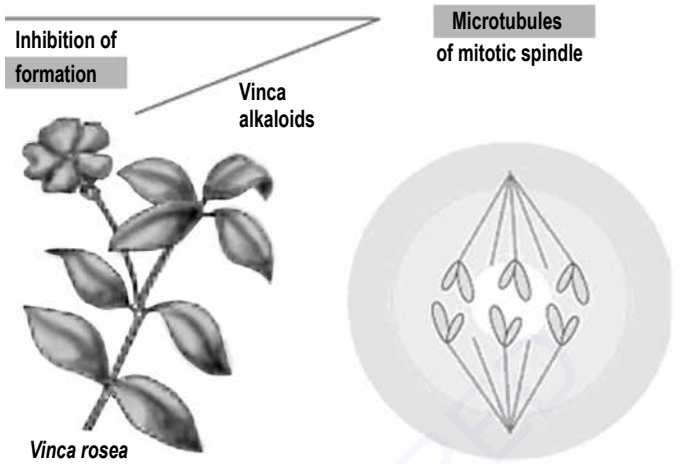

Fig. 21.6. Mechanism of action of alkaloids *(by H. Lüllmann, 2000)*

Vinblastine is used in the combined treatment of lymphomas and metastatic testicular carcinoma.

Steroid hormones. Glucocorticoids (e.g., prednisolone) inhibit the proliferation of lymphoid tissue. They are used in patients with acute lymphocytic leukemia and lymphomas. Sex hormones and their antagonists are used in the treatment of hormone-dependent cancer of the breast (in women), prostate and testis (in men).

Monoclonal antibodies. The mechanisms of tumor cell killing by antibodies ***(rituximab, ibritumomab, gemtuzumab, etc.)*** can be due to direct cell killing, such as through receptor blockade or agonist activity, induction of apoptosis, or delivery of a drug, radiation, or cytotoxic agent; immune-mediated cell killing mechanisms; regulation of T cell function; and specific effects on tumor vasculature and stroma. Because of their high target specificity, generally low toxicity and the ability to activate the immune system, the use of therapeutic antibodies for the treatment of cancer and hematoliogical malignancy is very promising.

Common side effects

1. The suppression of hemopoiesis, leukopenia, anemia, thrombocytopenia.
2. The suppression of immunity.
3. A toxic action on the CNS (headache, vertigo, nausea, vomiting).
4. A toxic action on the GI tract (a loss of appetite, dyspepsia).

5. Necrotic lesions in the skin and mucous membranes including necrotic stomatitis.

6. Alopecia.

All the listed side effects are reversible, but some of them are dangerous for a patient and must be treated.

TESTS FOR SELF-CONTROL

1. Only one drug inhibits leukopoiesis:
A. Fercovenum
B. Ferroplex
C. Pentoxilum
D. 6-Mercaptopurine
E. Methyluracil.

2. All the listed is correct, except:
A. Coamid is an additional drug for the treatment of hypochromic anemia
B. Ferroplex is a combined preparation containing iron and ascorbic acid
C. Folic acid inhibits DNA reduplication in erythrocytes precusors
D. Pentoxilum is used for the treatment of leukopenia
E. Inhibitors of leukopoiesis are cytostatics and immunity depressants.

3. The main effects of cyanocobalamin include:
A. The transformation of megaloblastic erythropoiesis into normoblastic one
B. The improvement of leukocytes forming
C. An increase in the amount of thrombocytes
D. An antiplatelet action
E. Reducing of the neurological symptoms of megaloblastic anemia.

4. Inhibitors of leukopoiesis are used to treat:
A. Acute leukemia
B. Cancer
C. Aplastic anemia
D. Psoriasis and some collagen diseases
E. Leukopenia.

5. A patient has the pale skin and mucous membranes, weakness, tachycardia. The total amount of red blood cells is 3.5×10^{12}/L. Colored index is

0.76. It is known, that he has gastritis with lower acidity of gastric juice. Point out a correct diagnosis and a basic preparation for the therapy.

A. Iron-deficient anemia, ferrum-lek
B. Hemolytic anemia, prednisolone
C. Anemia due to chronic renal failure, epoetin
D. Hemochromatosis, desferal
E. Megaloblastic anaemia, cyanocobalamin.

Answers:

1 – D; 2 – C; 3 – A, B, C, E; 4 – A, B, D; 5 – A.

Chapter 22 DRUGS ACTING ON BLOOD COAGULATION AND FIBRINOLYSIS

HEMOSTASIS AND FIBRINOLYSIS

Hemostasis is the arrest of bleeding from damaged blood vessels. It is a complex cascade of enzymatic reactions.

The damage of blood vessel causes vasospasm, platelet aggregation and adhesion. It results in the formation of platelet plug, activation of clotting factors, conversion of fibrinogen to insoluble fibrin, clot formation, and the stop of bleeding (Fig. 22.1). Natural clotting limitation factors are heparin and antithrombin III.

Fibrinolysis is the lysis of thrombus for the restoration of the blood flow: plasminogen (profibrinolysin) converts into plasmin (fibrinolysin) and causes the lysis of fibrin clot.

Pathology of hemostasis and fibrinolysis:

- A decrease in blood coagulation and (or) an increase in fibrinolysis result in bleeding
- An increase in blood coagulation and (or) a decrease in fibrinolysis result in thrombosis, thromboembolism and syndrome of disseminated intravasal blood coagulation.

DRUGS AFFECTING BLOOD COAGULATION AND FIBRINOLYSIS

Drugs affecting blood coagulation and fibrinolysis include coagulants, anticoagulants, antiplatelet drugs, fibrinolytic drugs, inhibitors of fibrinolysis (Fig. 22.2).

COAGULANTS

Coagulants are preparations increasing blood coagulation.

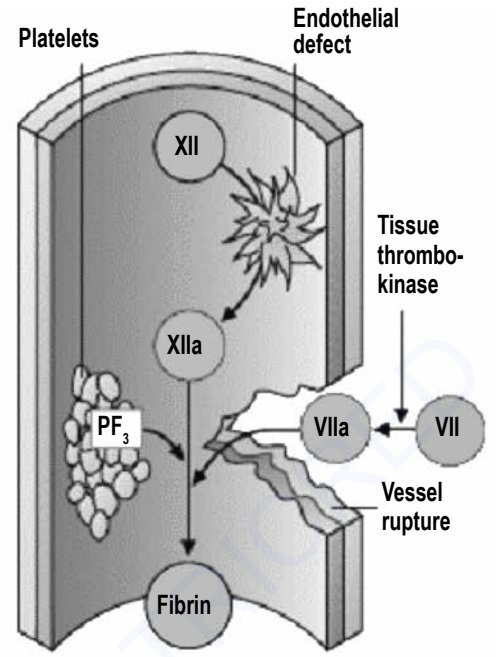

Fig. 22.1. Initial stage of blood coagulation *(by H. Lüllmann, 2000)*

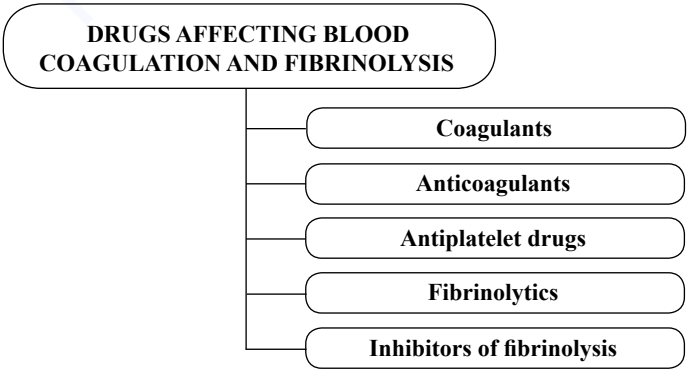

Fig. 22.2. Groups of drugs acting on blood coagulation and fibrinolysis

CLASSIFICATION

1. Direct-acting (are active *in vivo* as well as *in vitro*):
   - Thrombin;
   - Hemostatic sponge;
   - Fibrinogen;
   - Eptacog alfa (NovoSeven);
   - Calcium chloride;
   - Calcium gluconate.
2. Indirect- acting (are active only *in vivo*):
   - Menadione (Vikasol).
3. Drugs of other mechanism of action:
   - Etamsylate (Dicynone).

DIRECT-ACTING COAGULANTS

Thrombin is an active compound of the blood coagulation system, is used for the bleeding from capillary vessels, is applied only topically (IV administration may cause disseminated thrombosis). ***Hemostatic sponge*** is a thrombin preparation applied topically and dissolved in the wound.

Fibrinogen is a non-active compound of the blood coagulation system, is used by IV infusion for the bleeding from bigger vessels, hypofiibrinogenemia, disseminated intravasal blood coagulation.

Eptacog alfa (NovoSeven) ia a recombinant activated factor VII (VIIa); interacts with thrombin-activated platelets to produce thrombin burst leading to accelerated fibrin clot formation in the site of vascular injury; is approved for the use as an intravenous hemostatic agent in patients with congenital hemophilia, for acquired hemophilia, factor VII deficiency, and Glanzmann thrombasthenia; is not immunogenic in patients with hemophilia and has very low thrombogenicity.

Calcium chloride, calcium gluconate contain calcium ions which are the components of the blood coagulation system, stimulate the formation of active clotting factors, are used parenteraly for bleeding, for the prophylaxis of bleeding, for a decrease of capillary permeability. Properties of calcium salts are described in detail in Chapter 28.

INDIRECT-ACTING COAGULANTS

MENADIONE (VIKASOL)

- is an indirect-acting coagulant, a water-soluble synthetic vitamin K;
- is administered orally, IM, rarely IV; develops a therapeutic effect slowly in 12–18 hrs;
- takes part in the synthesis of clotting factors in the liver (Fig. 22.3);
- is used for the prophylaxis of bleeding, for chronic and repeated bleedings, radiation sickness, liver diseases, an overdose of indirect-acting anticoagulants;
- is contraindicated to patients with hypercoagulation, thrombosis and thromboembolism.

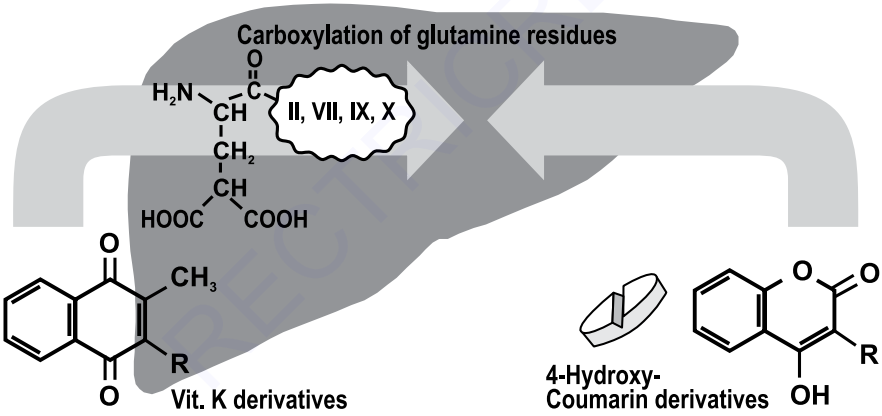

Fig. 22.3. Mechanism of action of vitamin K derivatives (vikasol) and their antagonists (coumarin derivatives) *(by H. Lüllmann, 2000)*

HEMOSTATIC DRUGS OF OTHER MECHANISM OF ACTION

ETAMSYLATE

- promotes angioprotective and proaggregant action, stimulates thrombocytopoiesis and release of blood platelets from the bone marrow;

- has a hemostatic action, which is due to activation of thromboplastin formation on damaged sites of small blood vessels and a decrease of PgI_2 (prostacyclin) synthesis; the stimulation of platelet aggregation and adhesion;
- stabilizes capillaries, reinforcing capillary membranes by polymerizing hyaluronic acid; reduces edema;
- is used for prophylaxis and control of capillary bleeding of different etiology (menorrhagia and metrorrhagia without organic pathology, transurethral resection of the prostate, hematemesis, melena, hematuria), epistaxis; secondary bleeding due to thrombocytopenia or thrombocytopathia, hypocoagulation, prevention of periventricular hemorrhages in prematurely born children.

ANTICOAGULANTS

Anticoagulants are drugs decreasing blood coagulation.

CLASSIFICATION

1. Direct-acting (are active *in vivo* as well as *in vitro*):
   – Heparin;
   – Fraxiparine;
   – Enoxaparin;
   – Fondaparinux;
   – Rivaroxaban.
2. Indirect-acting (are active only *in vivo*):
   – Warfarin;
   – Ethyl biscoumacetate (Neodicumarinum);
   – Phenindione (Phenylin).

DIRECT-ACTING ANTICOAGULANTS

HEPARIN

Heparin is a natural substance produced by mast cells. High concentration of heparin is observed in the lungs and in the wall of intestine. It belongs to acidic mucopolysaccharides (Fig. 22.4). A disaccharide component of heparin shows negative charges due to the carboxyl and sulfate groups.

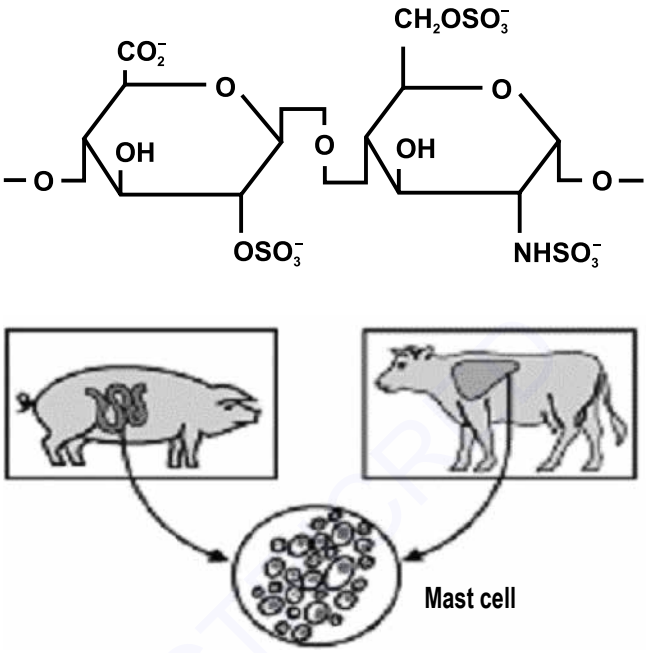

Fig. 22.4. Chemical structure of heparin (A) and its sources (B)
(by H. Lüllmann, 2000)

Pharmacokinetics

- is administered IV, IM, SC, topically;
- begins to act immediately after the IV administration and acts during 4–6 hrs;
- begins to act in 15–30 min after the IM administration and acts during 6–8 hrs;
- begins to act in 30–60 min after the SC administration and acts during 8–12 hrs;
- is metabolized in the liver by heparinase;
- is excreted with urine.

Mechanism of action

- heparin binds to antithrombin III, causes its conformational change that leads to the rapid inactivation of thrombin and some other clotting factors resulting in the inhibition of fibinogen conversion to fibrin (Fig. 22.5);

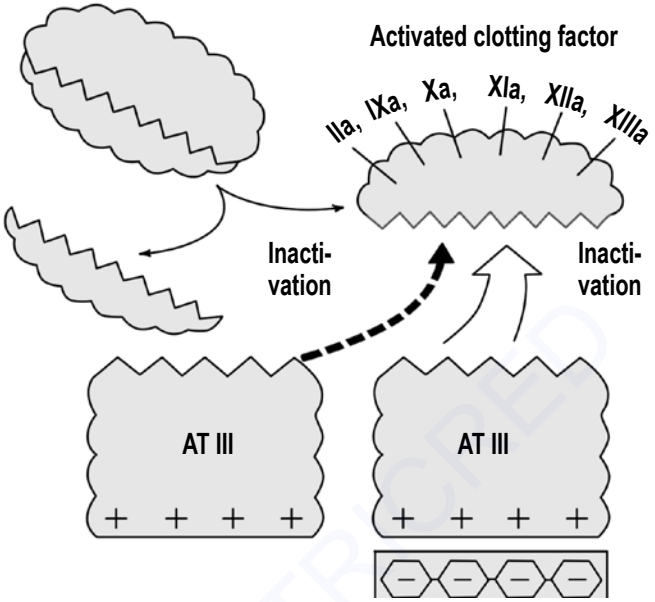

Fig. 22.5. Mechanism of action of heparin *(by H. Lüllmann, 2000)*

- heparin has a negative charge, due to which it is absorbed on blood cells, increases a negative charge of platelets resulting in a decrease of platelet aggregation and adhesion;
- heparin releases lipoprotein lipase from the endothelial cells.

Pharmacodynamics

- a strong rapid decrease in all stages of blood coagulation;
- a decrease in platelet aggregation;
- the improvement of microcirculation and coronary circulation;
- a decrease in lipids concentration in the blood plasma;
- a decrease in inflammation;
- the suppression of immunity;
- an increase in the synthesis of surfactant in the lungs;
- a decrease in blood pressure (in higher doses);
- a decrease in glucose level in the blood plasma (in higher doses);
- an increase in diuresis (in higher doses).

Indications

- acute thrombosis and thromboembolism
- myocardial infarction;
- ischemic stroke;
- prevention of thrombus formation after surgeries;
- hemodialysis or blood transfusion;
- thrombophlebitis;
- a syndrome of disseminated intravasal blood coagulation;
- atherosclerosis;
- autoimmune diseases;
- chronic non-specific diseases of the lungs.

The time of bleeding or the time of blood coagulation should be controlled!

Side effects

1. Bleeding
2. Hematomes
3. Micro- and macrohematuria
4. Thrombocytopenia
5. Allergy
6. Osteoporosis
7. Silvering of the hair

Contraindications

1. Hemorrhages
2. Hemorrhagic diathesis
3. Leukemia
4. Anemia
5. Malignant diseases
6. Gastric ulcer
7. Hypertension
8. Severe diseases of the liver and kidney

In overdose – induce of Protamine sulfate!

PECULIARITIES OF OTHER PREPARATIONS

Fraxiparine is a low molecular weight heparin (LMWH); is administered SC once a day; has bigger bioavailability, longer duration of action, less binding with plasma proteins than heparin; depresses activated Stuart-Prower factor more than thrombin; is used for the treatment of thromboflebitis, prevention of thrombus formation after the surgeries.

Enoxaparin is a LMWH; is used to prevent or to treat deep vein thrombosis, therapy of unstable angina and myocardial infarction; is given SC or IV; has such side effects as thrombocytopenia, elevations in serum aminotransferases level, hematuria, bleeding, anemia, ecchymosis, peripheral edema, injection site hemorrhage or pain.

Fondaparinux is an anticoagulant chemically related to low molecular weight heparins; is a synthetic pentasaccharide factor Xa inhibitor; is given SC daily; is used for prevention of deep vein thrombosis in the patients who have had orthope-

dic surgery, for the treatment of deep vein thrombosis and pulmonary embolism; the advantage over LMWH or unfractionated heparin is that the risk for heparin-induced thrombocytopenia is substantially lower.

Rivaroxaban is the first available orally active direct factor Xa inhibitor; inhibits both free factor Xa and factor Xa bound in the prothrombinase complex; is well absorbed from the gut and develops maximal inhibition of the factor Xa 4 hrs after a dose; the effects last 8–12 hrs, but factor Xa activity does not return to normal within 24 hrs; is used for prevention of venous thromboembolism in patients with atrial fibrillation, elective hip and knee replacement surgery; can cause bleeding, including severe internal bleeding (possible antidote (andexanet alfa) is being investigated).

INDIRECT-ACTING ANTICOAGULANTS

ETHYL BISCOUMACETATE (NEODICUMARINUM)

It is an indirect-acting anticoagulant, coumarin derivative (Fig. 22.6).

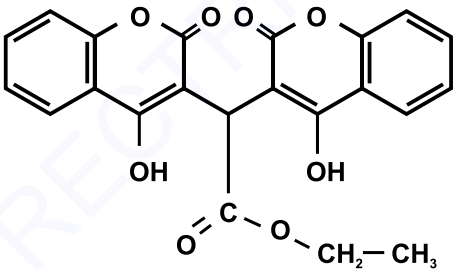

Fig. 22.6. Chemical structure of ethyl biscoumacetate

Pharmacokinetics

- is administered orally;
- is absorbed in the GI tract;
- binds to proteins in the blood plasma;
- is metabolized in the liver;
- begins to act in 2–3 hrs after the administration;
- develops maximal action in 12–30 hrs after the administration;
- acts during 48 hrs after the end of treatment;
- is excreted by urine.

Mechanism of action

Mechanism of action of ethyl biscoumacetate, warfarin, and other indirect-acting anticoagulants is the block of epoxide reductase in the liver.

The inhibition of this enzyme leads to the block in the creation of vitamin K active form and the inhibition of the synthesis of clotting factors (Fig. 22.3).

Pharmacodynamics

- a decrease in blood coagulation;
- an increase in fibrinolysis;
- a decrease in lipids concentration in the blood.

Indications

- acute thrombosis (together with or after heparin's usage);
- myocardial infarction;
- ischemic insult;
- thromboembolism;
- thrombophlebitis;
- the prevention of thrombus formation after surgeries.

Index of prothrombin should be controlled!

Side effects

1. Bleeding
2. Forming of hematomes
3. Hematuria
4. Dyspepsia
5. Suppression of the liver function
6. Allergy

Contraindications

1. Hemorrhages
2. Hemorrhagic diathesis
3. Gastric ulcer
4. Malignant diseases
5. Diseases of the liver and kidney
6. Pregnancy

For the treatment of overdose – Vikasol!

PECULIARITIES OF OTHER PREPARATIONS

Warfarin decreases blood coagulation by inhibiting vitamin K epoxide reductase, an enzyme that recycles oxidized vitamin K_1 to its reduced form after it has participated in the carboxylation of several blood coagulation proteins (prothrombin and factor VII); onset of the effect requires about 2 to 3 days and the duration of action of a single dose is 2–5 days.

Phenindione (Phenylin) is an indirect-acting anticoagulant; indandione derivative; has the same mechanism of action as warfarin; starts to act slower, has longer duration of action; may cause pink discoloration of urine resulting from excretion of the drug and its metabolites.

ANTIPLATELET DRUGS

Antiplatelets are preparations which inhibit platelet aggregation in the blood.

CLASSIFICATION

1. COX-inhibitors:
   – Acetylsalicylic acid (Aspirin).
2. Inhibitors of phosphodiesterase:
   – Dipyridamole;
   – Pentoxifylline.
3. Inhibitors of ADP-mediated aggregation:
   – Ticlopidine (Ticlide);
   – Clopidogrel.

PECULIARITIES OF PREPARATIONS

Aspirin irreversibly inhibits platelet COX-1. In such a way, it prevents the synthesis of thromboxane A_2 and decreases platelet aggregation (Fig. 22.7). This effect occurs in lower doses (less than 0.5 per day) and lasts more than 48 hrs (till 7 days). In higher doses aspirin also inhibits the synthesis of prostacycline. The drug is completely described in Chapter 13 as a non-narcotic analgesic.

Pentoxifylline is a methylated xanthine derivative, a competitive non-selective PDE inhibitor which raises intracellular cAMP, reduces inflammation and innate immunity; improves red blood cell deformability, reduces blood viscosity and decreases the potential for platelet aggregation and thrombus formation; is used to treat pain, cramping, numbness, or weakness in the arms or legs resulting from peripheral artery disease. Side effects are stomach discomfort, nausea, vomiting, indigestion, dizziness, flushing. Rare adverse reactions are angina, palpitations, bleeding, hallucinations, arrhythmias, and aseptic meningitis.

Dypiridamole inhibits adenosine desaminase and PDE in the platelets, increases cAMP concentration in the cells and inhibits thromboxane A_2 synthesis that leads to a decrease in platelet aggregation. It also increases the prostacycline level. A detailed description of the drug is represented in Chapter 17.

Ticlopidine irreversibly blocks purinergic receptors for ADP in platelet membranes. The inhibition of ADP-induced expression of glycoprotein IIb/IIIa receptors in the platelet membrane decreases platelet aggregation. Because of neutropenia and thrombotic thrombocytopenic purpura it is used if aspirin is not tolerated.

Clopidogrel is a prodrug, specifically and irreversibly inhibits the P2Y12 subtype of ADP receptor, which is important in the activation of platelets. Patients

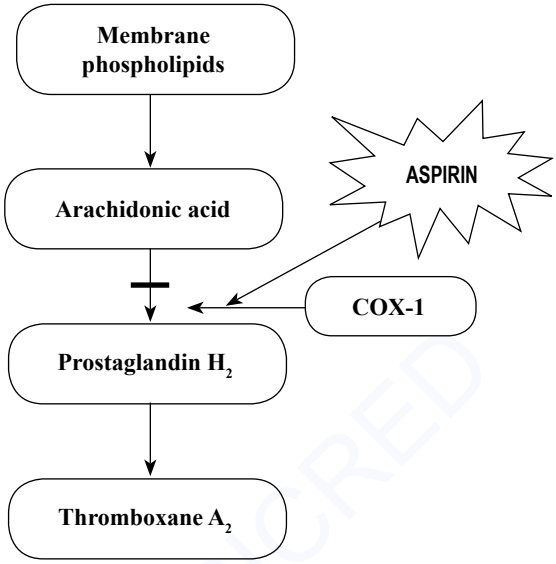

Fig. 22.7. Mechanism of antiplatelet action of aspirin

with variants in cytochrome P-450 have lower levels of the active metabolite and less inhibition of platelets by the drug. Onset of effects is about 2 hrs and lasts for 5 days; a loading dose is administered when a rapid effect is needed. Side effects include headache, nausea, itching, and heartburn, bleeding and thrombotic thrombocytopenic purpura.

Common indications to antiplatelets usage

- the prevention of thrombosis and re-thrombosis (as the discontinuation of anticoagulant therapy);
- the prophylaxis of myocardial infarction and insult;
- the prophylaxis of thrombosis after surgeries;
- angioplastics;
- the prevention of thrombosis in patients with prosthetic cardiac valves;
- thrombophlebitis.

DRUGS AFFECTING FIBRINOLYSIS

CLASSIFICATION

A. *Fibrinolytic drugs:*

1. Direct-acting:
   – Fibrinolysin.
2. Indirect-acting (activators of pro-fibrinolysin):

a) non-selective:
   – Streptokinase.

b) selective (tissue plasminogen activators):
   – Alteplase;
   – Tenecteplase.

B. *Inhibitors of fibrinolysis:*

1. Direct-acting:
   – Contrykal.
2. Indirect-acting:
   – Aminocaproic acid.

FIBRINOLYTICS

Fibrinolytics are drugs producing the lysis of the blood clot.

FIBRINOLYSIN

- is a protein from the donors' plasma, the active factor of fibrinolysis;
- is administered by IV infusion;
- has a direct action on fibrin and dissolves fibrin clot in the first hours after thrombosis;
- is used for the treatment of acute thrombosis, acute myocardial infarction, thrombophlebitis;
- may cause bleeding resulting from an increase in fibrinolysis, allergy, anaphylaxis, arrhythmia and hypotension;
- is contraindicated in bleeding, a cerebral vascular accident, recent trauma of the brain, surgery or uncontrolled hypertension.

STEPTOKINASE

- is a proteolytic enzyme from hemolytic streptococcus;

- acts indirectly, promotes the conversion of plasminogen to plasmin, causes systemic activation of fibrinolysis and degradation both of fibrin and fibrinogen resulting in the dissolving of thrombus (Fig. 22.8);
- has a plasma half-life of 23 min; is administered by IV infusion (intracoronary infusion in myocardial infarction);
- is more potent than fibrinolysin;
- does not cause heart arrhythmia.

TISSUE PLASMINOGEN ACTIVATORS

Alteplase (Actilise) is a tissue plasminogen activator (t-PA), a product of biotechnology; has a half-life of 5 min, is administered by IV infusion; has high affinity for fibrin and acts selectively on plasminogen bound with thrombus (Fig. 22.9).

Tenecteplase is an enzyme used as a thrombolytic drug; a t-PA produced by recombinant DNA technology; binds to the fibrin component of the thrombus and selectively converts thrombus-bound plasminogen to plasmin, which degradates the fibrin matrix of the thrombus; has a higher fibrin specificity and greater resistance to inactivation by its endogenous inhibitor compared to native t-PA; has plasma half-life of 20–24 min; is administered by IV infusion.

INHIBITORS OF FIBRINOLYSIS

Inhibitors of fibrinolysis are drugs with anti-enzymic activity which decrease fibrinolysis and proteolysis.

CONTRYKAL

- is a direct-acting inhibitor of fibrinolysis and proteolysis;
- is administered IV slowly or by IV infusion;
- binds to plasmin and inactivates it, inhibits the activity of trypsin (Fig. 22.8);
- inhibits fibrinilysis and stops bleeding caused by the activation of fibrinolysis; inhibits proteolysis and inflammation;
- is indicated in bleeding resulting from the activation of fibrinolysis; myocardial infarction; acute pancreatitis; prophylaxis of proteolytic complications after surgeries on the pancreas, thyroid gland, bigger salivary glands, and lungs;
- may cause allergy, nausea, vomiting, hypotension, tachycardia.

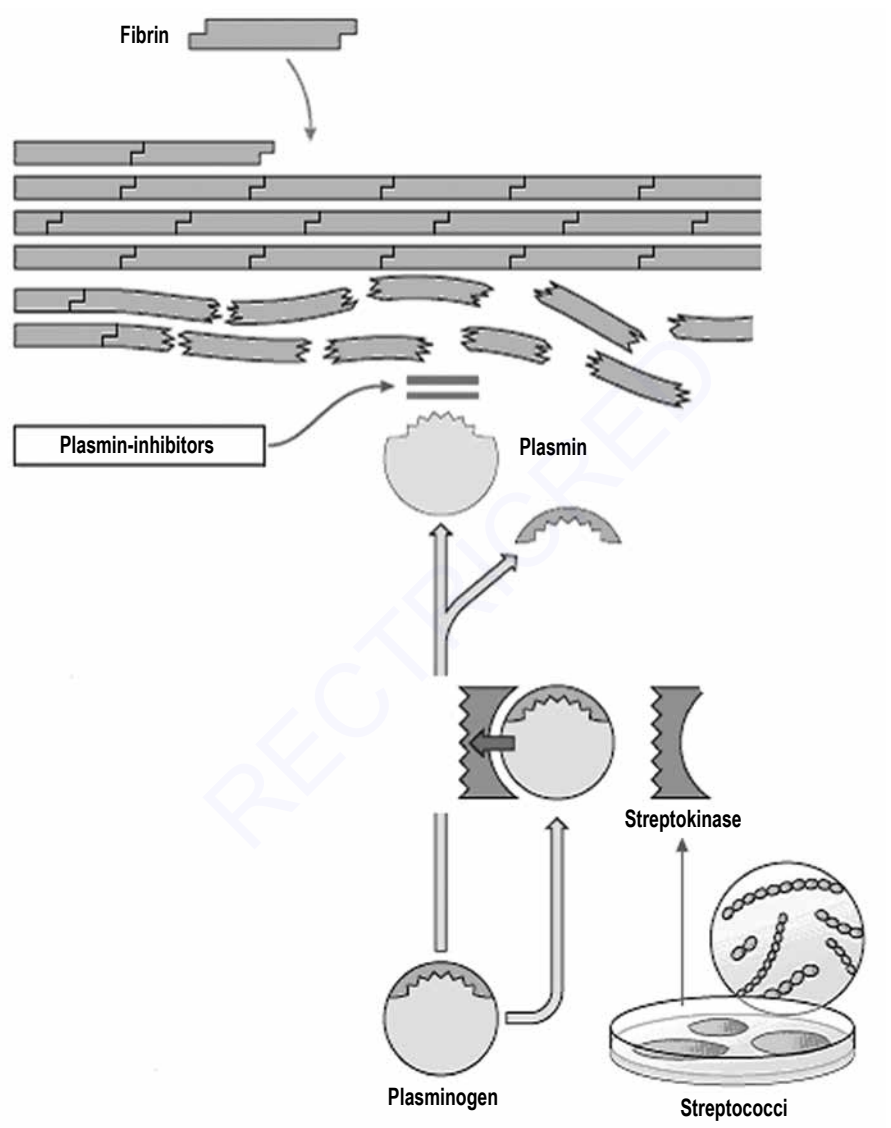

Fig. 22.8. Mechanism of action of streptokinase and plasmin inhibitors *(by H. Lüllmann, 2000)*

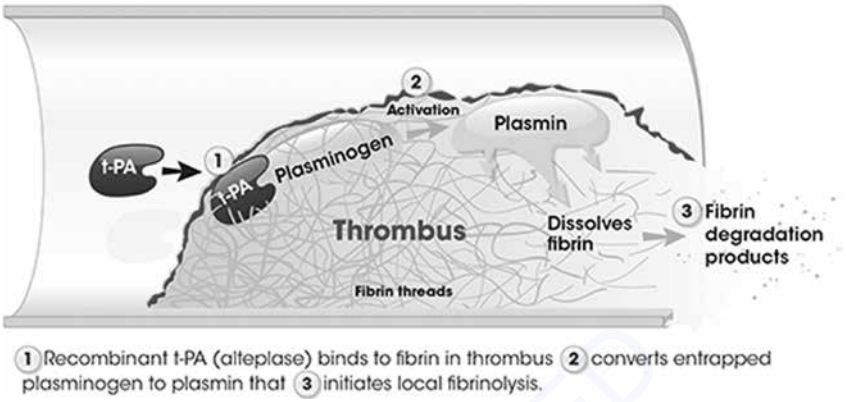

Fig. 22.9. Mechanism of action of tissue plasminogen activators (htt://www.picsearch.com)

AMINOCAPROIC ACID

- is an indirect-acting inhibitor of fibrinolysis;
- is administered orally and by IV infusion, acts during 4–6 hrs, is not metabolized, is excreted with urine;
- interacts with plasminogen and inhibits its transformation into plasmin, partly inhibits plasmin; inhibits proteolytic enzymes;
- inhibits fibrinolysis and decreases bleeding caused by the activation of fibrinolysis; suppresses proteolysis, decreases inflammation, has an anti-allergic action, stimulates the antitoxic function of the liver;
- has indications which are similar to that of contrykal; is also used in a syndrome of disseminated intravasal blood coagulation, obstetrics pathology (ablation placenta, uterine hemorrhages), liver diseases and hypoplastic anemia;
- may cause side effects, such as dizziness, hypotension, bradycardia, arrhythmia, skin rash, vomiting and nausea.

PHLEBOTONICS

Phlebotonics are a heterogenous class of drugs consisting of plant extracts (e.g., ***diosmin (detralex), aescusan)*** and synthetic compounds (e.g., ***calcium dobesilate***). They are known to improve venous tone, stabilize capillary permeability and increase lymphatic drainage. These drugs are used to treat chronic venous insufficiency, lymphoedema and hemorrhoids.

TESTS FOR SELF-CONTROL

1. Drug for the prevention of bleeding is only:
A. Heparin
B. Vikasol
C. Thrombin
D. Streptokinase
E. Contrykal.

2. Aminocapoic acid is:
A. A direct-acting anticoagulant
B. An indirect-acting anticoagulant
C. A fibrinolytic
D. An activator of fibrinolysis
E. An inhibitor of fibrinolysis.

3. Therapeutic uses of antiplatelet drugs include:
A. The prevention of secondary thrombosis
B. Acute thrombosis
C. Use of prosthetic heart valves
D. Arteriovenous shunt for hemodialysis
E. Thrombophlebitis.

4. Heparin is an anticoagulant which:
A. Is effective orally
B. Is effective *in vivo* as well as *in vitro*
C. Is an antagonist of vitamin K
D. Is bound with antithrombin and inactivates clotting factors
E. Is used to treat acute thrombosis.

5. A patient with acute myocardial infarction was treated with intravenous infusion of streptokinase. What is the goal of this drug administration?
A. To cause the lysis of thrombus directly
B. To transform plasminogen into plasmin
C. To prevent further thrombosis
D. To prevent platelets activation
E. To decrease the area of necrosis.

Answers:

1 – B; 2 – E; 3 – A, C, D, E; 4 – B, D, E; 5 – B.

Chapter 23 DRUGS ACTING ON RESPIRATORY SYSTEM

RESPIRATORY SYSTEM AND ITS PATHOLOGY

The respiratory system is one of the life-supporting systems of the body. The main function of respiration is to supply oxygen to the body and to remove carbon dioxide. It also participates in the pH constancy control of inner medium and in the temperature regulation.

Many drugs in the overdose may cause respiratory depression, but opioids cause some depression even in therapeutic doses.

The main disorders of the respiratory system are cough and bronchial asthma. The emergent conditions result from a deep suppression of the respiratory center, status asthmaticus, and pulmonary edema.

Cough is a protective reflex which guards the respiratory passways against the entrance of the foreign bodies and promotes their expulsion. Cough may be productive and non-productive. Productive cough is useful. Non-productive cough is useless and it should be stopped. If non-productive cough is due to thick secretion, it is reasonable to transform it into the productive one.

Bronchial asthma is a recurrent episodic shortness of breath caused by bronchoconstriction arising from airway inflammation and hyperreactivity.

Chronic asthmatic bronchitis is a persistent airway obstruction, chronic productive cough, and a major problem of episodic bronchospasm.

Chronic obstructive disease is a disorder of the respiratory tract resulting from generalized bronchial narrowing and the destruction of functional lung tissue (***emphysema***). It is usually characterized by an impaired expiratory outflow that responds poorly to therapy.

DRUGS ACTING ON THE RESPIRATORY SYSTEM

Drugs affecting the respiratory system are divided into 5 groups:
- respiratory stimulants;
- antitussives;
- expectorants;
- bronchodilators;
- drugs used in pulmonary edema.

RESPIRATORY STIMULANTS (ANALEPTICS)

The frequency and depth of breathing are regulated by the breathing center. ***Respiratory stimulants*** excite the respiratory center and then increase lung ventilation and gas metabolism, enhsance the oxygen content and decrease the carbon dioxide level. They improve the excretion of metabolites with perspirated air, stimulate oxidative processes, and normalize acid-based equilibrium. They may increase arterial pressure by the excitation of the vasomotor center.

Respiratory stimulants (analeptics) are described in detail in Chapter 14.

CLASSIFICATION

1. Direct-acting:
   – Etimizol.
2. Reflexly-acting:
   – Lobeline;
   – Solution of ammonia.
3. Mixed-acting:
   – Nikethamide (Cordiamine);
   – Camphor;
   – Sulfocamphocaine

PECULIARITIES OF PREPARATIONS

Etimizol is a purinergic direct-acting analeptic; increases the frequency and depth of respiration, dilates bronchi, promotes surfactant synthesis in the lungs; stimulates the production of glucocorticoids, has an anti-inflammatory, anti-allergic, and immunomodulative action, increases the tone of cardiac and skeletal muscles. It is used in the overdose of general anesthetics, asphyxia, bronchial asthma, and asphyxia of newbons.

Camphor is an analeptic with a mixed mode of action and expectorant properties which is used in the suppression of the respiratory center caused by infections and intoxications as well as in pneumonia.

Sulfocamphocaine is a derivative of the sulfocamphoral acid and procaine; stimulates the respiratory and vasomotor centers; is used in cases of poisoning with narcotic drugs, carbon oxide, in asphyxia and cardiac insufficiency.

Lobeline stimulates N-cholinoreceptors located in the carotide glomerules and excite the respiratory center reflexly. Is used as respiratory stimulant very seldom, more often in the case of poisoning with carbon oxide.

Solution of ammonia irritates sensitive nerve endings of nasal mucosa and then the respiratory center by a reflex in the case of cyncope.

ANTITUSSIVES

Antitussives are drugs suppressing cough which are used in the case of dry cough.

CLASSIFICATION

A. *Drugs of central action:*

1. Opioids:
   – Codeine phosphate;
   – Codterpine;
   – Ethylmorphine hydrochloride.
2. Non-opioid drugs:
   – Glaucine hydrochloride;
   – Butamirate citrate.

B. *Drugs of peripheral action:*

– Prenoxdiazin hydrochloride (Libexin).

PECULIARITIES OF PREPARATIONS

Codeine, ethylmorpine are alkaloids of opium and have all the properties of narcotic analgesics, but in therapeutic doses they are less potent than morphine on their analgesic activity and are highly effective in suppression of the tussive center; may cause tolerance and drug dependence. Codeine is described in Chapter 12 as narcotic analgesic.

Codterpine is a combined preparation containing codeine, sodium bicarbonate and terpinhydrate. Codeine is an opioid receptor agonist that reduces the excitabi-

lity of the cough center. Terpinhydrate enhances the bronchial glands secretion and has expectorant effect. Sodium bicarbonate increases pH of the bronchial mucus to the alkaline side, reduces the viscosity of the sputum, stimulates motor function of the cilliary epithelium in the bronchi. Indications are: dry cough in the diseases of the lungs and respiratory pathways.

Glaucine hydrochloride is an alkaloid; inhibits medulla center of the cough without tolerance and drug dependence; is taken by mouth to treat diseases of the lungs and bronchi accompanied by dry cough; may cause hypotension.

Butamirate citrate is a synthetic non-opioid antitussive, has a direct effect on the cough center; displays antitussive, moderate bronchodilator, expectorant and anti-inflammatory effects, improves oxygenation of blood; is used for dry cough of any etiology: cough in the pre- and postoperative period, during surgical interventions, bronchoscopy, whooping cough; is taken orally; may cause such side effects as skin rash, nausea, diarrhea, dizziness and allergic reactions.

Prenoxdiazin hydropchloride (Libexin) has broncholytic and local anesthetic effects, realizes its action in the bronchi; is administered orally; is used for dry cough; may produce the sensation of local anesthesia in the oral cavity.

EXPECTORANTS

Expectorants are drugs which transform non-productive cough into the productive one. Some of these drugs are described in the Chapter 4. They are devided into bronchosecretor drugs which assist liquid mucus expelling and mucolytics which melt mucus.

CLASSIFICATION

A. *Bronchosecretor drugs:*

1. Reflexly acting:
   – Infusion from the herb of *Thermopsis;*
   – Decoction from the root of *Althea;*
   – Mucaltin.
2. Directly acting:
   – Potassium iodide;
   – Sodium bicarbonate.

B. *Mucolytics:*

1. Synthetic:
   – Acetylcysteine;
   – Ambroxol;

– Bromhexine.

2. Enzymes:
   – Trypsin;
   – Chymotrypsin;
   – Ribonuclease.

AMBROXOL

Ambroxol is a bromine-containing compound (Fig. 23.1).

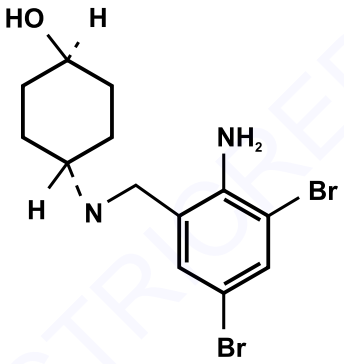

Fig. 23.1. Chemical structure of ambroxol

Pharmacokinetics

- is taken orally;
- is completely absorbed in the GI tract;
- binds with plasma proteins (90% of absorbed drug);
- develops maximal concentration in 0.5–3 hrs after the administration;
- displays high concentration in the lungs;
- penetrates the blood-brain barrier and placental barrier;
- has $T_{1/2}$ = 7–12 hrs;
- is excreted with urine and nursing mother's milk.

Mechanism of action

The drug stimulates serous cells of the bronchial mucous membrane, regulates the ratio between serous and mucous components in sputum (Fig. 23.2).

It activates hydrolytic enzymes, increases the release of lysosomes from the Clarck's cells.

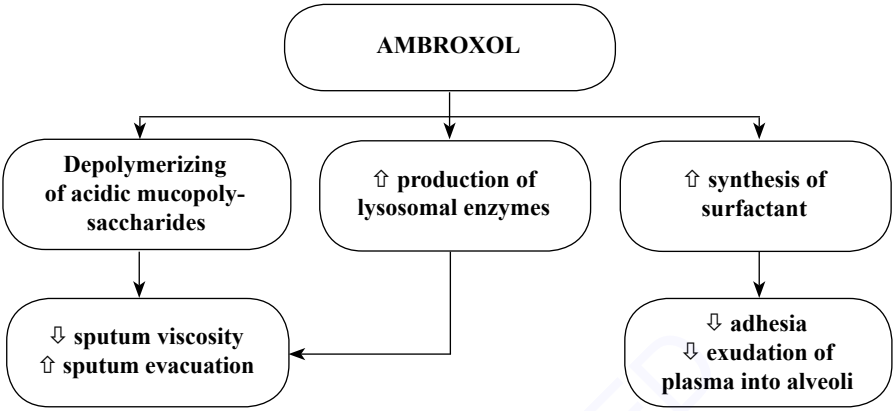

Fig. 23.2. Ambroxol's mechanism of action

It stimulates production of surfactant in the lungs and activates the transport function of ciliated cells.

Pharmacodynamics

- an expectorant action;
- a mucolytic action.

Indications

- acute and chronic diseases of airways accompanied by the formation of dense sputum and non-productive cough;
- pneumonia;
- bronchial asthma;
- bronchoectasis;
- respiratory distress-syndrome in newborns.

Side effects

1. Dyspepsia
2. Headache
3. Skin rash, urticaria

Contraindications

1. Ulcer of the stomach
2. Seizures
3. Pregnancy
4. Hypersensitivity

ACETYLCYSTEINE

It is an amino acid derivative, contains SH-group (Fig. 23.3).

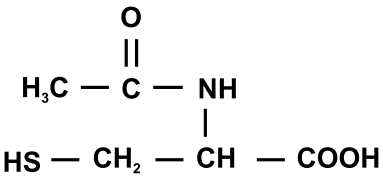

Fig. 23.3. Chemical structure of acetylcysteine

Pharmacokinetics

- is taken orally;
- is well absorbed in the gut;
- undergoes first-pass metabolism in the liver, that's why bioavailability is 10%;
- there is a dynamic balance between free acetylcysteine, protein bound drug, and its metabolites in the blood plasma;
- is distributed in the liver, kidney, lungs, and bronchial mucus;
- penetrates placenta;
- develops maximal concentration in 1 hr after the administration;
- has plasma half-life of 2 hrs;
- is excreted with urine and nursing mother's milk.

Mechanism of action

- SH-group of acetylcysteine tears disulfide connections in acidic mucopolysaccharides of sputum that leads to the depolymerization of mucoproteins and reducing of mucus viscosity;
- the drug has antioxidant properties;
- it stimulates the synthesis of glutathion, is a glutathion substitute.

Pharmacodynamics

- a mucolytic action;
- an antioxidant action;
- an antidote action in acute poisoning with paracetamol (as glutathion substitute).

Indications

- diseases of the bronchi and lungs accompanied by the formation of dense and serous-purulent sputum;
- acute and chronic bronchitis;

- tracheitis due to bacterial infection;
- pneumonia;
- bronchoectasis;
- bronchial asthma;
- synusitis;
- mucoviscedosis;
- the evacuation of viscous secretion from airways after surgeries or trauma;
- overdose of paracetamol.

Side effects

1. Dyspepsia, nausea, vomiting, stomatitis
2. Allergy (skin rash, itch, urticaria, rarely a spasm of the bronchi)
3. Nasal bleeding, hypotension, palpitation.
4. The retention of sputum if it is used together with antitussives

Contraindications

1. Ulcer of the stomach
2. Lungs bleeding
3. Hypersensitivity to the preparation
4. Age till 5

PECULIARITIES OF OTHER PREPARATIONS

Infusion from the herb of Thermopsis, decoction from the root of Althea, and Mucaltin are reflexly acting expectorants. They irritate receptors of the stomach mucosa, initiate reflexes by which increase the secretion of bronchial glands, the contractility of the epithelium and muscles and help mucus expelling.

Sodium bicarbonate and potassium iodide are directly acting expectorants. Potassium iodide is excreted through the bronchial glands, melts the mucus, and stimulates secretion. Sodium bicarbonate changes pH to the base district and stimulates the secretion of liquid sputum in the bronchi.

Trypsin and chymotrypsin are mucolytics from the group of proteolytic enzymes which tear peptide connections, change physicochemical properties of mucus. ***Desoxyribonuclease and ribonuclease*** produce the depolymerization of nucleic acids and in such a way reduce sputum viscosity and promote its evacuation. Enzymes are administered IM or by inhalation. They are used to treat purulent diseases of the bronchi, lungs, and pleura.

BRONCHODILATORS

BRONCHIAL ASTHMA AND ITS MANAGEMENT

Airflow obstruction in asthma is due to the inflammation of the bronchial wall, contraction of bronchial smooth muscle, increased mucus secretion causing short-

ness of breath and making respiration difficult. An asthmatic attack may be precipitated by the inhalation of allergens which interact with mast cells coated with immunoglobulin E, generated in response to a previous sensitivity to allergen. The mast cells release mediators, such as histamine, leukotrienes, and hemotaxic factors which promote a bronchiolar spasm and mucosal thickening from edema and cellular infiltration.

Many asthmatic attacks are not related to a recent exposure to allergen, but rather reflect bronchial hyperactivity of unknown origin which is somehow related to the inflammation of the airway mucosa.

The symptoms of asthma may be effectively treated by several drugs, but no one of the agents provides a cure for this obstructive lung disease.

The management of bronchial asthma includes:

- the avoidance of asthma triggers;
- the treatment of allergic inflammation;
- the dilation of the bronchi (Fig. 23.4).

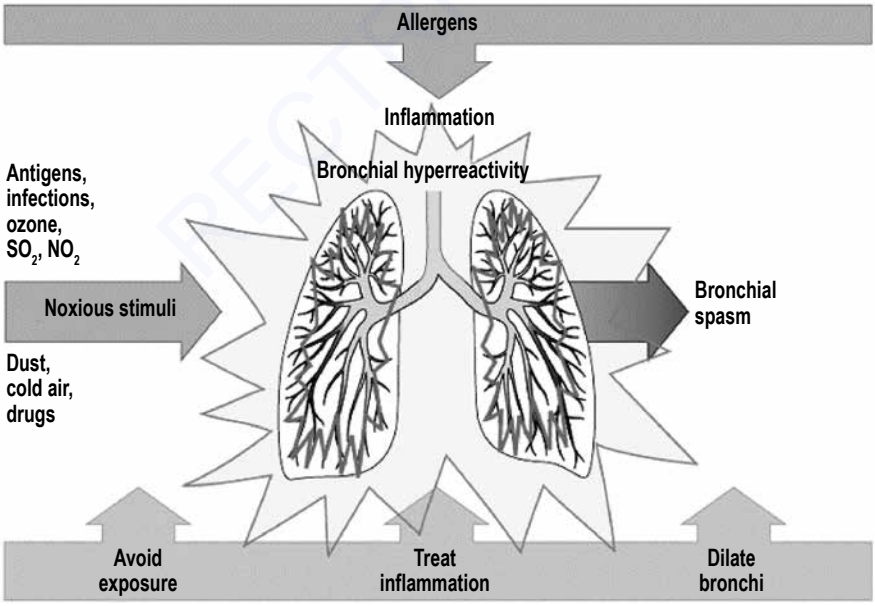

Fig. 23.4. Bronchial asthma and its management *(by H. Lüllmann, 2000)*

THEOPHYLLINE

Theophylline is 1.3-dimetylxantine (Fig. 23.5).

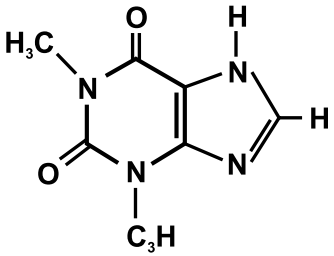

Fig. 23.5. Chemical structure of theophylline

Pharmacokinetics

- is administered orally, IV, by IV infusion;
- begins to act in 5–15 min after the IV administration;
- binds to plasma proteins (60% of drug);
- is widely distributed in tissues;
- is metabolized in the liver with the participation of cytochrome P-450;
- is excreted with urine; partially is excreted with nursing mother's milk;
- has a half-life depending on the patient's age and co-existing pathology (in adult patients with bronchial asthma it is 6–12 hrs; in elderly patients with CHF– more than 24 hrs).

Mechanism of action

- the drug blocks adenosine receptors;
- it inhibits PDE resulting in an increase of cAMP concentration and in a decrease of Ca^{++} contents inside the cells.

Pharmacodynamics

- the relaxation of the smooth muscles of the bronchi, GI tract, biliary system, and uterus;
- the dilation of coronary, cerebral, and pulmonary blood vessels;
- a decrease of peripheral vascular resistance;
- an increase in the tone of respiratory muscles, stimulation of the respiratory center in the brain medulla, the improvement of lungs ventilation and saturation of the blood by oxygen;
- a decrease in intracranial pressure and edema of the brain tissue;

- an antiplatelet action, the inhibition of thrombus formation, normalization of microcirculation;
- an anti-allergic action due to the inhibition of mast cells degranulation;
- a diuretic action due to a decrease of tubule reabsorption.

Indications

- bronchial asthma;
- spasm of the bronchi of different origin;
- chronic obstructive bronchitis;
- status asthmaticus;
- emphysema of the lungs;
- noctural apnea;
- apnea of a newborn;
- lungs hypertension;
- disturbances of cerebral blood circulation, liquor hypertension, edema of the brain caused by ischemic stroke.

Side effects

1. Restlessness, insomnia
2. Headache, tremor, seizures
3. Tachycardia, arrhythmia, hypotension, an increase in the frequency of angina attacks
4. Diarrhea, atony of the gut
5. Allergic reactions (skin rash, itch)

Contraindications

1. Hypersensitivity
2. Acute heart failure
3. Angina pectoris
4. Acute myocardial infarction
5. Heart arrhythmia
6. Hypotension, severe hypertension
7. Prone to seizures
8. Hyperthyroidism
9. Pregnancy, lactation
10. Hepatic and renal failure
11. Children till 14 (for IV administration)

Relative preparation containing complex of theophylline and ethylendiamine is named ***euphylline***. It is more soluble in water than theophylline, but has similar pharmacologic actions.

PECULIARITIES OF OTHER BRONCHODILATORS

Adrenergic agents with β-activity are the drugs of choice for mild intermitted asthma. These potent bronchodilators relax airway smooth muscles and inhibit the release of substances from mast cells which cause bronchoconstriction. The most common agents are β_2-adrenomimetics: ***salbutamol, fenoterol, terbutalin, salmeterol, and clenbuterol***.

Salbutamol, fenoterol, terbutalin are the drugs of short duration of action (4–5 hrs) and are used for the treatment of asthma attacks.

Salmeterol, clenbuterol have a prolonged action and are used for the prevention of asthma attacks.

$\beta_{1.2}$-adrenomimetics ***(orciprenaline sulfate)*** are used seldom.

In an acute attack, ***adrenaline hydrochloride*** and ***ephedrine hydrochloride*** may be administered.

M-cholinoblockers are less effective. ***Ipratropium bromide, atropine sulfate, platyphylline hydrotartrate*** are used as bronchodilators. They increase the cGMP concentration and decrease Ca^{++} concentration that leads to smooth muscles relaxation. Inhaled ipratropium bromide is useful in patients unable to take adrenergic agonists.

Myotropic broncholytics (xantines). When asthmatic symptoms cannot be controlled with adrenergic agents, addition of the methylxanthine derivatives may be appropriate. Myotropic bronchodilators relieve an airflow obstruction in acute asthma and decrease the symptoms of chronic disease.

Anti-allergic drugs. ***Cromolyn-sodium*** is an effective prophylactic agent which stabilizes the membrane of mast cells and prevents mediator release by blocking the calcium gate. The drug is not useful in the managing of an acute asthmatic attack. For the use in asthma, cromolyn-sodium is administered by inhalation. Because it is poorly absorbed only minor adverse effects are associated with it. The pre-treatment with cromolyn-sodium blocks allergen-induced and exercise induced bronchoconstriction. Not all the patients respond to cromolyn-sodium therapy, but those who do respond to the treatment show the improvement which is roughly equal to the improvement obtained from theophylline therapy.

Ketotiphen decreases histamine release and blocks H_1-histamine receptors. It is used for the prophylaxis of bronchospasm.

Fenspiride has an anti-exudative effect, interferes with the development of bronchospasm, displays the antagonism with mediators of inflammation and allergy: serotonin, histamine (at the level of H_1-histamine receptors) and bradykinin; has a spasmolytic effect. When administered in large doses, it reduces the production of various inflammation factors (cytokines, arachidonic acid derivatives, free radicals). Indications to use include bronchial asthma (maintenance therapy), bronchospasm, chronic bronchitis with respiratory failure, pharyngitis, otitis, sinusitis, whooping cough and allergic rhinitis.

There are also ***anti-leukotriene modulators (zafirlukast), leukotriene receptor antagonists, and leukotriene synthesis inhibitors (zileuton)***. They are administered orally or by inhalation, have a slow onset of action, long duration of action (12–24 hrs) and are used for the prophylaxis and chronic treatment of asthma.

Glucocorticoids. Prednisolone, dexamethasone, triamcinolone, and beclomethasone are used for the prevention of bronchial asthma attacks.

Combined preparations. ***Berodual*** causes a pronounced bronchodilating effect due to the action of its constituents ipratropium bromide and fenoterol. ***Seretid*** is a combined bronchodilator containing salmeterol and fluticasone propionate, which have different mechanisms of action.

DRUGS USED IN PULMONARY EDEMA

Edema of the lungs is an urgent state characterized by an increase of hydrostatic pressure in the lung vessels, exudation into alveoli, and disturbances in lungs ventilation. Pulmonary edema accompanies CHF, infections, intoxications.

Agents used in the treatment of pulmonary edema are:

1. Drugs decreasing hydrostatic pressure in the lung vessels:
   – *Sodium* nitroprusside and organic nitrates (nitroglycerine, isosorbide dinitrate);
   – Ganglioblockers (pentamine, hexamethonium, hygronium).
2. Broncholytics (euphylline).
3. Drugs with α-blocking properties (chlorpromazine).
4. Opioid analgesics (morphine hydrochloride).
5. Corticosteroids (prednisolone, dexamethasone).
6. Drugs improving heart contractility:
   – Cardiac glycosides (corglycon, digoxin, strophanthin);
   – Non-glycoside inotropics (dobutamine).
7. Drugs decreasing circulating blood volume:
   – Loop diuretics (furosemide, torasemide);
   – Osmotic diuretics in the conditions of tolerance *to furosemide* (mannitol, Urea pura).
8. Drugs that restore normal bronchial passage due to an antifoam action (vaporized alcohol).

TESTS FOR SELF-CONTROL

1. All the following concerning glaucine is correct, except:
A. It is a non-opiod antitussive
B. It has a central action
C. It suppresses cough
D. It decreases BP
E. It stimulates respiratory center.

2. Long-acting β-adrenergic agonist for the treatment of bronchial asthma is:
A. Adrenaline
B. Salbutamol
C. Fenoterol
D. Salmeterol
E. Isoprenaline.

3. Theophylline is:
A. Contraindicated in tachyarrhythmia
B. A synthetic catecholamine
C. A bronchodilator
D. A PDE inhibitor
E. An expectorant.

4. Ambroxol produces:
A. The stimulation of surfactant synthesis
B. An expectorant action
C. The dilation of bronchi
D. An anti-allergic action
E. The stimulation of respiration.

5. A patient with bronchial asthma addresses to his doctor with complaints of unpleasant palpitations that occur after the usage of an inhalation form of isoprenaline. The doctor advices him to use salbutamol. What is the mechanism of salbutamol's action?
A. The stimulation of β_1-adrenoceptors
B. The stimulation of β_2-adrenoceptors
C. The stimulation of α_1-adrenoceptors
D. The stimulation of α_2-adrenoceptors
E. The inhibition of M-chlolinoreceptors.

Answers

1 – E; 2 – D; 3 – A, C, D; 4 – A, B; 5 – B.

Chapter 24 GASTROINTESTINAL DRUGS

FUNCTIONS OF GASTROINTESTINAL TRACT AND THE MAIN GASTOINTESTINAL DISEASES

The main GI tract functions are digestion and absorption of the food. It also plays the role of one of the major endocrine systems in the body. Gastric exocrine cells secrete pepsinogen, hydrochloric acid, and an intrinsic factor. In addition to this, the cells of the gastric mucous membrane secrete mucus and bicarbonates, forming together a gel-like protecting layer. The most common disorders of gastric secretion are peptic ulcer and gastritis.

Under physiological conditions in the pancreatic gland most of digestive enzymes are contained in granules in the inactive form (zymogen). These enzymes are activated by enterokinase after they reach the duodenum. In acute pancreatitis, enzymes become activated inside the pancreatic tissue causing autodigestion. In chronic pancreatitis, enzyme insufficiency develops.

Disturbances of gastric motility may be manifested by nausea, vomiting, a gastroesophageal reflux and delayed gastric emptying. A vomiting reflex can be useful in the case of the ingestion of toxic substances, but it is in most cases an unpleasant side effect accompaning administration of many drugs.

Abnormalities of intestinal motility can be manifested mainly by constipation or diarrhea.

GASTROINTESTINAL DRUGS

Drugs acting on the GI tract are divided into several groups (Fig. 24.1).

Among them, there are agents influencing appetite, drugs used in disturbances of the gastric secretory function, preparations affecting gastric motility, agents

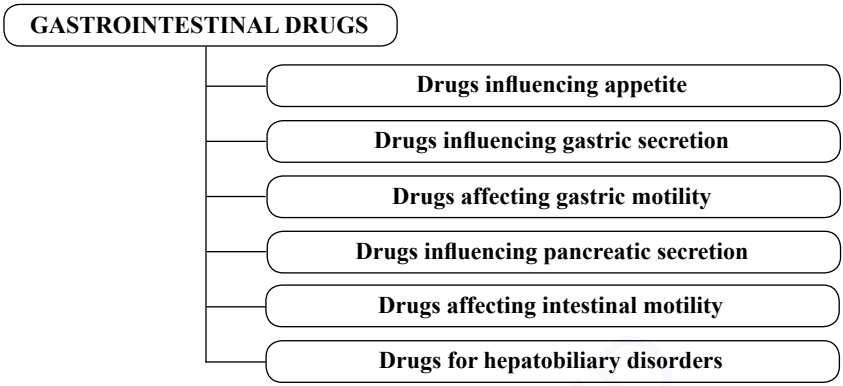

Fig. 24.1. Groups of gastrointestinal drugs

used in disturbances of pancreatic secretion, preparations used in hepatobiliary system disorders, and drugs affecting intestinal motility.

DRUGS INFLUENCING APPETITE

Drugs influencing appetite are preparations for the regulation of appetite used in gastrointestinal diseases, obesity, or anorexia.

CLASSIFICATION

A. *Stimulants of appetite (Appetizers):*

1. Bitters:
   – Tincture of *Absinthium*.
2. Hormonal preparations:
   – Insulin;
   – Retabolil.

B. *Suppressors of appetite (Anorexigens) and drugs for the treatment of obesity:*

1. Adrenergic:
   – Amfepranone (Phepranone);
   – Chlorpheniramine (Desopimon);
   – Mazindol.
2. Serotoninerghic:
   – Fenfluramine.
3. Lipase inhibitors:
   – Orlistat.

PECULIARITIES OF PREPARATIONS

Bitters are used as appetizers. They belong to drugs stimulating afferent nerve endings and are described in Chapter 4.

Insulin and retabolil are hormonal preparations with anabolic properties applied in cachexia. These drugs are described in Chapter 26.

Anorexigens are appetite suppressors for the treatment of severe obesity. They have the central mechanism of action, that's why these preparations are characterized in Chapter 15.

Orlistat is a saturated derivative of lipostatin, a potent natural inhibitor of pancreatic lipases. It prevents the absorption of fats from the human diet by acting as a lipase inhibitor and reducing caloric intake. Orlistat is designed to treat obesity. It can cause gastrointestinal side effects including steatorrhea.

DRUGS REGULATING GASTRIC SECRETORY FUNCTION

PEPTIC ULCER DISEASE AND GASTRITIS

Lesions of the mucosal wall that occur in the stomach or duodenum are referred to as ***peptic ulcer disease***. Although certain drugs can cause ulcers (in particular NSAIDs), the great majority of cases of peptic ulcer disease stems from infection with the bacterium *Helicobacter pylori.* Infection caused by *Helicobacter pylori* produces chronic ***gastritis*** which is the inflammation of the stomach lining.

Peptic ulcer disease takes two very different courses depending on the predominant location of the gastritis in the stomach. Some individuals produce excessive quantities of acid ***(hypersecretion of acid)***, and this leads to the development of ***duodenal ulcer*** (Fig. 24.2). This type of response occurs when gastritis is localized in the pyloric region.

If gastritis is located predominantly in the body of the stomach, the disease progresses in the form of ***atrophic gastritis***. The inflammation induces apoptosis of parietal cells, and there is eventual atrophy of the gastric glands. The result is ***hyposecretion of acid***. Continued tissue damage may lead to the development of ***gastric ulcer*** (Fig. 24.2).

Helicobacter pylori is classified as a carcinogen because infection increases the risk of the developing of certain types of ***gastric cancer***. This increased risk is almost exclusively associated with atrophic gastritis and gastric ulcer.

The strategy of pharmacotherapy of peptic ulcer disease and gastritis includes:

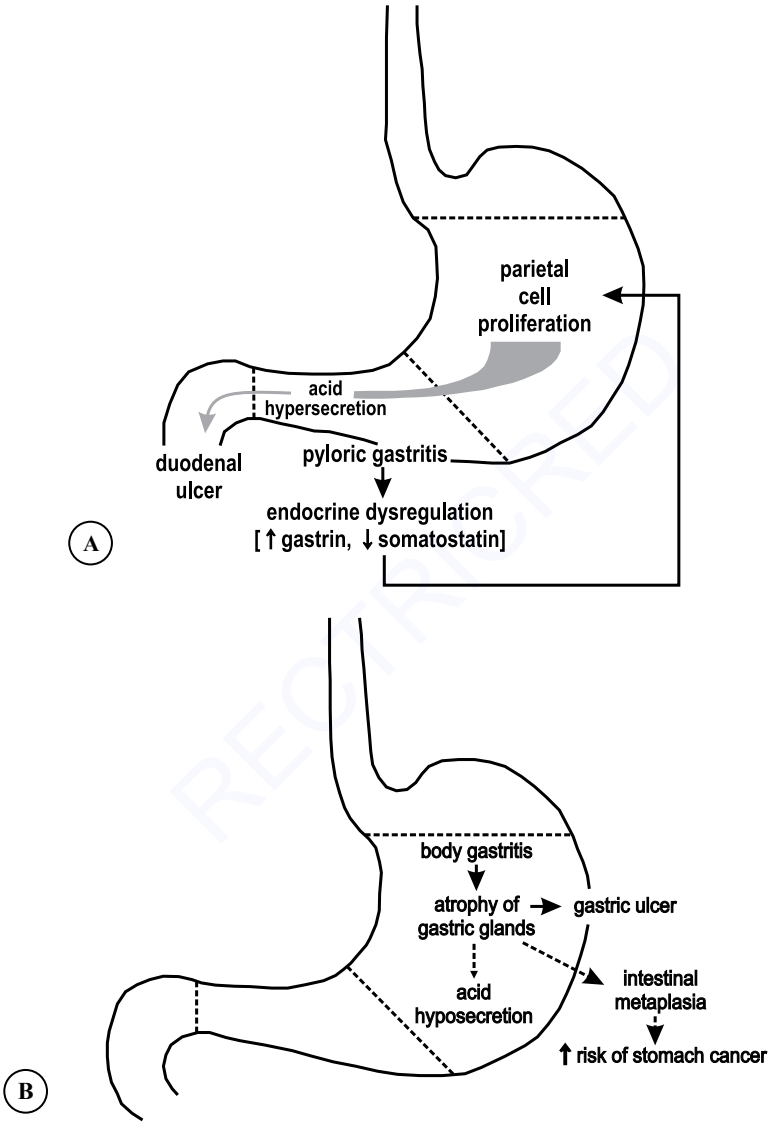

Fig. 24.2. Pathogenesis of peptic ulcer disease and gastritis:
A – duodenal ulcer and hyperacidic gastritis; B – gastric ulcer and hypoacidic gastritis
(http://www.picsearch.com)

- eradication of *Helicobacter pylori* through the use of antibiotics;
- reduction of acid secretion (Reducing the acidity in the stomach lumen promotes healing, and it also increases the effectiveness of the antibiotics);
- protection of gastric mucosa;
- replacement therapy in the condition of acid hyposecretion.

DRUGS USED IN PEPTIC ULCER DISEASE AND GASTRITIS

CLASSIFICATION

A. *Stimulants of gastric secretion:*
- – Pentagastrin;
- – Bitters.

B. *Drugs for replacement therapy:*
- – Pepsin;
- – Hydrochloric acid (diluted).

C. *Suppressors of gastric secretion:*

1. M-cholinoblockers:
   - – Atropine;
   - – Pirezepine.
2. H_2-histamine receptor blockers:
   - – Ranitidine;
   - – Famotidine.
3. Inhibitors of proton pump:
   - – Omeprazole;
   - – Pantoprazole;
   - – Lansoprazole.
4. Gastroprotectors (mucosal protector agents):

a) Coverings:
   - – Colloidal bithmus subcitrate (De-nol);
   - – Sucralfate.

b) Ulcer healing drugs:
   - – Misoprostol;
   - – Carbenoxolone.

D. *Antacids:*
- – Sodium bicarbonate;
- – Calcium carbonate;
- – Magnesium hydroxide;

– Aluminium hydroxide;
– Combined preparstions (Almagel, Maalox).

E. *Antimicrobial drugs for the treatment of peptic ulcer:*

– Metronidazole;
– Amoxicillin;
– Clarithromycin;
– Tetracycline.

DRUGS FOR STIMULATION OF GASTRIC SECRETION AND REPLACEMENT THERAPY

Pentagastrin is a synthetic polypeptide that has gastrin-like effects. It stimulates the secretion of gastric acid, pepsin, and intrinsic factor, and has been used as a diagnostic agent. In carcinoid syndrome, pentagastrin is also used as a stimulation test to elevate of several hormones. It has been used to stimulate ectopic gastric mucosa for the detection of Meckels diverticulum. Pentagastrin-stimulated calcitonin test is a diagnostic test for medullary carcinoma of the thyroid. Pentagastrin may cause panic attacks as a side effect.

Diluted hydrochloric acid, when taken before meals, reduces the pH in the stomach to 1.52, transforms pepsinogen to active pepsin and creates optimal pH for pepsin activity, reduces the peristalsis of the stomach and causes the gatekeeper's reflex. It promotes absorption of iron, stimulates the formation of gastrin; activates the formation of secretin and cholecystokinin by the mucosa of the duodenum. It is used for achilia, hypoacidic conditions, dyspepsia, hypochromic anemia (with iron preparations). As replacement therapy, very often it is used in mixture with pepsin. In the case of long-term use in large doses, acidosis and damage of teeth enamel is possible.

DRUGS INHIBITING GASTRIC SECRETION

OMEPRAZOLE

Omeprazole is a benzimidazole derivative (Fig. 24.3).

Pharmacokinetics

- is administered orally, IV, by IV infusion;
- after the oral administration, is absorbed in the small intestine with bioavailability of 35–60%;
- begins to act in 60 min; develops a maximal effect in 2 hrs after the administration and acts during more than 24 hrs;

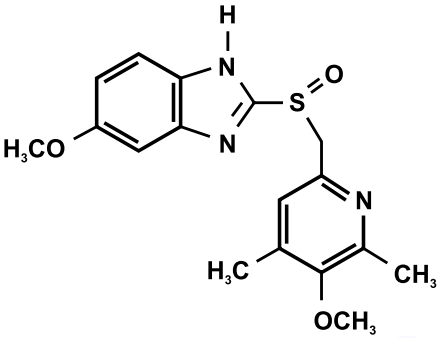

Fig. 24.3. Chemical structure of omeprazole

- binds to plasma proteins (90–95%);
- is metabolized in the liver with the formation of hydroxyomeprazole;
- has a half-life of 40–60 min;
- is excreted with urine (80%) and feces.

Mechanism of action

It inhibits H^+/K^+-ATPase which is necessary for the transport of H^+ from parietal cells of the gastric mucous membrane to the lumen of the stomach (proton pump) (Fig. 24.4).

Pharmacodynamics

- the inhibition of the final stage of basal and stimulating acid secretion.

Indications

- peptic ulcer disease;
- gastroesophagal reflux disease;
- chronic gastritis with the hypersecretion of acid;
- Zolinger – Ellison syndrome.

Side effects

1. Nausea, diarrhea, constipation, meteorism, pain in the stomach
2. Headache, weakness, depression, vision disturbances
3. Skin rash
4. Arthralgia, myalgia, eosinophilia

Contraindications

1. Pregnancy
2. Lactation
3. Childhood
4. Severe hepatic diseases

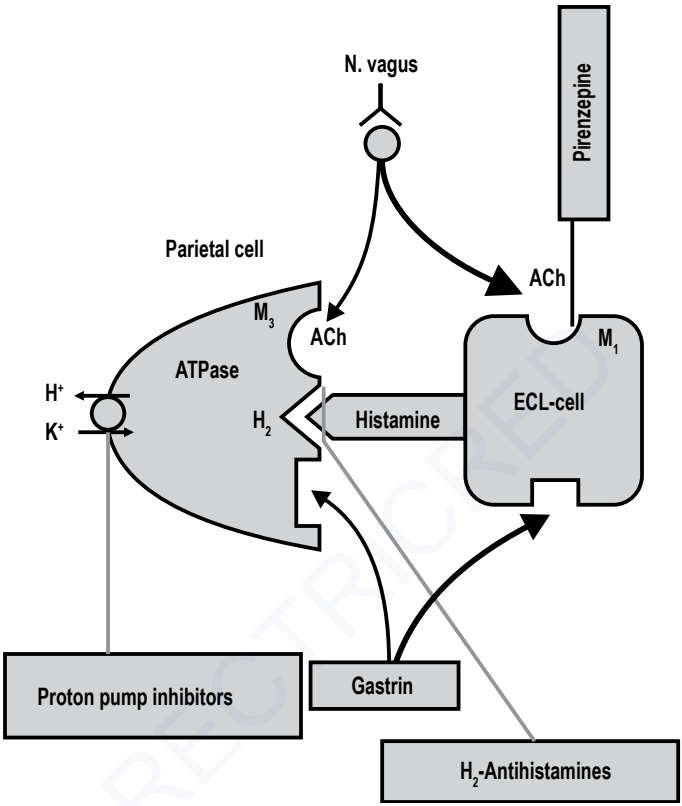

Fig. 24.4. Mechanism of action of proton pump inhibitors, H_2-antihistamines, and selective M-cholinoblockers *(by H. Lüllmann, 2000)*

PECULIARITIES OF OTHER PROTON PUMP INHIBITORS

Omeprazole, pantoprazole and lansoprazole differ in the details of chemical structure, bioavailability, half-life, etc., but the results of their clinical application are almost identical.

Lansoprazole has the highest bioavailability in the group, amounting to 80–90%, provides an earlier onset of clinical remission in comparison with omeprazole.

Pantoprazole, in contrast to omeprazole and lansoprazole, interacts significantly less with the cytochrome P-450 system. Co-administration of antacids, like food, does not affect the pharmacokinetics of the drug.

RANITIDINE

Ranitidine is H_2-antihistamine, an etylendiamine derivative (Fig. 24.5).

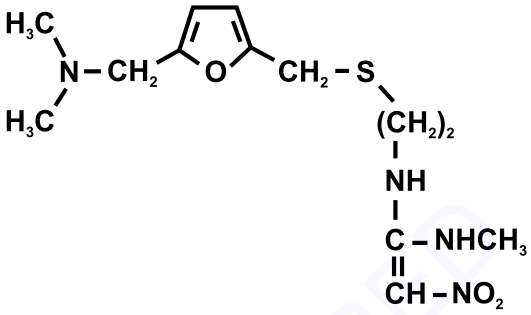

Fig. 24.5. Chemical structure of ranitidine

Pharmacokinetics

- is administered orally, IM, IV;
- is well absorbed in the GI tract: absorption is not disturbed by meal or antacids;
- starts to act in 15 min, develops a maximal concentration in 2 hrs, has a duration of action of 8–12 hrs;
- is excreted with urine during 24 hrs (40% of a dose).

Mechanism of action

It inhibits H_2-histamine receptors in parietal cells of the gastric mucous membrane (Fig. 24.4).

Pharmacodynamics

- the inhibition of gastric secretion;
- a decrease in the total volume of gastric juice;
- a decrease in pepsin activity.

Indications

- peptic ulcer disease;
- reflux-esophagitis;
- Zolinger – Ellison syndrome;
- bleeding from the upper regions of the GI tract;

- the prophylaxis of bleeding in patients suffering from peptic ulcer;
- the prophylaxis of gastric juice aspiration in a surgery under the general anesthesia.

Side effects

1. Headache, vertigo
3. Skin rash
4. An increase in the plasma concentration of hepatic enzymes
5. Thrombocytopenia
6. Hypersensitivity

Contraindications

1. Pregnancy
2. Lactation
3. Childhood
4. Severe renal and hepatic diseases
5. Gastric malignancy

PECULIARITIES OF OTHER H_2-HISTAMINE RECEPTOR BLOCKERS

Famotidine (Quamatel) is a histamine H_2 receptor antagonist that inhibits stomach acid production. Unlike cimetidine, the first H_2-antagonist, it has no effect on the cytochrome P-450 enzyme system, and does not appear to interact with other drugs. The dose of the drug is less than the dose of ranitidine. Medical uses include the treatment of gastric and duodenal ulcers, Zollinger – Ellison syndrome and multiple endocrine adenomas, gastroesophageal reflux disease, esophagitis, prevention of NSAID-induced peptic ulcers and aspiration pneumonitis in surgery patients.

OTHER GROUPS AND PREPARATIONS

M-cholinoblockers are the inhibitors of acid production. ***Atropine*** is a non-selective preparation rarely used in peptic ulcer disease. ***Pirenzepine*** is a selective cholinoreceptor antagonist, unlike atropine, prefers the M_1 type of cholinoreceptors. These drugs are described in Chapter 6.

Antacid drugs are preparations for acid neutralization. Antacids are absorbable ($NaHCO_3$) and non-absorbable ($CaCO_3$, $Mg(OH)_2$, $Al(OH)_3$) (Fig. 24.6).

They contain H^+-binding groups, such as CO_3^{2-}, HCO_3^- or OH^-. Non-absorbable agents are preferred. In this case, systemic absorption of counter ions or basic residues is minor. Antacid drugs are taken between meals (1 and 3 hrs after meals and at bedtime).They can cause a reduced absorption of other drugs, the phosphate depletion of the body with an excessive intake of $Al(OH)_3$. Because $Mg(OH)_2$ produces a laxative effect and $Al(OH)_3$ produces constipation, these two antacids are frequently used in the combination (e.g., well known combined preparations almagel and maalox).

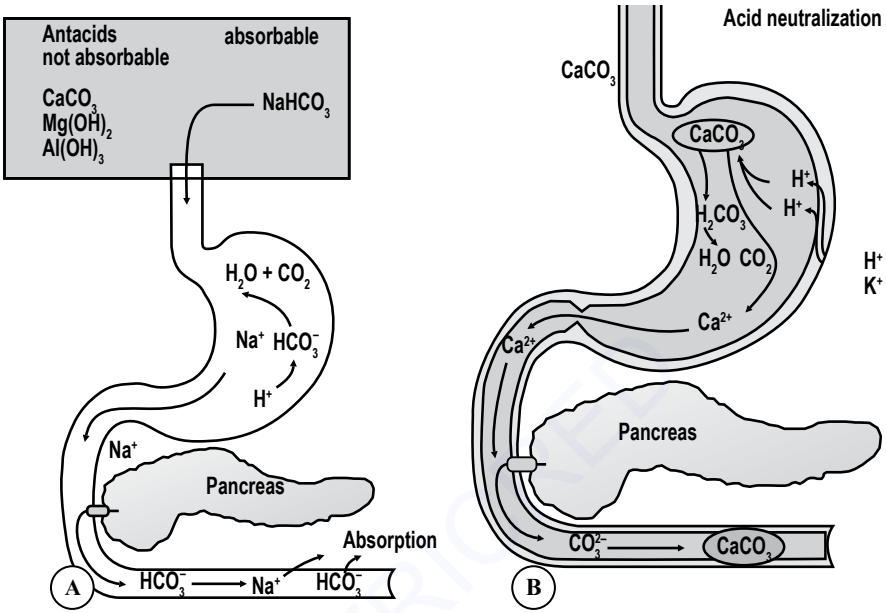

Fig. 24.6. Mechanism of action of absorbable (A) and non-absorbable antacids (B) *(by H. Lüllmann, 2000)*

Protective drugs are represented by coverings and ulcer healing drugs. ***Sucralfate*** contains aluminium hydroxide residues. It is suspension for oral administration minimally absorbed from the gut. The drug is taken on an empty stomach. Sucralfate forms an ulcer-adherent complex with proteinaceous exudate at the ulcer site (Fig. 24.7). A sucralfate-albumin film provides a barrier to diffusion of hydrogen ions, inhibits pepsin activity in gastric juice by 32%. The drug is indicated in the short-term (up to 8 weeks) treatment of active duodenal ulcer. It is well tolerated, rarely may cause constipation, diarrhea, dry mouth, gastric discomfort, indigestion, nausea, vomiting, pruritus, rash, dizziness, insomnia, sleepiness, vertigo.

Bismuth subcitrate forms a protective cover on the surface of ulcers and erosions, stimulates regeneration by the accumulation of an epidermal growth factor, increases prostaglandin E_2 synthesis, promotes the production of mucus and bicarbonates, inhibits the activity of pepsin, has an anti-helicobacter action. It is used to treat peptic ulcer disease, chronic gastritis, peptic ulcers caused by NSAIDs and functional dyspepsia. The drug has no significant side effects (it causes black discoloration of feces, rarely nausea, vomiting, diarrhea, rash).

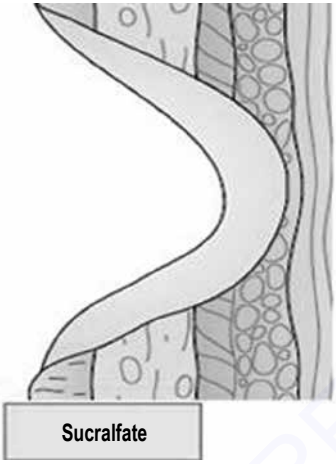

Fig. 24.7. Sucralfate's mechanism of action *(by H. Lüllmann, 2000)*

Misoprostol is a semisynthetic prostaglandin. It binds to Pg receptors, promotes mucus production and inhibits acid secretion, improves the trophy of the gastric mucous membrane (Fig. 24.8). Additional systemic effects (diarrhea, the risk of precipitating contractions of the gravid uterus) limit its therapeutic utility.

Antibiotics and metronidazole are used for the eradication of *Helicobacter pylori* (Fig. 24.9). The properties of these antimicrobial agents are described in Chapters 31, 33. They are applied in a combination with omeprazole.

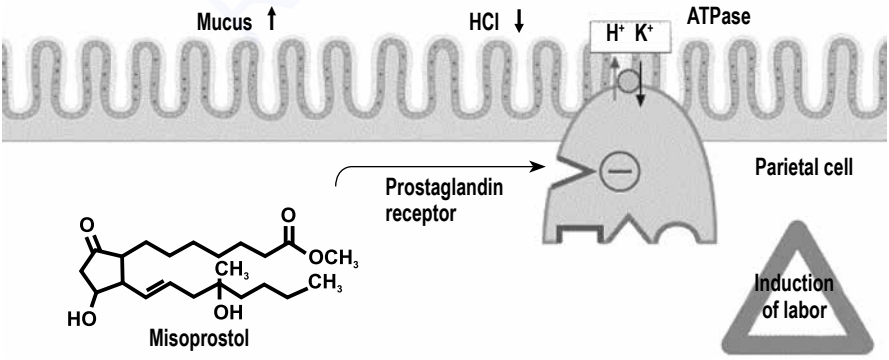

Fig. 24.8. Chemical structure and mechanism of action of misoprostol *(by H. Lüllmann, 2000)*

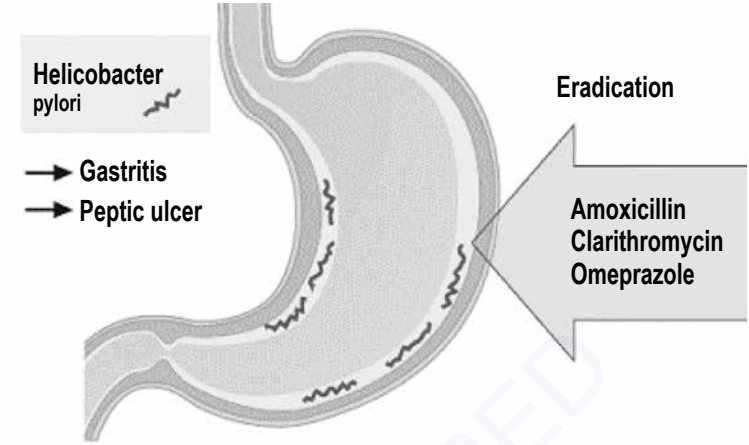

Fig. 24.9. Antimicrobial agents for eradication of *Helicobacter Pylori* *(by H. Lüllmann, 2000)*

DRUGS AFFECTING GASTRIC MOTILITY

MAIN DISORDERS OF GASTRIC MOTILITY

Vomiting is frequently occurred disturbance of gastric motility. It is a reflex regulated by the emetic center and central trigger zone (CTZ) in the brain medulla. The emetic center may be activated by impulses from the vestibular apparatus, visual, olfactory, and gustatory inputs. Psychic stimuli can also cause the stimulation of vomiting center. The main neurotransmitters involved in the control of vomiting are acetylcholine, histamine, serotonin, dopamine, and substance P (Fig. 24.10).

CLASSIFICATION

A. *Prokinetics:*
- Metoclopramide.

B. *Emetics:*
- Apomorphine;
- *Ipecacuanna* preparations.

C. *Antiemetics:*
1. Cholinergic antagonists:
   - Scopolamine (Hyoscine).
2. H_1-antihistamines:

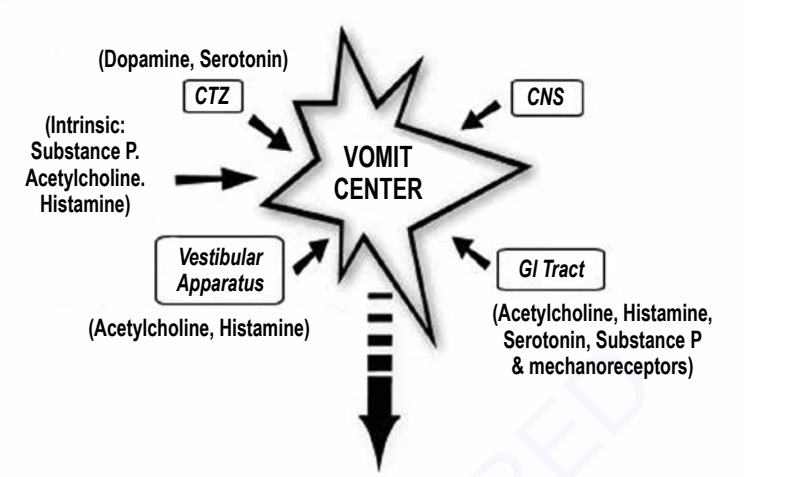

Fig. 24.10. Neurotransmitters participating in a vomit reflex *(http://www.picsearch.com)*

   - Promethazine;
   - Diphenhydramine.
3. Neuroleptics:
   - Chlorpromazine.
4. D_2-dopamine receptor antagonists:
   - Metoclopramide;
   - Domperidone.
5. 5-HT_4-antagonists:
   - Ondancetron.

METOCLOPRAMIDE

The drug is a synthetic centrally acting agent, an oxibenzamide derivative (Fig. 24.11).

Pharmacokinetics

- is administered orally, IM, IV;
- starts to act in 1–3 min after the IV injection and in 10–15 min after the IM administration;
- penetrates CNS and placenta;
- has a duration of prokinetic effect of 3 hrs, of antiemetic action – 12 hrs;
- is excreted with urine in unchanged state (85% of a dose).

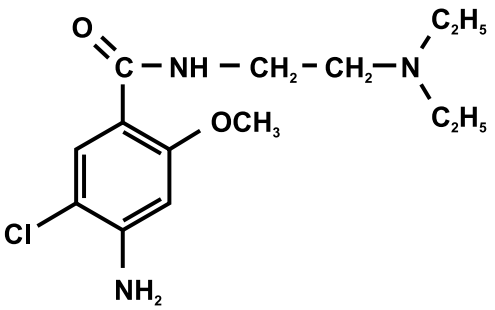

Fig. 24.11. Chemical structure of metoclopramide

Mechanism of action

- metoclopramide is a specific blocker of D_2-dopamine receptors;
- it is 5-HT_3-antagonist;
- it inhibits chemoreceptors of the trigger zone;
- the drug inhibits the sensitivity of visceral nerves translating impulses from the pylorus and duodenum to the emetic center.

Pharmacodynamics

- a decrease in vomiting and nausea;
- an increase in the tone of the stomach and intestine;
- the promotion of gastric evacuation;
- the prevention of esophagal and pyloric reflux;
- the stimulation of intestinal peristalsis;
- the normalization of the tone of the bile bladder and bile secretion;
- the stimulation of prolactin secretion.

Indications

- vomiting and nausea of different origin;
- disturbances of the gut motility in dyspepsia, reflux-esophagitis, gastroduodenitis, peptic ulcer, meteorism, and postoperative atonia of the stomach and intestine;
- X-ray investigations of the gut.

Side effects

1. Constipation, diarrhea, dry mouth
2. Weakness, somnolence, headache, depression, akatasia, extrapyramidal disturbances in children, hyperkinesis, a spasm of the face muscles, parkinsonism
3. Allergic reaction (skin rash)
4. An increase in the toxicity of ethyl alcohol and neuroleptics

Contraindications

1. Hypersensitivity
2. Gastrointestinal bleeding
3. Bowel occlusion
4. Ulcer perforation
5. Abdominal surgeries
6. Pheochromocitoma
7. Epilepsy
8. Extrapyramidal disorders
9. Pregnancy (during the first trimester)
10. Childhood
11. Severe renal and hepatic diseases
12. Job needed a quick motor reaction

PECULIARITIES OF OTHER PREPARATIONS

Emetic drugs are the stimulants of CTZ and the vomiting center. ***Ipecacuanna*** is a reflexly acting agent nowdays applied rarely. ***Apomorphine*** is centrally acting drug, a D_2-dopamine receptor agonist. It is used in acute poisonings. These preparations are described in Chapter 4.

Domperidone (Motilium) is a peripherally selective dopamine D_2-receptor antagonist. The drug is used to relieve nausea and vomiting; to increase the transit of food through the stomach by increasing gastrointestinal peristalsis; and to promote lactation by release of prolactin. It can be used to relieve gastrointestinal symptoms in Parkinson's disease because it blocks peripheral D_2-receptors, but does not cross the blood-brain barrier in normal doses. Side effects include dry mouth, abdominal cramps, diarrhea, nausea, rash, and hyperprolactinemia with related endocrinal and sexual disturbances.

Ondansetron (Zofran) is a serotonin 5-HT_3-receptor antagonist used to prevent nausea and vomiting caused by cancer chemotherapy, radiation therapy, or surgery. It is also useful in gastroenteritis and treatment of morning sickness and hyperemesis gravidarum of pregnancy. The drug is well-tolerated. Side effects are constipation, diarrhea, dizziness, headache, ototoxicity (if injected too quickly), and prolongation of the QT interval resulting in dangerous heart rhythm disturbances.

Scopolamine is M-cholinoblocker (see Chapter 6) effective in the prophylaxis of motion sickness. The drug should be taken 30 min before the start of travel and repeated every 4 to 6 hrs. Scopolamine applied transdermally can provide effective protection for up to 3 days.

Diphenhydramine is H_1-histamine receptor antagonist (see Chapter 8) is used as antiemetic to prevent kinetosis, cytotoxic drug-induced, or postoperative vomiting, emesis due to radiation sickness.

Phenothiazines (e.g., chlorpromazine) may suppress nausea and vomit that follow the surgery or are due to opiod analgesics, gastrointestinal irritation, uremia, an elevated intracranial pressure.

DRUGS AFFECTING INTESTINAL MOTILITY

DISTURBANCES OF INTESTINAL MOTILITY AND THEIR PHARMACOLOGICAL MANAGEMENT

Smooth muscles of the gut are characterized by propulsive wave-like movements ***(peristalsis)*** (Fig. 24.12). The activation of intramural mechanoreceptors and some humoral agents (cholecystokinin) induce ascending contraction and descending relaxation, whereby the intraluminal bolus is moved in the anal direction.

Activation of opioid receptors in the enteric nerve plexus results in the inhibition of peristalsis. The stimulation of M-cholinoreceptors leads to an increase in the tone and motility of the intestine.

Abnormalities of intestinal motility can manifest by ***constipation***, ***diarrhea***, and ***spasm*** of the smooth muscles (spastic colitis, colic).

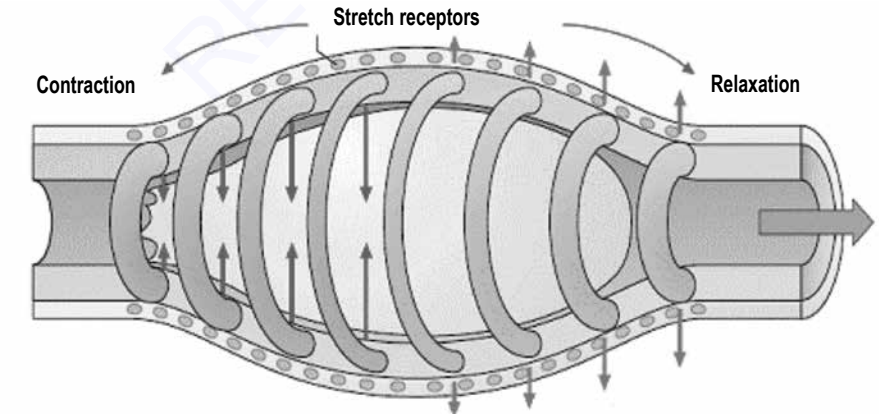

Fig. 24.12. Intestinal peristalsis as a target for drugs regulating motility of the gut *(by H. Lüllmann, 2000)*

The pharmacological management of disturbances of the intestinal motility includes:

- the use of laxatives (purgatives) to treat constipation;
- the use of antidiarrheal drugs (opioids, adsorbents, astringents) to treat non-infectious diarrhea;
- the use of antimicrobial drugs to treat diarrhea caused by infection;
- the apply of cholinoblockers and myotropic spasmolytics to treat spasticity in the gut.

CLASSIFICATION

A. *Agents increasing intestinal motility (Laxatives and purgatives):*

1. Bulk laxatives:

a) Osmotic purgatives:
   - Magnesium sulfate;
   - Sodium sulfate;
   - Lactulose.

b) Bulk-forming agents:
   - *Laminaria saccharina;*
   - Methylcellulose.

2. Irritant laxatives (purgatives cathartics):

a) Small intestine irritant purgative:
   - Castor oil.

b) Large bowel irritant purgatives:
   - anthraquinone derivatives (preparations from *Senna, Frangula, Rheum*);
   - synthetic preparations (Bisacodyl, Sodium picasulfate (Guttalax).

3. Lubricant laxatives:
   - Liquid parafin.

B. *Agents decreasing intestinal motility (Spasmolytics and antidiarrheals):*

1. Cholinoblockers:
   - Atropine;
   - Plathyphylline;
   - Hexamethonium.
2. Myotropic spasmolytics:
   - Papaverine;
   - Drotaverine.
3. Opioid receptor agonist:
   - Loperamide (Imodium).

PECULIARITIES OF PREPARATIONS

Laxatives promote and facilitate bowel evacuation by acting locally to stimulate intestinal peristalsis or to soften bowel contents. They are described in Chapter 4.

Bulk laxatives are divided into osmotic purgatives and hydrophilic colloids (bulk gels). ***Osmotically active laxatives*** (so-called saline cathartics) elicit bowel discharge 1–3 hrs after the administration. They are used to purge the bowel before the surgery or to hasten the elimination of ingested poison. ***Bulk-forming agents*** consist of the indigestible plant cell wall, take up water in the bowel and are used for the prophylaxis of constipation.

Irritant laxatives exert an irritant action on the enteric mucosa. According to the site of action they are divided into small bowel irritants (castor oil) and large bowel irritants (antraquinone derivatives and diphenolmethane derivatives).

The oral administration of 10–30 ml of ***castor oil*** is followed within 0.5–3 hrs by discharge of watery stool. Because of its massive effect, castor oil is more suitable for the treatment of acute constipation or for the rapid elimination of orally ingested poison (except lipophilic toxins).

Antraquinone derivatives are used in the form of galenical preparations and produce discharge of soft stool in 6–8 hrs after the administration. ***Synthetic preparations*** also act after the latency of 6–8 hrs. Indications to colon irritant purgatives are chronic constipation, the prevention of straining at stool following surgery, myocardial infarction, or stroke, and provision of relief in painful diseases of the anus. They should not be given in abdominal complaints of unclear origin.

Lubricant laxatives (liquid paraffin) are non-absorbable and make feces softer and more easily passed. They are used for chronic constipation and provision of relief in painful diseases of the anus. Liquid paraffin may cause such side effects as a decrease in absorption of fat-soluble vitamins, formation granulomas in enteric lymph nodes or lipoid pneumonia (after the aspiration into the bonchial tract).

Antidiarreals. Loperamide is an opioid antidiarrheal of the first choice. It is administered orally; has a half-life of 9–14 hrs; due to high affinity to the intestinal wall and intensive first-pass metabolism, does not enter the systemic blood circulation. Loperamide binds to opioid receptors in the wall of intestine that results in the inhibition of the release of acetylcholine and prostaglandins. In such a way it decreases peristalsis and increases the tone of the anal sphincter. The drug is indicated in acute and chronic non-infectious diarrhea. It may cause such side effects as allergic reactions, weakness, headache, somnolence or insomnia, dry mouth, dyspepsia, nausea, vomiting, ileus, meteorism, constipation, megacolon and disturbances of defecation. Loperamide must not be applied in the infectious diarrhea.

M-cholinoblockers and spasmolytics are used to delay a spasm of intestinal musculature and to relieve spasmotic pain in the abdomen. These preparations are described in Chapters 6, 17, 19.

DRUGS USED IN DISTURBANCES OF PANCREATIC SECRETION

MAIN PANCREATIC DISORDERS

The pathology of pancreatic gland is displayed as ***acute or chronic pancreatitis.*** An acute inflammation of the pancreas is accompanied by the activation of proteases in the gland tissue resulting in autolysis, pancreanecrosis, severe pain, and systemic activation of proteolysis and fibrinolysis.

Chronic pancreatitis leads to excretory insufficiency of the pancreas and disruped digestion of proteins, fats, and carbohydrates (creatorrhea, steatorrhea, etc).

The pharmacological management of pancreatitis includes:

- use of proteolysis inhibitors in acute pancreatitis and pancreonecrosis;
- replacement therapy with combined enzymic preparations in chronic pancreatitis.

CLASSIFICATION

1. Drugs used in acute pancreatitis (inhibitors of proteolysis):
   - Aprotinin;
   - Contrykal;
   - Aminocaproic acid.
2. Drugs used in chronic pancreatitis (combined enzyme preparations):
   - Pancreatin;
   - Mezym forte;
   - Festal.

PECULIARITIES OF PREPARATIONS

Inhibitors of pancreatic enzymes are most essential in the treatment of acute pancreatitis. ***Aprotinin and contrykal*** are directly acting inhibitors of proteolysis and fybrinolisis. ***Aminocaproic acid*** has a mixed mechanism of action, inhibits proteolytic enzymes, excerts anti-allergic and antitoxic actions. These preparations are described in Chapters 22, 28.

Enzyme replacement therapy is used in chronic pancreatitis (see Chapter 28). ***Combined preparations containing protease, amylase, and lipase*** are suitable in this case. With the oral administration of pancreatic enzymes, allowance must be made for their partial inactivation by gastric juice. Therefore, they are administered in acid-resistant medicinal forms.

DRUGS USED IN HEPATOBILIARY SYSTEM DISORDERS

MAIN HEPATOBILIARY DISORDERS

The main liver functions are detoxification and bile secretion. Liver lesions are manifested as ***acute hepatitis, chronic hepatitis, and cirrhosis.***

Cholecystitis and ***cholelithiasis*** are also widely spread diseases of the hepatobiliary system. Following its secretion from the liver into bile, water insoluble cholesterol is held in solution in the form of micellar complexes with bile acids and phospholipids. When more cholesterol is secreted than can be emulsified, it precipitates and form ***gall stones***.

CLASSIFICATION

1. Agents stimulating bile secretion (choleretics):
   – Osalmid (Oxaphenamidum);
   – Cholenzym;
   – Allochol.
2. Agents promoting bile release (cholekinetics):
   – Atropine;
   – Papaverine;
   – Drotaverine;
   – Magnesium sulfate.
3. Gall stone dissolving drugs:
   – Chenodeoxycholic acid;
   – Ursodeoxycholic acid.
4. Hepatoprotectors:
   – Ademetionine (Heptral);
   – Thioctic acid (Dialipon, α-lipoic acid);
   – Arginine glutamate (Glutargin);
   – Silimarin (Darsil);
   – Thiatriazolne;
   – Essentiale.

PECULIARITIES OF PREPARATIONS

Choleretics stimulate the production and secretion of dilute bile fluid. Among them there are drugs containing bile or essential bile acids as well as synthetic preparations. Bile containing drugs are cholenzym and allochol.

Cholenzym contains dry bile, lyophilized tissues of animals' pancreas and intestine. Due to the presence of bile acids and enzymes, the drug improves secretion and motility of the gut. It is indicated in gastritis, achilia and enterocolitis.

Allochol is a combined preparation containing dry bile, dry extracts of *Allium* and *Urtica*, and activated charcoal. Beside the influence on bile secretion, it stimulates secretion and motility in the gut, normalizes microbial state. The drug is used in constipation, dyspepsia.

Osalmid (Oxaphenamidum) is a synthetic preparation with choleretic, spasmolytic, and anti-inflammatory effects. It does not elevate the concentration of chelates, bilirubin, and cholesterol in bile. The drug is used in chronic cholecystitis.

Cholekinetics stimulate the gallbladder to contract and empty (e.g., magnesium sulfate, cholecystokinin). Some of them decrease spasm of smooth muscles of the gallbladder and biliary pathways (atropine, papaverine, drotaverine) and in such a way promote the release of bile. Cholekinetics are employed to test the gallbladder function for diagnostic purposes as well as to treat colic, acute or chronic cholecystitis (cholekinetics with a spasmolytic action).

Dissolving of cholesterol-containing gallstones can be achieved by a long-term oral administration of ***chenodeoxycholic acid (CDCA) or ursodeoxycholic acid (UDCA)***. They are stereoisomeric bile acids presented in a small amount in bile. CDCA is absorbed in the small intestine, undergone conjugation in the liver, and excreted into the bile that leads to the elevation of bile acids concentration in bile. Under such condition the solubility of cholesterol increases and cholesterol-containing stones can be dissolved slowly. The daily dose is 8–10 mg, the course of treatment – 1–2 years. UCDA is more effective and better tolerated than CDCA. Both preparations may cause diarrhea, an elevation of liver enzymes in plasma. Stone formation may recur after the cessation of a successful therapy.

Hepatoprotectors are preparations protecting hepatocytes from different aggressive factors. They are divided into the plant preparations and drugs containing essential phospholipids, amino acid derivatives, etc.

Ademetionine (Heptral) is a hepatoprotector with antidepressant activity described in Chapter.15.

Thioctic acid (α-lipoic acid, Dialipin) is an antioxidant. It participates in the oxidative decarboxylation of pyruvic acid and α-keto acids, helps to reduce blood

glucose and increase glycogen amount in the liver, stimulates cholesterol metabolism. The drug improves liver function, reduces the damaging effect of the toxins, including alcohol. It has hepatoprotective, hypolipidemic, and hypoglycemic action. Indications are liver diseases, diabetic and alcoholic polyneuropathy. Side effects include allergic reactions, and thrombocytopathy, hemorrhagic rash, thrombophlebitis, increased intracranial pressure, difficulty breathing, hypoglycemia, convulsions, diplopia with IV administration.

Glutargin is a combination of arginine and glutamic acid, which play an important role in the neutralization and excretion of ammonia. Glutargin also has hepatoprotective effect due to its antioxidant, antihypoxic and membrane-stabilizing properties. In alcoholic intoxication, the drug stimulates the utilization of alcohol, displays antitoxic effect. In the pathology of pregnancy, it produces vasodilator and antihypoxic effects, reduces the hypoxia of the fetus. Indications are acute and chronic hepatitis, poisoning by hepatotropic poisons; hepatic encephalopathy, precoma and coma accompanied by hyperammonemia; acute alcohol poisoning, alcoholic encephalopathy and coma; complications in the third trimester of pregnancy.

Thiotriazoline is a morpholinium salt of thiazole acid. The pharmacological effect is due to antiischemic, membrane-stabilizing, antioxidant and immunomodulatory properties. The drug produces compensatory activation of anaerobic glycolysis and an increase of oxidation processes in the Krebs cycle with the preservation of the intracellular ATP fund. The presence in the structure of thiol and tertiary nitrogen causes the activation of the antioxidant system. Influence of thiazole acid leads to the inhibition of lipid peroxidation in the myocardium, reduction of its sensitivity to catecholamines, stabilization and reduction of necrosis and myocardial ischemia. The drug prevents the destruction of hepatocytes, reduces lipid infiltration and centrolobular necrosis of the liver, promotes reparative regeneration of hepatocytes; increases the rate of synthesis and excretion of bile, normalizes its chemical composition. Indications to use include hepatitis, cirrhosis of the liver, toxic liver lesions, coronary heart disease and side effects of some other drugs.

Essentiale is a combined preparation containing essential phospholipids (phosphotidilcholine) and vitamins (pyridoxine, cyanocobalamin, nicotinic acid, pantothenate). It is administered orally or by IV infusion. The drug improves lipid metabolism, protein synthesis, and oxidative phosphorilation, inhibits lipid peroxidation, stabilizes cell membranes. In such a way, it protects liver tissue against hepatotoxic poisons, inhibits hepatic necrosis, promotes the restoration of hepatocytes structure and functions. Essentiale is used in acute and chronic hepatitis, cirrhosis, hepatic coma, fat embolism, poisoning with hepatotoxic agents, liver lesions caused by diabetes mellitus, atherosclerosis, before and after surgeries in the hepatobiliary system. It has no serious side effects and contraindications.

Silimarin (Darsil) is a plant preparation containing flavonoids from *Silybum mariarum* (Fig. 24.13). It demonstrates hepatoprotection grounded on antioxidant, membrane-stabilizing, anti-inflammatory effects and is indicated in acute and chronic hepatitis, cirrhosis, intoxications with hepatotoxic substances. The drug is well tolerated.

Fig. 24.13. *Silybum mariarum* containing hepatoprotective flavonoids

DRUGS FOR TREATMENT OF METEORISM

Meteorism (tympanites, intestinal gas) is a medical condition in which excess gas accumulates in the gastrointestinal tract and causes abdominal distension.

SIMETHICONE

Simethicone is a silicone compound of the group of polydimethylsiloxanes with the properties of defoamer. It changes the surface tension of the bubbles of intestinal gas, inhibits their formation and promotes their destruction. The gases released in this way can be absorbed by the walls of the intestine or removed with peristalsis. During Ro-investigation, it prevents the interference and overlapping images; promotes better contrast of the mucous membrane of the colon. The drug is not absorbed in the body and after passing through the gut is excreted unchanged. Indications are meteorism, Remmeld's syndrome, aerophagia, formation of gases in the postoperative period, preparation for diagnostic procedures of the abdominal cavity.

Adsorbing drugs (activated charcoal, enterosgel) also can be used in meteorism (see Chapter 3).

PREPARATIONS OF PROBIOTICS

The World Health Organization's definition of probiotics is “live microorganisms which, when administered in adequate amounts, confer a health benefit on the host”. Live probiotic cultures are available in fermented dairy products and probiotic fortified foods. However, tablets, capsules, powders, and sachets containing the bacteria in a freeze-dried form are also available: ***hylak forte (Antidiarrheal microorganisms), lactobacterin (Lactobacillus acidophilus), bifidumbacterin (Bifidobacterium bifidum), linex (Lactic acid producing microorganisms combi-***

nation). They are used for antibiotic-associated diarrhea, cholesterol level control, gastroenteritis, inflammatory bowel disease in adults, acute diarrhea and rotavirus infections in children. The manipulation of the gut microbiota is complex and may cause bacteria-host interactions. Some people, such as those with immunodeficiency, short bowel syndrome, central venous catheters, cardiac valve disease and premature infants, are at higher risk for adverse events.

TESTS FOR SELF-CONTROL

1. Ranitidine inhibits gastric secretion induced by:
A. Histamine
B. Pentagastrin
C. Acetylcholine
D. NSAIDs
E. None of the listed.

2. The preparation which prevents the activation of proteolytic enzymes in the pancreas is:
A. Pancreatin
B. Festal
C. Aprotinin
D. Omeprazole
E. Atropine.

3. An ulcer-healing effect of bismuth subcitrate is based on:
A. Acid neutralization
B. An increase in prostaglandin synthesis
C. The irradication of *Helicobacter pylori*
D. The inhibition of proton pump
E. The blockage of M-cholinoreceptors.

4. The true statements concerning laxatives and antidiarrheals are:
A. Osmotic laxatives are used to remove the poison from intestine
B. Castor oil is applied for the elimination of lipophilic toxins
C. Antraquinone derivatives act in 6–8 hrs after the administration
D. Loperamide is an antidiarrheal drug of the first choice
E. Lopepamide is M-cholinoblocker.

5. A patient has duodenal ulcer accompanied by the hypersecretion of gastric juice. He is prescribed with a potent inhibitor of gastric secretion which belongs to "proton pump" inhibitors. This drug is:

A. Pirenzepine
B. Omeprazole
C. Ranitidine
D. Bisacodyl
E. Metoclopramide.

Answers:

1 – A; 2 – C; 3 – B, C; 4 – A, C, D; 5 – B.

Chapter 25 DIURETICS. ANTI-GOUT DRUGS. DRUGS ACTING ON THE MYOMETRIUM. DRUGS USED TO TREAT ERECTILE DYSFUNCTION

NEPHRON AND ITS FUNCTION

Urine formation is the function of the kidney. ***Nephron*** is the basic structural and functional unit of the kidney (Fig. 25.1). It includes vascular glomerulus, capsule, proximal tubule, loop of Henle, distal tubule, collecting tubule. Its chief function is to regulate water and soluble substances by filtering the blood, reabsorbing necessary substances and excreting the rest of urine. Nephrons eliminate wastes from the body, regulate blood volume and pressure, control levels of electrolytes and metabolites, and regulate blood pH. Its functions are vital to life and are regulated by hormones, such as antidiuretic hormone, aldosterone, and parathyroid hormone.

The cell of the renal epithelium has apical and basal membranes.

On ***the apical membrane*** there is a passive transport of Na^+ through pores with the participation of permeases. The synthesis of permeases is controlled by aldosterone.

On ***the basal membrane*** there is an active transport of ions by biological pumps. Energy for this process is produced by K^+/Na^+-ATP-ase, succinate dehydrogenase. Glucose, amino acids, inorganic phosphate, and some other solutes are reabsorbed via secondary active transport through co-transport channels driven by the sodium gradient out of the nephron.

Carbonic anhydrase takes part in the forming of H^+ and HCO_3^-, which are exchanged on Na^+ on the apical membrane or reabsorbed together with it on the basal membrane.

Because of its importance in body fluid regulation, the ***nephron is a common target of drugs that treat high blood pressure and edema***. These drugs, called

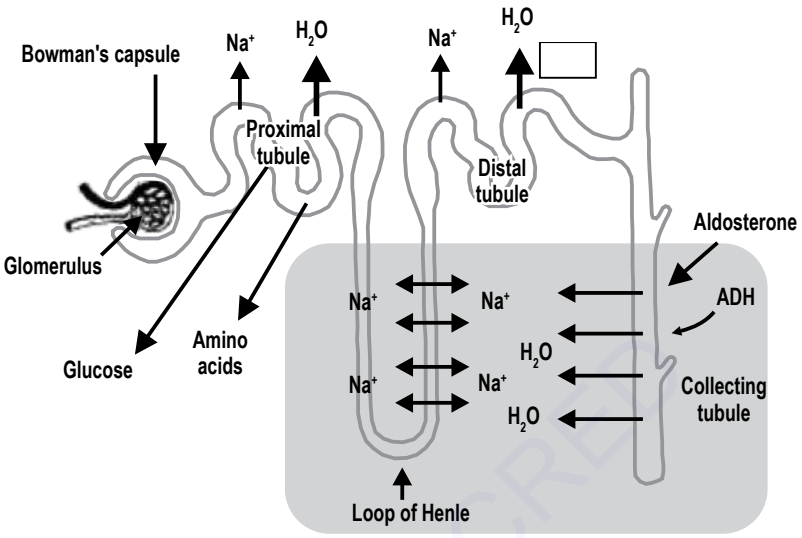

Fig. 25.1. Structure and function of nephron *(http://www.picsearch.com)*

diuretics, inhibit the ability of the nephron to retain water, increasing the amount of urine produced.

The management of urine formation may be achieved by:

- an increase of glomerular filtration;
- a decrease of tubular reabsorption (the most preferable way: primarily the reabsorption of sodium and chloride is decreased; excretion of water is secondary to excretion of salts).

DIURETICS

Diuretics are drugs which increase water and salts excretion from the body by a direct action on kidney functions.

CLASSIFICATION

1. Thiazides:
   - Hydrochlorothiazide (Dichlothiazide);
   - Indapamide.
2. Loop diuretics:
   - Furosemide (Lasix);

- Ethacrynic acid;
- Torasemide.

3. Carbonic anhydrase inhibitors:
   - Acetazolamide (Diacarb).
4. Potassium-sparing diuretics:
   - Spironolactone;
   - Triamterene.
5. Osmotic diuretics:
   - Mannitol;
   - Urea.

HYDROCHLOROTHIAZIDE

It is a thiazide diuretic (Fig. 25.2).

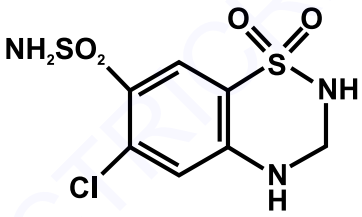

Fig. 25.2. Chemical structure of hydrochlorothiazide

Pharmacokinetics

- is administered orally;
- is quickly absorbed in the gut (60–80% of a dose);
- develops effect in 2 hrs after the administration and acts during 12 hrs;
- is excreted with urine in an unchanged state;
- penetrates placental barrier and may be excreted with nursing mother's milk.

Mechanism of action

- hydrochlorothiazide is secreted into the tubular fluid by proximal tubule cells;
- in the distal convoluted tubules, it blocks K^+/Na^+-ATP-ase and succinate dehydrogenase and inhibits energetic metabolism (Fig. 25.3);
- inhibition of energy production blocks Na^+, Cl^- symporter that is associated with the luminal (basal) membrane;

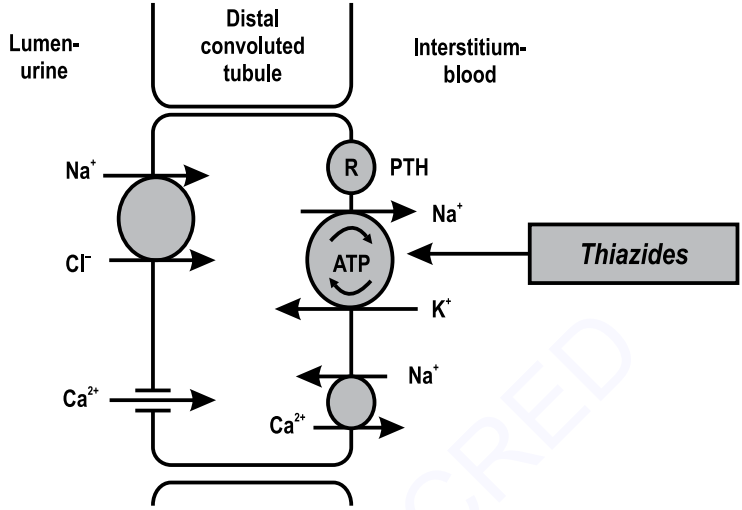

Fig. 25.3. Mechanism of action of hydrochlorothiazide

- a decrease in active transport of Na^+ to the blood leads to the elevation of Na^+ concentration in the cell and inhibition of passive transport of Na^+ and Cl^- through the apical membrane;
- Na^+, CL^-, K^+, and water stay in primary urine and are excreted. The result is a diuretic action.

Pharmacodynamics

- an enhance in Na^+ and Cl^- excretion (the effect on Na^+ is small because most of the Na^+ has already been absorbed prior to reaching the distal tubule);
- an enhance in K^+ excretion;
- a reduce in uric acid excretion;
- a decrease in Ca^{++} excretion, an enhance in the excretion of Mg^{++};
- an increase of diuresis and a decrease in the volume of blood;
- the reduction of peripheral vascular resistance and lowering of BP;
- a decrease in diuresis in patients with diabetes insipidus;
- a decrease in the intraocular pressure.

Indications

- hypertension;
- edema caused by CHF or hepatic cirrhosis;

- treatment with corticosteroids and estrogens;
- renal disturbances (nephrotic syndrome, acute glomerulonephritis, chronic renal failure);
- diadetes insipidus;
- glaucoma.

Side effects

1. Electrolyte abnormalities: volume depletion, hypokalemia, hyponatremia, hypochloremia, hypochloremic alkalosis, hypercalcemia, and hypomagnesemia
2. Hyperuricemia
3. Hyperglycemia
4. Increased plasma levels of LDL-cholesterol, and triglycerides
5. Sexual dysfunction (impotence)
6. Heart arrhythmias due to hypokalemia
7. Worsening of renal and hepatic insufficiency
8. A variety of drug interactions: a decrease in the efficacy of anticoagulants and uricosurics; an increase in the toxicity of cardiac glycosides and antiarrhythmic drugs

Contraindications

1. Anuria
2. Gout
3. Hepatic dysfunction
4. Hypercalcemia
5. Pancreatitis
6. Pregnancy

PECULIARITIES OF OTHER DIURETICS

FUROSEMIDE

- is a loop diuretic, or high ceilling diuretic;
- is administered IM, IV, orally; after the IV injection, starts to act in 5–10 min, develops a maximal effect in 20–60 min and acts during 1.5–3 hrs; after the oral administration starts to act in 30–60 min and acts during 4–6 hrs; has bioavailability of 50–70%; binds to plasma proteins (95–99%); is metabolized in the liver by conjugation with glucuronic acid; has $T_{½}$ = 0.5–1.5 hrs; is excreted with urine; is active under the conditions of acidosis as well as under the conditions of alkalosis;
- has the mechanism of action similar to the mechanism of thiazides, but the site of action is a thick ascending limb of the loop of Henle (Fig. 25.4). This limb has a high reabsorptive capacity and is responsible for the reabsorbing 25% of the filtered load of Na^+. The loop diuretics act by blocking of Na^+, K^+, and Cl^- symporter. Because of the large absorptive capacity and the

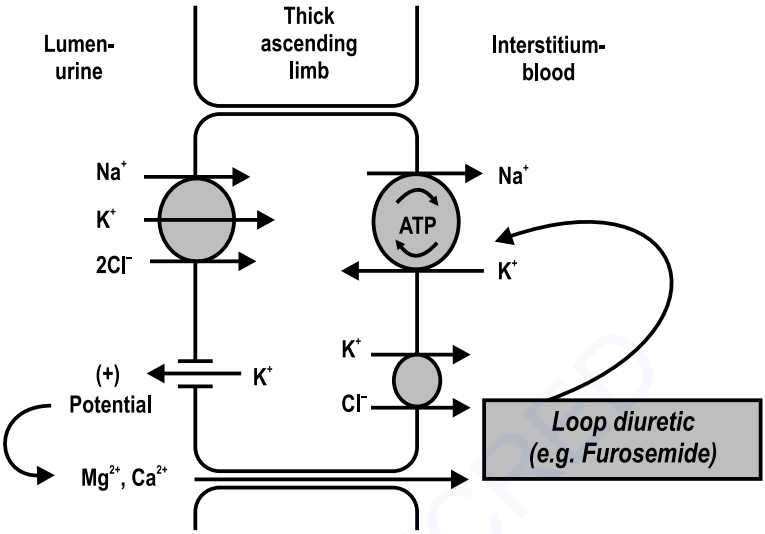

Fig. 25.4. Mechanism of action of furosemide

amount of Na^+ delivered to the ascending limb, loop diuretics have a profound diuretic action. Excretion of Cl^- is greater than Na^+ one; large doses promote ureic acid excretion. The osmotic gradient for water reabsorption is also reduced, resulting in the increased water excretion. The reduction in the cellular K^+ also results in a loss of Ca^{++} and Mg^{++};

- displays a potent and quick diuretic action with a significant increase in Na^+, K^+ and Cl^- excretion; maintains the renal blood flow and does not inhibit glomerular filtration;
- is indicated in edema of the lungs, edema of the brain, forced diuresis in acute poisonings, hypertensive emergency, acute glaucoma, chronic edemas associated with CHF, cirrhosis, renal diseases and hypercalcemia;
- may cause side effects, such as hypokalemia, disturbances in electrolytes balance and renal ureac acid secretion, hypotension, vertigo, collapse, arrhythmia, thrombotic complications, dry mouth, nausea, vomiting, diarrhea, pancreatitis, weakness, skin rash, ototoxicity, rarely aplastic anemia, leukopenia and hematuria;
- is contraindicated in acute glomerulonephritis, acute renal failure, anuria, obturation of urinary pathways, hepatic coma, pancreatitis, disturbances in electrolyte balance, gout, diabetes mellitus, hypotension, lupus erhythematosus, first half of pregnancy or lactation.

ETHACRYNIC ACID

- is a loop diuretic;
- is administered orally and IV; after the oral administration, starts to act in 30–60 min, develops maximal effect in 2 hrs, and acts during 6–9 hrs; after the IV injection, begins to act quickly and is suitable for emergency help;
- has the mechanism of action and pharmacodynamics similar to that of furosemide, but does not increase bicarbonate excretion;
- is indicated similar to furosemide, is effective in the treatment of bromides accumulation in the body;
- has no significant influence on the electrolytes balance in the blood, but is tolerated worse than furosemide, especially in patients with renal insufficiency.

TORASEMIDE

- is a loop diuretic;
- is mainly used in the management of edema associated with CHF; is also used at low doses for the management of hypertension;
- compared with other loop diuretics, torasemide has a more prolonged diuretic effect than equipotent doses of furosemide and relatively decreased potassium loss; does not induce ototoxicity.

INDAPAMIDE

- is a thiazide-like diuretic;
- is used in hypertension and edema due to CHF;
- side effects are hypokalemia, fatigue, orthostatic hypotension and allergic reactions.

ACETAZOLAMIDE

- is a carbonic anhydrase inhibitor with a sulfonamide structure;
- is the prototype for this class of drugs;
- has the mechanism of action connected with changes in the reabsorption of HCO_3^-. HCO_3^- is reabsorbed in the proximal tubules and requires the activity of carbonic anhydrase. HCO_3^- reabsorption takes place in a circuitous way. Intracellularly carbonic anhydrase converts H_2O and CO_2 to the carbonic acid (H_2CO_3). H_2CO_3 dissociates into H^+ and HCO_3^-. The HCO_3^- is transported across the basal membrane. H^+ is secreted into the tubular lu-

men in exchange for Na^+. The H^+ combines with a filtered HCO_3^- to form H_2CO_3 which immediately dissociates into H_2O and CO_2, that is reabsorbed. Therefore, filtered bicarbonate is reabsorbed for every H^+ secreted. Carbonic anhydrase inhibitors, by blocking the enzyme, prevent the reabsorption of $NaHCO_3^-$, and hence diuresis occurs (Fig. 25.5);

- produces HCO_3^- loss; increases Na^+ and K^+ excretion; decreases the renal blood flow; lowers intraocular pressure and intracranial pressure due to the inhibition of carbonic anhydrase in these tissues;
- is not used for its diuretic properties; is used to reduce intraocular pressure in glaucoma, to treat epilepsy, altitude and motion sickness;
- may cause side effects, such as metabolic acidosis, sedation, and paresthesia; because of the structural similarity to sulfonamides, acetazolamide can cause bone marrow depression and allergic reactions.

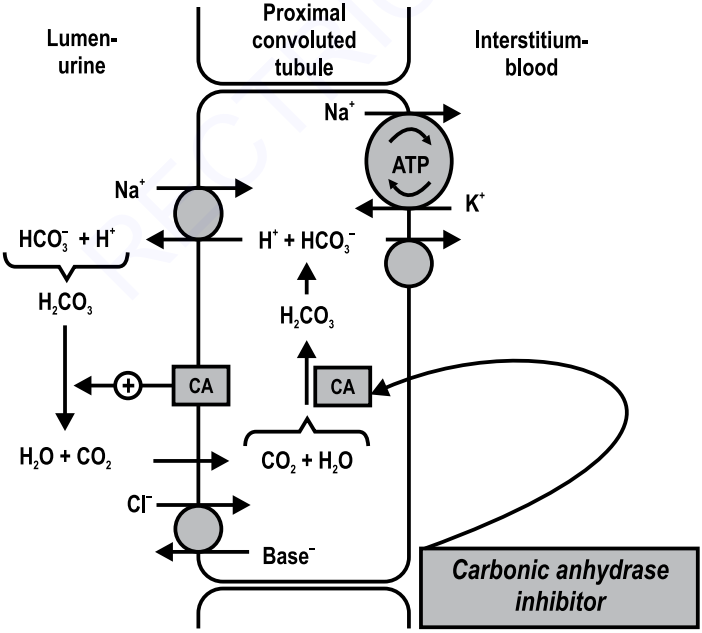

Fig. 25.5. Mechanism of action of acetazolamide: CA – carbonic anhydrase

SPIRONOLACTONE

- is a potassium-sparring diuretic;
- is taken orally; is metabolized to canrenone which is an active drug molecule; develops therapeutic effect in 2–5 days;
- is a competitive antagonist of aldosterone in gene expression, inhibits synthesis of permeases that results in the inhibition of a passive transport of Na^+ through the apical membrane in collecting tubules; does not act on the excretion of K^+; the diuretic and natriuretic effects of spironolactone are modest (Fig. 25.6);
- is used as an adjunct to other diuretics to reduce a loss of K^+; in hyperaldosteronism, CHF refractory to cardiac glycosides, myastenia;

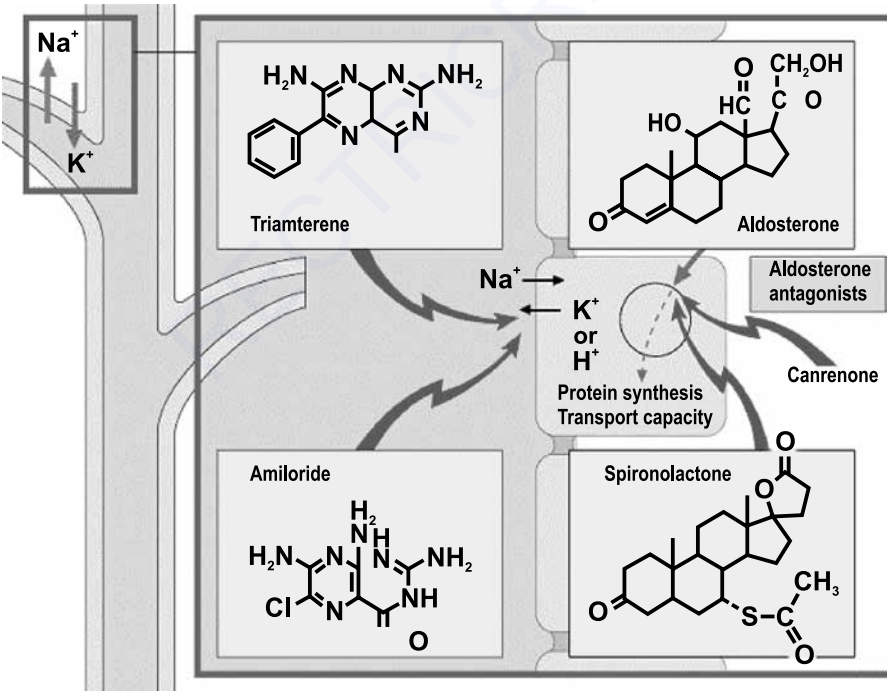

Fig. 25.6. Chemical structure and mechanism of action of potassium-sparring diuretics *(by H. Lüllmann, 2000)*

- may cause hyperkalemia, gastrointestinal disturbances, diarrhea, somnolence, disturbances in the menstrual function in women, ginecomastia and impotence in men (due to anti-androgenic activity).

TRIAMTERENE

- is a potassium-sparring diuretic;
- is taken orally, has a weak slow action;
- by its chemical structure, is similar to hydrotating Na^+ and closes Na^+ pores in the apical membrane of the cells in collecting tubules (is a Na^+ channel inhibitor); increases excretion of Na^+ and water; reduces K^+ loss (Fig. 25.6); is used together with other diuretics for the treatment of hypotension (This enhances the effects of the more potent diuretics and counteracts the K^+ loss seen with these diuretics);
- may cause hyperkalemia, nausea, vomiting and dizziness.

OSMOTIC DIURETICS

- are represented by ***mannitol and urea;***
- are administered by IV infusion;
- have the mechanism of action connected with an increase of the osmolarity of blood, the extraction of H_2O from systemic body compartments, an increase of the extracellular fluid volume and the renal blood flow. Osmotic diuretics are filtrated at the glomerulus, but are poorly reabsorbed, as a result, they increase the osmolarity of primary urine. These agents bind water osmotically and retain it in the tubular lumen. When Na^+ is taken up into the tubule cell, H_2O cannot follow in a usual amount. The fall in the urine Na^+ concentration reduces the Na^+ reabsorption in the proximal tubules. The result is a large volume of dilute urine;
- are used for edema of the brain (especially, mannitol), edema of the lungs, forced diuresis in acute poisonings, oliguria, anuria, the prophylaxis of acute renal failure in such situations as cardiovascular surgeries, traumatic shock and hemolytic transfusion reactions;
- may cause headache, nausea, vomiting, chest pain, an increase in blood volume resulting in the heart decompensation and hyponatremia.

MEDICINAL PLANTS AND PLANT PREPARATIONS WITH DIURETIC PROPERTIES

- medicinal plants with diuretic propertiies are ***Equisetum*** (the herb) and ***Orthosiphonum*** (leaves) (Fig. 25.7);
- are taken orally as infusions;
- increase the excretion of water with a minimal action on the electrolyte balance, have an antimicrobial and anti-inflammatory action;
- are used for the treatment of renal diseases, diseases of urinary pathways, and chronic edemas;
- have no significant side effects;
- plant preparation ***Lespenephryl*** contains biologically active substances from *Lepidum capitatum*. Pharmacological action is diuretic and antiazotemic. The drug promotes increased renal filtration, reduces azotemia, increases the excretion of nitrogenous metabolites. It is used for latent and compensated stages of chronic renal failure without significant side effects.

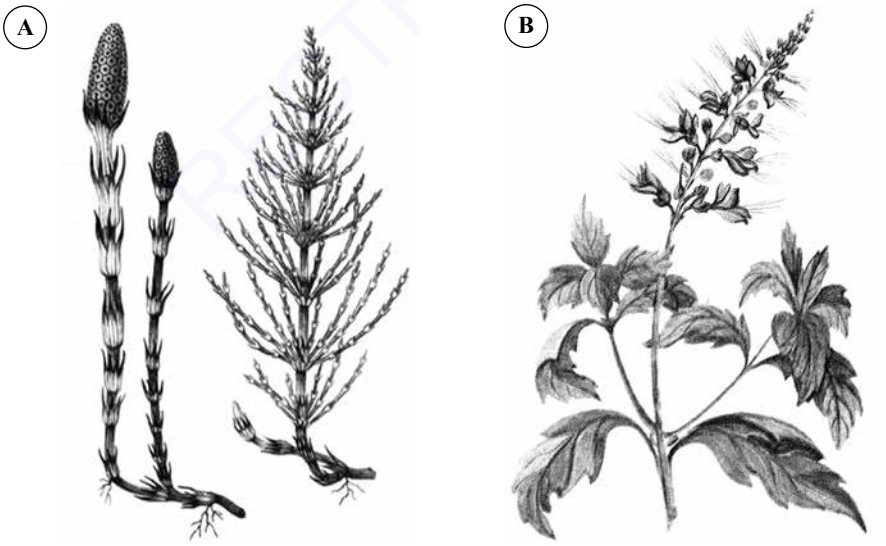

Fig. 25.7. Medicinal plants with diuretic action
A – *Equisetum;* B – *Orthosiphonum*

DRUGS USED IN THE TREATMENT OF GOUT

GOUT AND PRINCIPLES OF ITS THERAPY

Gout is a metabolic disease that results from hyperuricemia, an elevation in the blood of the uric acid, the end product of purine degradation. The typical ***gout attack*** consists of a highly painful inflammation of the first metatarsophalangeal joint. Gout attacks are triggered by the precipitation of sodium urate crtystals in the synovial fluid of joints.

The pharmacological management of gout includes:

- treatment of the gout attack with colchicine, indomethacin, phenylbutazone and glucocorticoids;
- prophylaxis of gout attacks with the diet low in purines, uricostatics and uricosurics.

CLASSIFICATION

A. *Uricostatics (They decrease urate production):*

– Allopurinol;

B. *Uricosurics (They promote renal excretion of uric acid):*

1. Drugs inhibiting reabsorption of the uric acid:
   – Probenecid;
   – Etebenecid.
2. Drugs increasing the solubility of urates:
   – Urodan.
3. Drugs decreasing forming of urate concrements:
   – Urolesan.

ALLOPURINOL

- is a hypoxantine (purine) on its chemical structure;
- is taken orally; is transformed into the active metabolite alloxantine (oxypurinol);
- inhibits xanthine oxidase and in such a way decreases the synthesis of the uric acid, prevents uricosemia, inhibits the development of gout;
- is used for the prophylaxis a gout attack and urolithiasis;
- is well tolerated, rarely may cause skin reactions.

PECUILIARITIES OF OTHER PREPARATIONS

Probenecid is taken orally, saturates the organic acid transport system in the proximal renal tubules, makes it unavailable for urate reabsorption; is contraindicated in patients with urate stones in the urinary tract.

Etebenecid is a synthetic preparation which blocks an active reabsorption of the uric acid in the proximal tubules and is used for the treatment of chronic gout.

Urodan is a combined preparation in granules for the oral administration; contains substances binding to urates and increasing their solubility.

Urolesan is a combined preparation with plant ingredients; decreases forming of urite concrements in the kidneys.

DRUGS ACTING ON THE MYOMETRIUM

UTERUS CONTRACTIONS AND THEIR PHARMACOLOGICAL MANAGEMENT

Uterus is a muscular organ of the reproductive system capable to contractions. Towards the end of pregnancy uterine contractions increase in the force and frequency and become fully coordinated in the labor. Uterine motility is controlled by the autonomic nervous system and hormones. The stimulation of α-adrenoceptors results in an increase of uterus contractility, the stimulation of β-adrenoceptors leads to the relaxation of the uterus. The important factors of humoral regulation of contractile myometrium function are pituitary hormones, sex hormones, and Pg. A pituitary hormone oxytocin stimulates uterus contractions on the ground of the increased level of estrogens.

The management of myometrium contractility includes:

- the stimulation of rhythmic contractions during labor;
- an increase in uterine tone for the arrest and prevention of postpartum uterine bleeding;
- a decrease in the tone of the myometrium to prevent premature labor or spontaneous abortion;
- a decrease in the uterine cervix tone during the labor.

DRUGS ACTING ON UTERUS CONTRACTILITY

CLASSIFICATION

A. *Drugs stimulating myometrium (Uterotonics):*

1. Stimulants of rhythmic contractions:

a) prostaglandins:

– Dinoprost;
– Dinoprostone.

b) hormones:

– Oxytocin;
– Estron;
– Estradiol dipropionate.

c) other preparations:

– Neostigmine;
– Castor oil;
– Calcium chloride.

2. Stimulants of uterine tone:

a) ergot alkaloids:

– Ergometrine maleate.

b) agonists of oxytocin receptors:

– Carbetocin (Pabal).

B. *Uterine relaxants (Tokolytics):*

1. β-adenomimetcs:

– Partusisten;
– Hexaprenaline (Gynipral).

2. Antagonists of oxytocin receptors:

– Atosiban (Tractocile).

3. Other preparations:

– Magnesium sulfate;
– Nifedipine;
– Aspirin;
– Progesterone;
– α-tocopherol acetate.

C. *Drugs decreasing uterine cervix tone:*

– Atropine sulfate;
– Magnesium sulfate;
– Drotaverine;
– Lydase.

OXYTOCIN

- is an octapeptide, a hormone of posterior pituitary (Fig. 25.8);
- is administered IM, IV, into the wall of uterus, intranasally; starts to act in 1 min after the IV administration;
- acts on oxytocin receptors on the cell membranes in the myometrium, causes the depolarization of membranes and an influx of calcium, increases excitability, stimulates rhythmic contractions of the myometrium, promotes labor activity; also stimulates milk production and ejection;
- is used for the stimulation of labor activity, the treatment of postpartum uterine bleeding, the stimulation of lactation;
- may cause nausea, vomiting, heart arrhythmia in the fetus, urine retention, the elevation of BP, thetanic contraction of the myometrium, hyperstimulation of labor activity resulting in the fetus hypoxia and a rupture of the uterus;
- is contraindicated in a danger of the uterus rupture, hypoxia of the fetus or abnormal position of the fetus.

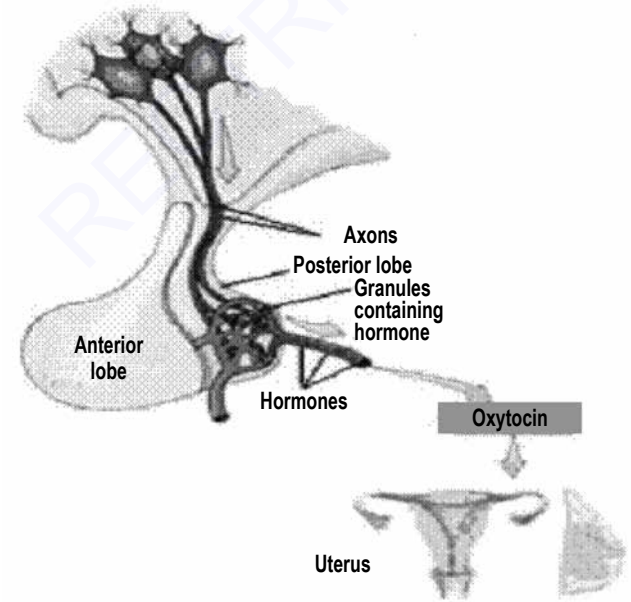

Fig. 25.8. Oxytocin as hormone of posterior pituitary *(http://www.picsearch.com)*

PECULIARITIES OF OTHER PREPARATIONS

Dinoprost (PgF$_{2\alpha}$) is administered IV, intravaginally, intra-amnionally; acts on specific structures in the myometrium, increases the sensitivity to oxytocin, produces the stimulation of rhythmic contractions of the myometrium in any terms of pregnancy, relaxes the cervix of the uterus; is used for the stimulation of labor and initiation of artificial abortion; may cause side effects, such as nausea, vomiting, diarrhea, tachycardia, spasm of the bronchi, an increase in BP and an elevation of intraocular pressure; is contraindicated in patients with scars of the uterus, severe diseases of the cardiovascular system, liver, and kidney; bronchial asthma or glaucoma.

Dinoprostone (PgE$_2$) is similar to dinoprost, but may be taken orally; does not cause spasm of smooth muscles and an increase in BP.

Ergometrine maleate is an ergot alkaloid (Fig. 25.9); is taken orally or administered IM, IV; increases the uterus tone and terminates postpartum bleeding caused by a low tone of the myometrium; realizes its effect through α_1-adrenoceptors and serotonin (5-HT) receptors; is used for the treatment of postpartum bleeding and slow postpartum involution of the uterus; is not used for the stimulation of labor; should not be used before the birth of placenta; is toxic; may cause acute and chronic poisoning (ergotismus) connected with vasoconstriction, trophy disturbances, and psychic disorders.

Fig. 25.9. Ergot *(Secale cornutum)* containing ergometrine

Carbetocin (Pabal) is an eight amino acid long analogue of oxytocin and has a similar mechanism of action. It can be administered IV or IM. Contractile effects of the uterus are apparent within 2 min and can be observed for 1 hr. The drug has a much longer lasting effect than oxytocin. Carbetocin functions as an agonist at peripheral oxytocin receptors, particularly in the myometrium, with lesser affinity for myoepithelial cells. It has been approved for use immediately following an elective cesarean section to restore uterine tone and prevent hemorrhage. Side effects are nausea, vomiting, abdominal pain, itching skin, increased body temperature, trembling and weakness, back and chest pain, dizziness, anemia, chills and sweating, metallic taste, tachycardia and respiratory distress.

Atosiban (Tractocile) is a competitive antagonist of oxytocin receptors. It is used as an IV medication as la-

bor repressant to halt premature labor. The drug antagonises uterine contractions and induces uterine quiescence. The onset of uterus relaxation following atosiban is rapid, uterine contractions being significantly reduced within 10 min. Atosiban is indicated to delay imminent pre-term birth in pregnant adult women. It is useful in the improving pregnancy outcome of *in vitro* fertilization-embryo transfer in patients with repeated implantation failure.

Hexoprenaline (Gynipral) is a selective β_2-adrenergic receptor agonist used in the treatment of asthma and as a tocolytic agent. It is administered for acute tocolysis (rapid suppression of labor in the case of acute intrauterine asphyxia of the fetus; before the manual rotation of the fetus from transverse position; in the complicated labor activity or before caesarean section); massive tocolysis (inhibition of premature labor with flattened cervix of the uterus); prolonged tocolysis (the risk of premature birth, uterine contractions without shortening and widening of the cervix). Possible side effects include headaches, anxiety, tremor, sweating, dizziness, nausea, vomiting, intestinal atony, increased activity of liver transaminases, tachycardia, lowering of BP; ventricular extrasystole, cardialgia; hyperglycemia, hypokalemia and hypocalcemia at the beginning of therapy. In newborns the drug may cause hypoglycemia and acidosis, bronchospasm or anaphylactic shock.

Many ***other drugs which are used as uterotonics and uterus relaxants*** belong to different pharmacological groups and are described between autonomics, hormonal preparations, spasmolytics, etc. in Chapters 5, 6, 7, 17, 19, 26, 27.

DRUGS USED TO TREAT ERECTILE DYSFUNCTION

Erectile dysfunction is the inability to maintain penile erection for the successful performance of sexual activity. It is due to many physical and psychological causes: vascular disease, diabetes, drugs side effects, depression, prostatic surgery.

Sexual stimulation results in smooth muscle relaxation of the *corpus cavernosum*, increasing the inflow of blood. The mediator of this response is nitric oxide (NO). NO activates guanylate cyclase, which forms cGMP and produces smooth muscle relaxation through a reduction in the Ca^{++} concentration. The duration of action of cyclic nucleotides in the *corpus cavernosum* is controlled by the action of PDE-5.

Phosphodiesterase-5 (PDE-5) inhibitors (sildenafil, vardenafil, and tadalafil) are now the first-line therapy for men with erectile dysfunction.

Sildenafil, vardenafil, and ***tadalafil*** inhibit PDE-5, the isozyme responsible for degradation of cGMP in the *corpus cavernosum*. The action of PDE-5 inhibitors is to increase the flow of blood into the *corpus* cavernosum at any given level

of sexual stimulation. At recommended doses, they have no effect in the absence of sexual stimulation. PDE-5 inhibitors are indicated for the treatment of erectile dysfunction of organic or psychogenic origin.

Sildenafil and vardenafil should be taken 1 hr prior to anticipated sexual activity with erectile enhancement observed up to 4 hrs after the administration. Tadalafil has a slower onset of action, but longer half-life resulting in enhanced erectile function for at least 36 hours.

Side effects of PDE-5 are headache, flushing, dyspepsia, and nasal congestion. Disturbances in color vision (loss of blue/green discrimination) occur with sildenafil. PDE-5 inhibitors should not be used more than once per day. PDE-5 inhibitors must be used with caution in patients with a history of cardiovascular diseases. Because of the ability to potentiate the activity of NO, these agents are contraindicated to patients taking preparations of organic nitrates.

TESTS FOR SELF-CONTROL

1. A loop diuretic for the forced diuresis in acute poisoning is:
A. Hydrochlorothiazide
B. Spironolactone
C. Ergometrine maleate
D. Furosemide
E. Triamterene.

2. All the concerning dinopost and dinoprostone is true, except:
A. They are prostaglandins
B. They stimulate uterus contractions
C. They are effective only at the end of pregnancy
D. They relax the uterine cervix
E. They are used for the stimulation of labor and induction of abortion.

3. Osmotic diuretics:
A. Are administered by IV infusion
B. Cause dehydratation of body tissues
C. Block carbonic anhydrase in the proximal tubules
D. Reduce Na^+ reabsorption in the proximal tubules
E. Has a weak diuretic action.

4. The correct statements concerning the treatment of gout are:
A. Colchicine is used to treat a gout attack

B. Allopurinol is a uricosuric agent
C. Allopurinol is an inhibitor of xantine oxidase
D. Probenecid is a uricostatic
E. Uricostatics are used for the prevention of a gout attack.

5. A patient has chronic cardiac insufficiency and essential hypertension. A doctor advices him to include into the treatment regimen a potassium-sparing diuretic. The drug is an antagonist of aldosterone, but its therapeutic effect develops slowly. Which of the listed drugs is recommended to the patient?
A. Furosemide
B. Amiloride
C. Spironolactone
D. Mannitol
E. Urea.

Answers

1 – D; 2 – C; 3 – A, B, D; 4 – A, C, E; 5 – C.

Chapter 26 HORMONAL PREPARATIONS

HORMONES AND HORMONAL PREPARATIONS

Hormones are substances produced by endocrine glands into the blood which achieve humoral regulation of body functions.

Hormonal preparations are medicinal forms of hormones used for the treatment of diseases.

Antihormones are drugs which decrease effects of hormones by the inhibition of their secretion or binding to hormonal receptors.

Hormonal drugs are divided into the several groups by their origin and clinical properties: hypothalamic and pituitary hormones, thyroid hormones, hormones of the parathyroid glands, hormones of the pancreas, adrenal cortex, and gonadal glands (Fig. 26.1). They may be classified according to the mode of action and chemical structure.

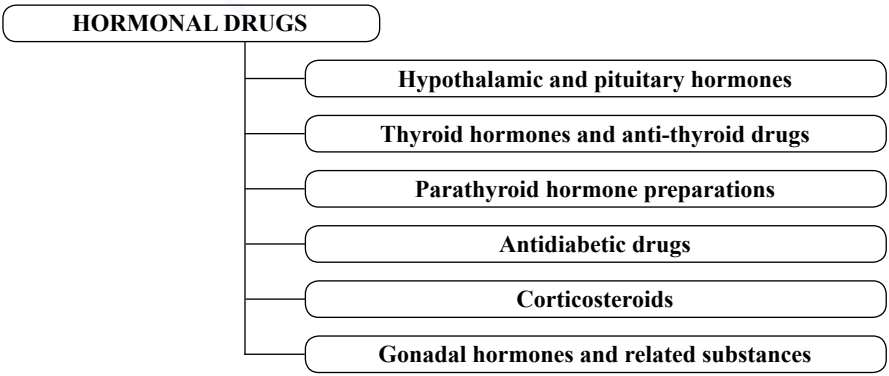

Fig. 26.1. Main groups of hormonal preparations

CLASSIFICATION OF HORMONES ACCORDING TO THE MODE OF ACTION

A. *Kinetic hormones* (oxytocin, vasopressin).
B. *Morphogenic hormones* (somatotropin, thyroid hormones).
C. *Metabolic hormones:*
1. Anabolic (androgens, insulin).
2. Catabolic (epinephrine, glucocorticoids).

CLASSIFICATION OF HORMONES ACCORDING TO THE CHEMICAL STRUCTURE

A. *Amino acids derivatives* (e.g., epinephrine, L-thyroxine, Triiodthyronine hydrochloride).
B. *Peptides* (e.g., Corticotropin, Somatotropin, Menopaustic gonadotropin, Chorionic gonadotropin, Oxytocin, Adiurecrin, Calcitonin, Parathyroidin, Insulin).
C. *Steroids:*
1. Glucocorticoides (e.g., Hydrocortisone acetate, Prednisolone, Dexamethasone, Triamcinolone, Flumetasone pivalate).
2. Mineralcorticoides (e.g., Desoxycorticosterone acetate (DOCSA).
3. Estrogens (e.g., Estron, Estradiol benzoate, Ethinylestradiol).
4. Progestins (e.g., Progesterone).
5. Androgens (e.g., Testosterone propionate).
6. Anabolic steroids (e.g., Methandienone, Nandrolone phenylpropionate, Nandrolone decanoate).

Common mechanisms of action

Hormones exert their effects through different mechanisms:
- by binding to the cell surface receptors (oxytocin, vasopressin, corticotropin, insulin, etc). Hormones acting on the cell membrane receptors realize their effects by the alteration of the intracellular cAMP (e.g., hypothalamic and anterior pituitary hormones), by Ca^{++} and the generation of inositolphospate/diacilglycerol (e.g., posterior pituitary hormones), or by a direct transmembrane activation of tyrosine kinase (e.g., insulin);
- by binding to intracellular cytoplasmic receptors (glucocorticoids, mineralcorticoids, estrogens, progestins, androgens);
- by interaction with nuclear receptors (thyroxine, triiodthyronine).

The hormone's level in the blood is regulated according to the principle of "back-cross" (Fig. 26.2). The rate of hormone secretion is controlled by a homeo-

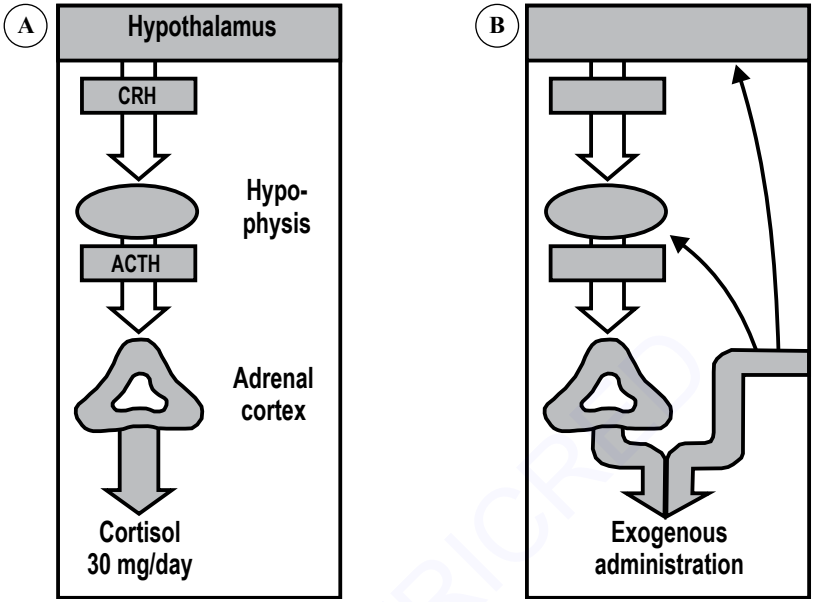

Fig. 26.2. Feedback regulation of cortisol production:
A – cortisol production under normal condition; B – a decrease in cortisol production with a cortisol dose < daily production *(adapted by H. Lüllmann, 2000)*

static negative feedback mechanism. Negative feedback is triggered by overproduction of an "effect" of the hormone.

Types of hormonal therapy

Hormonal therapy is the therapy by hormonal preparations.

There are such types of hormonal therapy:

- replacement therapy, which is the use of hormonal drugs for the hypofunction of the endocrine gland (e.g., insulin for diabetes mellitus);
- patogenesis therapy, which is the use of hormonal preparations for diseases unconnected with hormones deficit (e.g., insulin for cachexia);
- pharmacodynamic therapy is the usage of non-hormonal properties of hormones (e.g., steroid viadril for IV anesthesia);
- stimulation therapy is the usage of hormones of the anterior pituitary for the stimulation of peripheral glands (e.g., corticotropin after the withdrawal of corticosteroids);

- antihormonal therapy is the usage of antihormones (e.g., methimazole for hyperthyroidism).

Principles of hormonal therapy

- an individual selection of the dose for each patient (e.g., 1IU of insulin for the utilization of 3–5 g of sugar excreted with urine per day and a dose of insulin is calculated on the base of daily excretion of glucose);
- taking into account of biological rhythms (e.g., glucocorticoids are more effective in the morning when it's their peak concentration in the organism);
- a long-term treatment, sometimes during the whole life (e.g., insulin for type 1 diabetes mellitus);
- gradual abolishing for restoration of normal function of the endocrine gland inhibited by the exogeneous hormone administration ;
- stimulation therapy at the end of treatment (e.g., corticotropin before the abolishing of glucocorticoids.

HYPOTHALAMIC HORMONES

CLASSIFICATION

1. Gonadorelin analogues:
   – Buserelin;
   – Triptorelin.
2. Prothyrelin analogues:
   – Protirelin.
3. Somatostatin analogues:
   – Ocreotide;
   – Lanreotide.

PECULIARITIES OF PREPARATIONS

Buserelin is a synthetic analogue of gonadotropin releasing hormone (GnRH), a nonapeptide. It is administered intranasally and by injection. The half-life is 72–80 min. It is an agonist of the GnRH receptor with high potency for induction of luteinizing hormone (LH) and follicle stimulating hormone (FSH) which activate gonadal hormone production, stimulate spermatogenesis in men and induce ovulation in women. With chronic administration of buserelin, the GnRH receptor becomes desensitized, that results in a loss of LH and FSH secretion and a decrease of gonadal hormones production, diminished spermatogenesis in men, and anovu-

lation in women. The drug is used in the treatment of hormone-responsive cancers (prostate cancer and premenopausal breast cancer), endometriosis, uterine fibroids, precocious puberty, as a component of transgender hormone therapy, and in the assisted reproduction. During the initial phase of the therapy, transient activation of the tumor is possible. Side effects that occur later during the treatment are mainly due to low sex hormone levels.

Triptorelin is a decapeptide, GnRH agonist. It is administered SC, IM, may be used as depo-preparation; is eliminated 3 times slower than the natural GnRH. Pharmacodynamics is similar to the same of buserelin. The inhibitory effect is developed 3–4 weeks after the start of treatment and is reversible. Indications and side effects are similar to those of buserelin.

Protirelin is a tripeptide, synthetic analogue of thyrotropin releasing hormone (TRH). It promotes the release of thyroid stimulating hormone (TSH) and increases the concentration of prolactin. $T_{1/2}$ is short (5 min). It is used in the diagnosis of pituitary insufficiency in patients with hypothyroid conditions and in women with hypo- and agalactia. Side effects are fluctuations in BP, headache, photophobia, anxiety, sweating, abdominal pain, xerostomia and allergic reactions.

Octreotide (Sandostatin) is an octapeptide that mimics natural somatostatin. It is administered SC and IV and has a half-life up to 100 min. The drug inhibits secretion of many hormones, such as gastrin, cholecystokinin, glucagon, growth hormone, insulin, secretin, pancreatic polypeptide, TSH, and vasoactive intestinal peptide, reduces secretion of fluids by the intestine and pancreas, decreases gastrointestinal motility and inhibits contraction of the gallbladder, inhibits the action of certain anterior pituitary hormones, causes vasoconstriction, and reduces portal vessely pressure in bleeding varices. The drug is more potent inhibitor of growth hormone, glucagon, and insulin than natural hormone. Octreotide is used for the treatment of growth hormone producing tumors of pituitary gland, diarrhea associated with carcinoid syndrome, and acromegaly. It is given for management of acute hemorrhage from esophageal varices; labeled by radioactive isotopes, is used in nuclear medicine for imaging and treatment of neuroendocrine tumors. The most frequent side effects are headache, hypothyroidism, cardiac conduction changes, gastrointestinal reactions, gallstones, hyper- or hypoglycemia, and injection site reactions.

Lanreotide is a synthetic analogue of somatostatin which blocks the release of several other hormones including growth hormone, TSH, insulin and glucagon. Lanreotide binds to the same receptors as somatostatin, although with higher affinity to peripheral receptors, and has similar activity. It has much longer half-life and produces prolonged effects. The drug is used in the management of acromegaly and symptoms caused by neuroendocrine tumors. Side effects are pain at the injection site and gastrointestinal disturbances.

PITUITARY HORMONES

CLASSIFICATION

1. Anterior pituitary hormones and related substances:
   - Corticotropin;
   - Somatotropin;
   - Human menopausal gonadotropin (hMG) (Menotropin);
   - Human chorionic gonadotropin (hCG);
   - Follitropin alpha;
   - Follitropin beta.
2. Posterior pituitary hormones and related substances:
   - Oxytocin;
   - Demoxytocin (Desamino oxytocin);
   - Vasopressin;
   - Desmopressin;
   - Terlipressin.
3. Antagonists of pituitary hormones (antigonadotropins):
   - Danazol.

PECULIARITIES OF PREPARATIONS

Corticotropin is a short peptide; stimulates the secretion of corticosteroids by the cortex of the adrenal glands; has anti-inflammatory and anti-allergic effects resulting from an increase in cortisol secretion; is administered IM to treat the hypofunction of the adrenal cortex, adrenocortical atrophy after the withdrawal of corticosteroids, rheumatism, collagenosis, bronchial asthma, and severe allergy, displays side effects which are similar to adverse reactions of corticosteroids.

Somatotropin is a large polypeptide from the anterior pituitary; is produced by the recombinant DNA technology; stimulates protein synthesis and promotes bone growth; is used to treat growth-hormone insufficiency in children, pituitary dwarfness; is contraindicated to patients with closed epiphyses or with an increased intracranial mass.

Human menopausal gonadotropin (hMG), or menotropin, and human chorionic gonadotropin (hCG) regulate reproduction. hMG contains FSH and LH, causes ovarian follicular growth and maturation. hCG is a placental hormone and LH agonist promoting ovulation. In men, the treatment with hCG causes external sexual maturation, and the treatment with hMG stimulates spermatogenesis. Gonadotropins are used in hypogonadotropic hypogonadism, delayed puberty,

ovulation dysfunction and sterility in women, hypospermia and sterility in men as well as in the methods of assisted reproduction.

Follitropin alfa is a follicle stimulating drug obtained by genetic engineering. It binds to receptors in target cells, increases the level of estrogens and proliferation of the endometrium, stimulates the development of follicles and ovulation, promotes the development of multiple follicles. Indications include infertility in women due to hypothalamic-pituitary dysfunction accompanied by oligo- or amenorrhea as well as stimulation of hyperovulation. The drug may cause ovarian hyperstimulation syndrome.

Follitropin beta is a recombinant FSH. Compensating the deficiency of this hormone, it regulates the normal growth and maturation of the follicles, the synthesis of sex hormones. By specific activity, it exceeds FSH, extracted from the urine of women during the postmenopause. Indications are female infertility in anovulation; carrying out programs of assisted reproduction, including *in vitro* fertilization (for induction of superovulation).

Danazol is a synthetic androgen derived from etisterone. It has a reversible antigonadotropic effect by inhibiting the release of GnRH, or suppressing the production of pituitary gland FSH and LH in men and women. Danazol can directly suppress steroidogenesis, interacts with androgenic, progesterone and glucocorticoid receptors in target tissues, binds to steroid-binding globulin. The drug is characterized as a weak androgen and anabolic, a weak progestogen, and a functional antiestrogen. It has the immunosuppressive effect; decreases the pain syndrome and causes the recession of endometriotic foci in the patients with endometriosis. The drug is used primarily in the treatment of endometriosis, also can be used for the management of menorrhagia, fibrocystic breast disease, immune thrombocytopenic purpura, premenstrual syndrome, breast pain, and hereditary angioedema. The use of danazol is limited by masculinizing side effects.

Oxytocin stimulates uterus contractions and promotes contractions of myoepithelial cells in the mammary glands; is used in weak labor activity, hypotonic metrorrhagia, for the promotion of milk ejection; is contraindicated in abnormal fetal presentation, fetal distress, and the risk of uterine rupture development (see Chapter 25).

Demoxytocin (Desamino oxytocin) is a synthetic analogue of oxytocin and has similar activities, but is more potent and has longer half-life. Unlike oxytocin, demoxytocin is administered as buccal tablets. It is used to induce labor, promote lactation, and to prevent and treat postpartum mastitis.

Adiurecrin (Vasopressin) binds to V_2-receptors in the kidney to increase water reabsorption in collecting tubules; stimulates V_1-receptors in vascular smooth muscles, the liver, and other tissues to regulate the vascular tone, the tone of smooth

muscles, and blood coagulation; is used in diabetes insipidus, shock, hemorrhage, hemophylia and atony of the gut; may cause water intoxication, hyponatremia, enhanced BP, spasm of the bronchi, headache or tremor.

Desmopressin is a synthetic version of vasopressin, It may be given in the nose, IV, orally, or sublingually, is degraded more slowly than vasopressin, and requires less frequent administration. It works at the level of the renal collecting duct by binding to V_2 receptors, has antidiuretic effect and little effect on BP. Desmopressin is used to treat central diabetes insipidus, nocturnal enuresis, and nocturia. The drug can be used to promote the release of von Willebrand factor (with subsequent increase in factor VIII) in patients with coagulation disorders such as von Willebrand disease, hemophilia A, and thrombocytopenia. Common side effects include headaches, diarrhea, and low blood sodium that results in seizures.

Terlipressin is an analogue of vasopressin used as vasoactive drug in the management of low BP when norepinephrine does not help. Like vasopressin, it constricts arterioles, veins and venules (especially in the abdominal cavity), lowers the pressure in the portal system, stimulates constriction of the esophagus smooth muscles, increases intestinal tone and motility, and stimulates myometrium activity regardless of pregnancy. Indications include bleeding from the esophageal varices, stomach and duodenal ulcers or genitourinary system, metrorrhagia, intraoperative abdominal and gynecological bleeding, norepinephrine-resistant septic shock, and hepatorenal syndrome. Side effects are headache, pallor, difficulty breathing, increased BP, slow heart rate, heart failure, abdominal pain, nausea, vomiting, uterine contraction and necrosis at the site of IM injection.

THYROID HORMONES AND ANTITHYROID DRUGS

CLASSIFICATION

1. Thyroid hormones:
   - Levothyroxine (L-thyroxine);
   - α-Triiodthyronine hydrochloride;
   - Thyreocomb.
2. Antithyroid drugs:
   - Methimazole (Thiamazole, Mercazolil).
3. Iodine preparations:
   - Sodium iodide;
   - Potassium iodide.

THYROID HORMONES

L-thyroxine, triiodthyronine hydrochloride and thyreocomb have common effects and indications. They are taken orally. Triiodthyronine is more active than other preparations. Thyreocomb is a combined preparation containing synthetic thyroid hormones levothyroxine and lyothyronine together with potassium iodide. An overdose of thyroid hormones manifests in hyperthyroidism.

Pharmacodynamics	Indications
An increase in catabolism of proteins, lipids, and carbohydrates An increase in basal metabolism An increase in body temperature An increase in the activity of sympathetic nervous system Participation in the growth and mental development in children	Hypothyroidism (myxedema, cretinism) Diffuse non-toxic goiter Thyroiditis

ANTITHYROID DRUGS

Antithyroid drugs are preparations for the treatment of hyperthyroidism (thyrotoxicosis, Basedow's disease).

METHIMAZOLE (THIAMAZOLE)

- is taken orally; concentrates in the thyroid gland;
- blocks peroxidase and suppresses thyrosine's iodination. A result is a decrease in the synthesis of thyroid hormones and the reduction of symptoms of hyperthyroidism (Fig. 26.3);
- is used to treat hyperthyroidism;
- may cause side effects, such as agranulocytosis, leukopenia, skin rash, fever, joint pain, the depigmentation of the hair, paradontitis and necrotic stomatitis.

IODINE PREPARATIONS

Preparations of iodine are used:

– for the replacement of iodine deficit in hypothyroidism;
– for the prophylaxis of hypothyroidism and goiter;
– for hyperthyroidism (a feedback decreasing of thyroid secretion, the decreasing of size and vascularity of the gland).

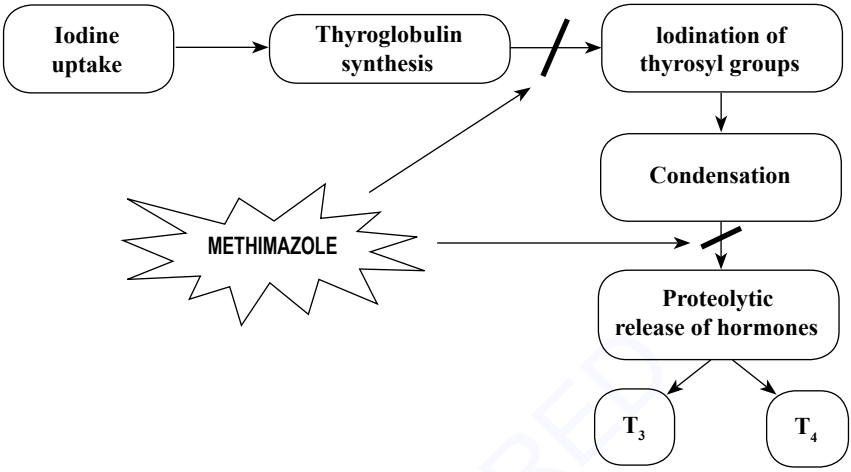

Fig. 26.3. Mechanism of action of methimazole

HORMONES REGULATING METABOLISM OF CALCIUM AND PHOSPHATE

CALCITONIN

Calcitonin is produced by C-cells of thyroid gland (Fig. 26.4). It is a protein, that is why it is not administered orally. ***Calcitrin and miacalcic*** are calcitonin's preparations. Calcitrin is a substance obtained from the thyroid gland of pigs and is administered IM or SC. ***Miacalcic*** contains salmon calcitonin and is administered by injection or nasal spray. Since salmon calcitonin has a higher affinity for receptors (compared to mammalian calcitonins), its effect is expressed to the greatest extent both in strength and in duration.

Pharmacodynamics	Indications
An increase in the activity of osteoblasts	Osteoporosis
A decrease in the activity of osteoclasts	Padget's disease
The inhibition of bone resorption	Bone fractures
The oppression of bones decalcification	Bone pain in neoplastic malignant diseases
A decrease in the calcium level in blood serum	Hypercalcemia
	Caries, severe paradontitis
The inhibition of gastric and exocrine pancreatic secretion	Hypercalcemia
	Nephrocalcinosis
	Combined therapy of acute pancreatitis

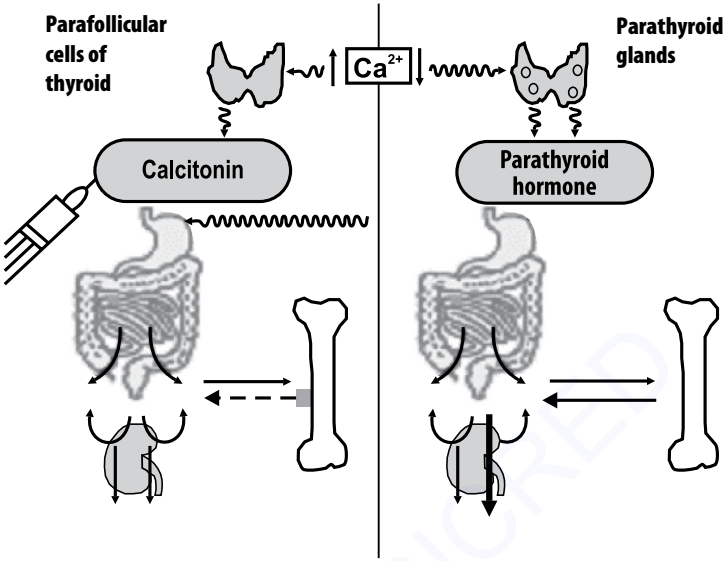

Fig. 26.4. Action of calcitonin and parathyroidin on calcium metabolism *(by H. Lüllmann, 2000)*

PARATHYROIDIN

Parathyroidin is an antagonist of calcitonin (Fig. 26.4). It is a polypeptide produced by parathyroid glands. It is only administered parenterally.

Pharmacodynamics

An increase in calcium absorption in the intestine
An increase in calcium reabsorption in the kidney
A decrease in phosphate reabsorption in the kidney
An increase in serum calcium and a decrease in serum phosphate
An increase in resorption of bone tissue due to activation of osteoclasts
A decrease in bone mineralization
Synergism to vitamin D

Indications

Hypoparathyroidism (tetanus, spasmophylia)
Allergic diseases

Teriparatide is a recombinant protein form of parathyroid hormone consisting of the first 34 amino acids, which is the bioactive portion of the hormone. Its intermittent use activates osteoblasts more than osteoclasts that leads to an overall

increase in bone. The drug is an effective bone growing agent used to treat some forms of osteoporosis and to speed bone fracture healing.

INSULIN AND HYPOGLYCEMIC DRUGS

DIABETES MELLITUS

Diabetes mellitus is a heterogeneous group of syndromes characterized by hyperglycemia caused by relative or absolute deficiency of insulin. The classic symptoms of diabetes mellitus are polydipsia, polyphagia and polyuria.

There are two types of diabetes mellitus:

– insulin dependent diabetes mellitus (IDDM) or type I;
– non-insulin dependent diabetes mellitus (NIDDM) or type II.

Type I diabetes (10–20% of all cases) is a result of the destruction of β-cells and must be relayed on injected insulin.

Type II diabetes (80–90% of diagnosed diabetes) is a result of β-cells inability to produce an appropriate quantity of insulin or insulin resistance in target organs. Blood glucose level may be controlled by weight reduction, diet, and oral hypoglycemic drugs.

ANTIDIABETIC DRUGS

Antidiabetic drugs are hormonal preparations and synthetic drugs for the treatment of diabetes mellitus.

CLASSIFICATION

A. *Insulin preparations:*

1. Fast-acting (begin to work within 5–15 min and are active for 3–4 hrs):
   – Aspart;
   – Lispro;
   – Glulisine.
2. Short-acting (begin working within 30 min and is active about 5–8 hrs):
   – Regular insulin;
   – Actrapid;
   – Humulin R.
3. Intermediate-acting (begin working in 1–3 hrs and is active 16–24 hrs):
   – Protaphane;
   – Monotard.

4. Long-acting (begin working within 1–2 hrs and continue to be active, without major peaks or dips, for about 24 hrs):
   – Glargine.
5. Ultra-long acting (begin working within 30–90 min and continues to be active for greater than 24 hrs):
   – Degludec.
6. Combination insulin products (begin to work with the shorter acting insulin and remain active for 16–24 hrs):
   – Novolog Mix 70/30;
   – Novomix 30;
   – Humalog Mix.

B. *Oral hypoglycemic agents:*

1. Sulfonylureas:
   – Glibenclamide;
   – Glycvidone;
   – Glycolide.
2. Biguanides:
   – Metformin.
3. α-glucosidase inhibitors:
   – Acarbose.
4. Glinides (Prandial glusose regulators):
   – Repaglinide.
5. Thiazolidinediones (insulin sensitizers):
   – Pioglitazone.

REGULAR INSULIN

Insulin is a short protein consisting of two chains that are connected by disulfide bonds. It is synthesized by β-cells of the pancreas.

Sources of insulin (Fig. 26.5):

– pork and buff pancreas;
– special strain of genetically modified *Escherichia coli*.

Pharmacokinetics

- is administered SC, IV (in hyperglycemic emergency);
- starts to act in 15–30 min; has duration of action of 5–8 hrs;
- is inactivated by insulinase in the liver and kidney.

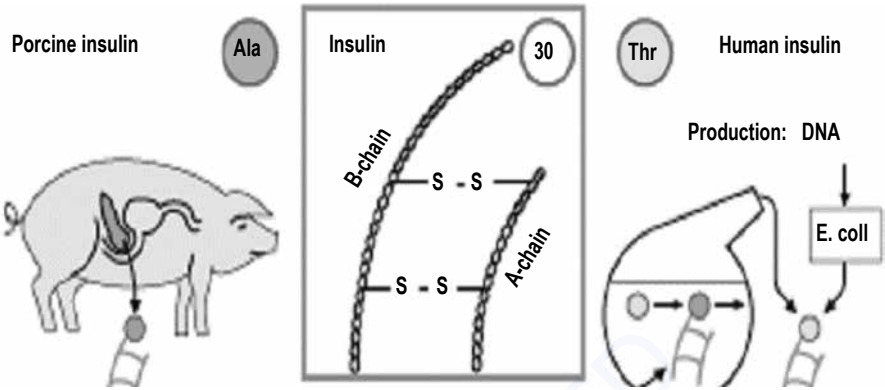

Fig. 26.5. Sources of insulin *(by H. Lüllmann, 2000)*

Pharmacodynamics

An increase in glucose entry into the cells
A decrease in gluconeogenesis
An increase in utilization of glucose in the cells
An increase in glycogen synthesis in the liver and skeletal muscles
Lowering of the glucose level in the blood (hypoglycemic action)
An increase in protein synthesis
The promotion of cells proliferation (growth factor)
The regulation of lipid metabolism
A decrease in ketoacidosis.

Indications

Diabetes mellitus (type I, type II)
Diabetic (hyperglycemic) coma
Gestational diabetes
Cachexia
Furunculosis
Liver diseases
Insulin-comatous therapy of schizophrenia
For better availability of glucose during IV infusion.

Side effects

1. Hypoglycemia (tachycardia, confusion, vertigo, sweating, hypoglycemic coma);
2. Lypodystrophy in the site of administration;
3. Low blood potassium;
4. Allergy.

INSULIN PREPARATIONS OF PROLONGED ACTION

Protaphane is a suspension of the crystals of human biosynthetic insulin; is administered SC; has start of action in 1.5 hrs, maximal effect within 4–12 hrs and duration of action near 24 hrs.

Monotard is an intermediate-acting insulin preparation containing biosynthetic human zinc-insulin as suspension of amorphous and crystalline particles; is administered SC; has start of action in 2.5 hrs, maximal effect within 7–15 hrs and duration of action near 24 hrs.

Insulin glargine is a long-acting biosynthetic human insulin preparation. After SC administration into the subcutaneous fat tissue, it forms microprecipitates, from which small amounts of insulin glargine are continuously released, providing a smooth (without peaks) profile of the concentration-time curve as well as a long duration of action of the drug; is administered only SC once a day.

Insulin degludec is an analogue of human insulin, ultra-long acting preparation; duration of action is more than 42 hrs due to formation of soluble stable multihexamers (insulin depot) in the subcutaneous fat. Multihexamers gradually dissociate, releasing insulin degludec monomers resulting in a slow and prolonged delivery of the drug into the blood, providing a long-term planar profile of action and a stable hypoglycemic effect.

DIABETIC (HYPERGLYCEMIC) AND INSULIN (HYPOGLYCEMIC) COMA

Diabetic (hyperglycemic) coma

Signs:

This coma develops due to a high blood sugar level and is characterized by unconsciousness, hyperemia of the skin, a low tone of skeletal muscles and eyes, specific odor from the exhaled air and urine, hyperglycemia and ketoacidosis.

Emergency help:

- regular insulin (IV);
- 0.9% solution of sodium chloride for a decrease in hyperosmolarity of the blood (IV infusion);
- 4% solution of sodium bicarbonate for a decrease in acidosis (IV infusion);
- thiamine as synergist of insulin (a bigger dose).

Insulin (hypoglycemic) coma

Signs:

This coma results from a low blood sugar level caused by an overdose of insulin. It is characterized by slow development, the pre-coma period, unconscious-

ness, sweating, cold pale skin, a high tone of skeletal muscles and eyes, seizures, the absence of specific odor, hypoglycemia.

Emergency help:

– sweet tea and white bread by mouth during pre-coma;
– 40% solution of glucose (IV) in a comatous condition;
– epinephrine, prednisolone, or glucagon as contra-insular hormones.

ORAL HYPOGLYCEMIC DRUGS

Oral hypoglycemic drugs are synthetic non-hormonal preparations which can lower the glucose level in the blood. Preparations from each group are characterized by a common mechanism of action and pharmacological properties.

Mechanism of action

1. ***Sulfonylurea derivatives (Glibenclamide, Glycvidone, Glycolide):***
   - an increase of insulin release from the pancreas;
   - the reduction of plasma glucagon concentration;
   - the potentiation of insulin action on target cells.
2. ***Biguanides (Metformin):***
   - an increase of glycolysis in the tissues
   - the inhibition of hepatic gluconeogenesis;
   - a decrease in glucose absorption in the GI tract;
   - the reduction of the plasma glucagon level;
   - a decrease in the absorption of lipids in the gut and the reduction of body weight;
   - lowering of hyperlipidemia.
3. ***α-glucosidase inhibitors (Acarbose):***
   - a competitive inhibition of a-glucosidase;
   - a decrease of monosaccharides absorption;
   - a decrease in the blood sugar level.
4. ***Prandial glucose regulators (Repaglinide):***
   - very rapid onset and short duration of action in stimulating insulin secretion;
   - restoration of the insulin secretion pattern at mealtimes (prandial phase)-without stimulating insulin secretion in the "postabsorptive" phase.
5. ***Thiazolidinediones:***

   an increase in the tissue insulin sensitivity.

Indications

Type II non-insulin-dependent diabetes in patients after the age of 35 years old.

Side effects

1. Hypoglycemia.
2. Gastrointestinal disturbances.
3. Itch.
4. Anemia.
5. Hyponatremia, hypotension, disulfiram-like reaction (after the administration of some drugs).

GLUCAGON

- is a peptide hormone, produced by α-cells of the pancreas;
- is given IV, IM, or SC;
- binds to the glucagon receptor, located in the cell membrane;
- works to raise the concentration of glucose and lipids in the bloodstream, is considered to be the main catabolic hormone of the body; produces the effect opposite to that of insulin;
- is used to treat low blood sugar, β-adrenoblocker overdose, calcium channel blocker overdose, and those with anaphylaxis who do not improve with epinephrine;
- can cause such common side effects as vomiting, low blood potassium and hypotension.

ADRENAL STEROIDS (CORTICOSTEROIDS)

Adrenal steroids are steroidal hormones produced by the adrenal cortex or their synthetic analogues (Fig. 26.6).

CLASSIFICATION

A. *Glucocorticoids:*

1. Short-acting (8–12 hrs):
   – Hydrocortisone acetate.
2. Intermediate-acting glucocorticoids (18–36 hrs):
   – Prednisolone;
   – Methylprednisolone;
   – Triamcinolone.
3. Long-acting glucocorticoids (1–3 days):
   – Dexamethasone.

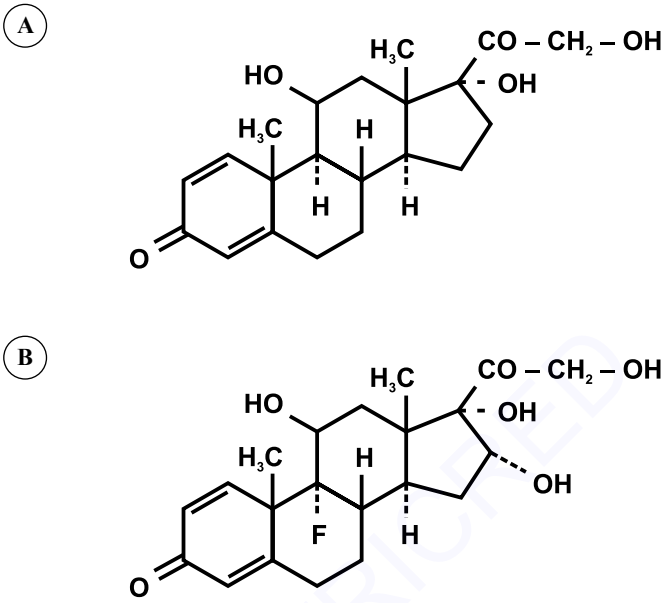

Fig. 26.6. Chemical structure of some adrenal steroids:
A – hydrocortisone; B – triamcinolone

4. Topically active glucocorticoids:
   – Beclomethasone dipropionate;
   – Fluocinolone acetonide;

B. *Mineralocorticoids:*
   – Desoxycorticosterone acetate.

GLUCOCORTICOIDS

Glucocorticoids are adrenal steroids with a prevalent action on metabolism and inflammation. All glucocorticoids produce common pharmacological effects. They have some common indications, contraindications, and side effects. As a rule, contraindications are not taking into acount if the drug is used for emergency help.

Pharmacokinetics

- are administered IM, IV, topically, by inhalation; all drugs may be taken orally;

- are well absorbed in the GI tract;
- bind to plasma proteins (90% of a dose);
- are metabolized in the liver;
- are excreted with urine in the form of metabolites (glucuronides and sulfates).

Pharmacodynamics	Indications
An increase in protein catabolism	Collagenosis, severe rheumatism, arthritis, arthrosis
An increase in gluconeogenesis	Bronchial asthma
An increase in glucose level in the blood	Allergic diseases of the skin and mucous membranes
The regulation of lipids distribution, an increase in lipolysis	Autoimmune diseases
The retention of sodium and water	Transplantation of the organs
An increase in excretion of potassium and calcium	Acute leukemia
A decrease in all phases of inflammation	Shock
The suppression of immunity	Hypoglycemic coma
The suppression of allergic reactions	Anaphylactic shock
Changes in the blood film (eosinopenia, lymphopenia)	Adrenal insufficiency (natural hormones are preferable)
The inhibition of lymphoid tissue proliferation	
An increase in the resistance to stress	

Glucocorticoids are among the most potent anti-inflammatory agents. They inhibit all three stages of inflammation. The inhibition of alteration and exudation is due to the reduction of blood vessels permeability, the inhibition of hyaluronidase activity, the stabilizing of mast cells membranes and a decrease in histamine liberation, the stabilizing of lysosomal membranes and a decrease in the release of lysosomal enzymes, the inhibition of leukocytes activity in the site of inflammation (Fig. 26.7). In contrast to NSAIDs, glucocorticoids inhibit phospholipase A, disturb synthesis of arachidonate and consequently inhibit prostaglandins synthesis. Their influence on the proliferation stage is based on the inhibition of protein synthesis and fibroblasts activity.

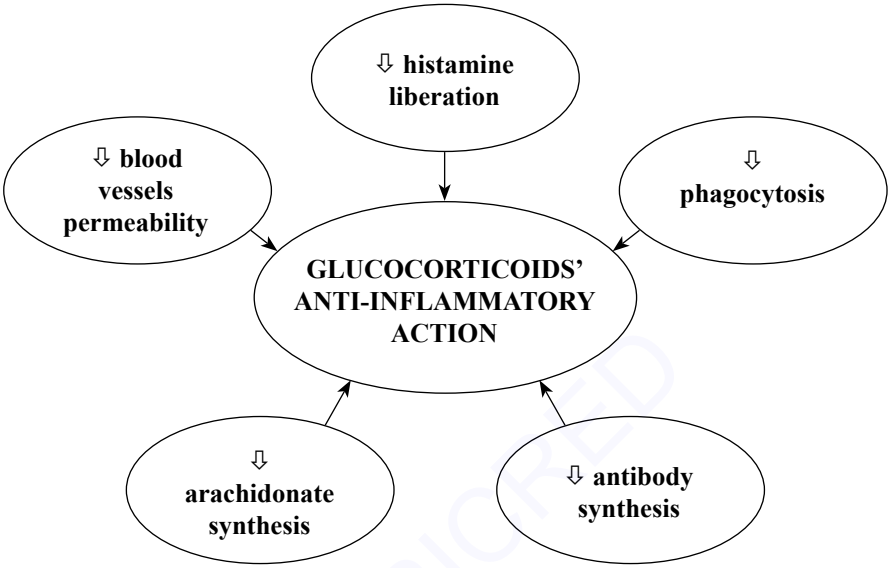

Fig. 26.7. Components of glucocorticoids anti-inflammatory action

Side effects

1. The suppression of the pituitary-adrenal function
2. Immune suppression and an increase in susceptibility to infection
3. Gastric ulceration
4. Hypertension
5. An increase of blood coagulation resulting in thrombosis
6. Edema, retention of sodium and water
7. An increase of appetite resulting in the enhanced body weight
8. Hypokalemia
9. Osteoporosis, severe caries
10. Hyperglycemia (steroid diabetes)
11. Dystrophy of skeletal muscles
12. Disturbances in the function of other endocrinal glands
13. Psychic disorders (depression, insomnia, somnolence, "steroid psychosis")

Contraindications

1. Hyperfunction of the adrenal cortex
2. Hypertension
3. Severe CHF
4. Nephritis
5. Acute endocarditis
6. Ulcerative disease of the stomach and duodenum
7. Syphilis
8. Active forms of tuberculosis
9. Diabetes mellitus
10. Osteoporosis
11. Psychosis
12. Pregnancy

PECULIARITIES OF PREPARATIONS

Hydrocortisone is in the form of ointment, eye ointment, suspension for injections; is used topically to treat allergic eye diseases, aseptic burns of the eyes or after the eye surgeries (not earlier than 7 days after the operation); is also applied in allergic skin diseases and administered in arthritis, arthrosis (into the joint), bronchial asthma.

Prednisolone is a synthetic derivative of hydrocortisone; is more potent than hydrocortisone in 3–4 times; is administered orally, IM, IV, or applied topically in the form of ointment or eye drops; has $T_{½}$ of 2–3 hrs.

Methylprednisolone, as compared to prednisolone, has a slightly higher (by 20%) glucocorticoid activity, minimal mineralocorticoid action; less often causes undesirable reactions (especially psychic disorders, changes in the appetite, and ulcerogenic effect); is used mainly for patogenesis therapy; is preferable in patients with mental disorders, obesity, peptic ulcer.

Dexametasone contains fluorine; is more active than hydrocortisone and prednisolone; has less side effects; is administered orally, IM, IV or applied topically in the form of ointment or eye drops; has $T_{½}$ of 3–4.5 hrs; is characterized by 72 hrs duration of anti-inflammation effect after the oral administration.

Triamcinilone (Kenalog) contains fluorine; has a prolonged action; has $T_{½}$= 1.5–3.3 hrs which is not correlated with a duration of action; develops maximal effect in 24–48 hrs and acts during 6 weeks; is used to treat arthritis, arthrosis, joint lesions caused by collagenosis or rheumatism; is injected in the site of lesion in psoriasis, neurodermitis, lupus erythematosus; is not administered IV; has less side effects than other preparations (less retention of sodium and water, less diabetogenous action).

Fluocinolone acetonide (Flucinar) is a fluorine-containing preparation for the topical application in dermatology; is used in the form of ointment, penetrates the upper layer of epidermis and stays in the skin during 15 days; is indicated in allergic and inflammatory diseases of the skin, psoriasis, lupus erythematosus; should not be used for the long-time treatment or on the large area of lesion; may cause generalization of infection if used without antimicrobial drugs.

Beclomethasone dipropionate is used in the form of inhalations for the prevention of a bronchial asthma attack; penetrates into the airway mucosa, but has a short half-life in the body, so that systemic effects and toxicity are greatly reduced.

MINERALCORTICOIDS

DESOXYCORTICOSTERONE ACETATE

- is administered IM and sublingually;
- regulates reabsorption of sodium, promotes retention of phosphate, calcium, carbonate, water, and sodium;
- supports BP and the muscular tone;
- is used to treat adrenocortical insufficiency and myastenia;
- may cause edema, hypertension and hypokalemia.

ANTAGONISTS OF ADRENAL STEROIDS

Metyrapone inhibits the synthesis of adrenal steroids; is used for the treatment of adrenal hyperfunction (Cushing's syndrome).

Aminoglutethimide reduces the synthesis of hormonally active steroids; is used to treat breast cancer and adrenal cortex malignances.

Ketoconazole is an antifungal drug; inhibits the synthesis of gonadal and adrenal steroids; is used to treat Cushing's syndrome.

Spironolactone is an antagonist of aldosterone; it binds to mineralcorticoid receptor and inhibits sodium reabsorption in the kidney; antagonizes aldosterone and testosterone synthesis; is used as diuretic and for the treatment of hirsutism in women.

GONADAL HORMONES AND RELATED SUBSTANCES

Gonadal hormones are steroidal hormones produced by the male and female gonadal glands which regulate the development of sex characteristics and reproduction.

CLASSIFICATION

A. *Male gonadal hormones and related substances:*

1. Androgens:
   - Testosterone propionate;
   - Methyltestosterone.
2. Antiandrogens:
   - Flutamide;
   - Finasteride;

– Cyproterone acetate.

3. Anabolic steroids:
   – Methandienone (Methandrostenolone);
   – Nandrolone phenylpropionate (Phenobolin);
   – Nandrolone deconoate (Retabolil).

B. *Female gonadal hormones and related substances:*

1. Estrogens:
   – Estron;
   – Estradiol benzoate;
   – Estriol;
   – Ethinylestradiol;
   – Synoestrol;
   – Diethylstilbestrol.
2. Combined preparations:
   – Klimonorm.
3. Antiestrogens:
   – Clomiphene citrate;
   – Tamoxifen citrate.
4. Progestins:
   – Progesterone;
   – Hydroxyprogesterone caproate;
   – Allilestrenol;
   – Dydrogesterone;
   – Norethisterone.
5. Antiprogestins:
   – Mifepristone.

ANDROGENS

Androgens are male gonadal hormones produced mainly by testis or their synthetic analogues.

TESTOSTERONE PROPIONATE

- is administered IM;
- takes part in the development of primary and secondary sex characteristics, maintains fertility in men; has an anabolic action; maintains normal bone density;

- is used to treat hypogonadism in men; may be used in a combined therapy of certain anemias, wasting syndromes, senile osteoporosis, severe burns, breast cancer in women before 60;
- may cause side effects, such as masculinization in women, an altered bone development in children, the inhibition of gonadotropin release and reduction of spermatogenesis; gynecomastia in men, hepatitis and edema.

PECULIARITIES OF OTHER PREPARATIONS

Methyltestosterone is a synthetic analogue of testosterone and has the same androgenic properties; is not destroyed in the gut; is taken sublingually for better bioavailability; is 3–4 times less active than testosterone propionate; is used for a long-lasting therapy of male hypogonadism, pathological climax in men, impotence connected with the hypofunction of testis, climacteric disturbances and breast cancer in women; displays side effects similar to adverse effects of testosterone.

ANTIANDROGENS

- ***antiandrogens (androgen antagonists, or testosterone blockers)*** are drugs that prevent androgens' biological effects in the body;
- there are few different types of antiandrogens: adrogen receptor antagonists divided into steroidal antiandrogens ***(Cyproterone acetate)*** and nonsteroidal antiandrogens ***(Flutamide)***; androgen synthesis inhibitors ***(Finasteride)*** and antigonadotropins ***(Leuprorelin, Cetrorelix)***;
- antiandrogens are used to treat androgen-dependent conditions: prostate cancer, enlarged prostate, scalp hair loss, overly high sex drive, and early puberty (in males); acne, seborrhea, excessive hair growth, scalp hair loss, and high androgen levels (in women). They are also used as a component of feminizing hormone therapy for transgender women;
- side effects in men include breast enlargement, feminization, hot flushes, sexual dysfunction, infertility, and osteoporosis. In women, antiandrogens can cause low estrogen levels and associated symptoms like hot flushes, menstrual irregularities, and osteoporosis in premenopausal women.

ANABOLIC STEROIDS

Anabolic steroids are derivatives of androgens with a strong anabolic effect and residual androgenic activity.

Pharmacodynamics	Indications
An increase in protein synthesis	Cachexia
The retention of nitrogen, phosphor, and calcium	Asthenia
The stimulation of tissue regeneration	Wounds, ulcers
An increase in mass of skeletal muscles	Bone fractures, osteoporosis
The improvement in trophy of the myocardium	Ischemic heart disease
A decrease in glucose level in blood	Myopathy
The stimulation of hemopoiesis	Diabetes mellitus (additional drug)
	Anemia (additional drug)
	Prolonged treatment with glucocorticoids

Side effects

1. Edema.
2. An increase in body weight.
3. Liver disturbances.
4. Masculinization in women.

The anabolics should not be used in sportsmen as a doping.

PECULIARITIES OF PREPARATIONS

Methandienone (Methandrostenolone) has an anabolic activity equal to the same of testosterone, but is 100 times less active as androgen than testosterone; is taken orally 1–2 times a day.

Nandrolone phenylpropionate (Phenobolin) is administered IM; has a duration of action of 7–15 days.

Nandrolone decanoate (Retabolil) has a strong and long-lasting anabolic action; develops therapeutic effect in 3 days, displays maximal effect for 7 days and acts during 3 weeks; has a minimal androgenic and virilizing action.

ESTROGENS

Estrogens are female gonadal hormones produced by ovaries or their synthetic analogues.

ESTRONE (FOLLICULIN)

- is a natural estrogen;
- is administered IM, transdermally, vaginally; is metabolized in the liver and excreted with urine;

- takes part in female sexual development, maintains the proliferation phase of menstrual cycle, increases uterus sensitivity to oxytocin and acetylcholine, has some metabolic effects (the inhibition of bone resorption, stimulation of calcium transport, reduction of the cholesterol level in blood), increases blood coagulation
- is used for primary hypogonadism in young female, replacement therapy in menopause (postmenopausal hormone therapy) (Fig. 26.8), a lack of the development of the ovaries or castration, for osteoporosis and stimulation of labor (together with oxytocin)
- may cause side effects, such as nausea, vomiting, edema, headache, hypertension, breast tenderness

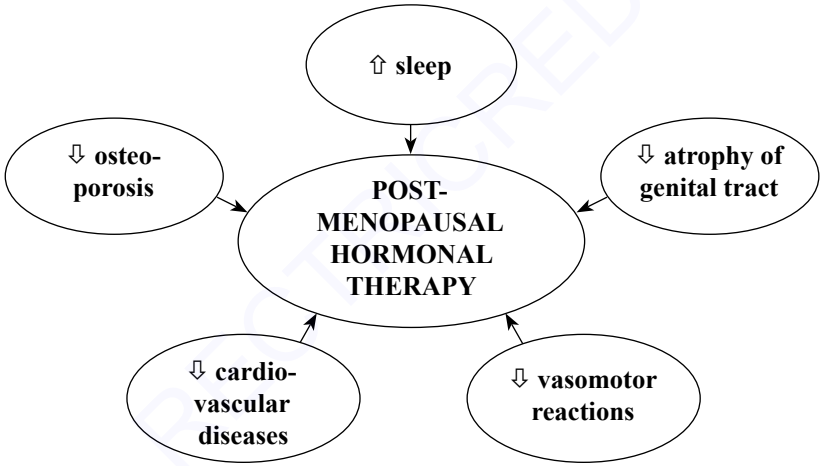

Fig. 26.8. Main effects of postmenopausal hormonal therapy by estrogens

PECULIARITIES OF OTHER PREPARATIONS

Estradiol dipropionate is a natural estrogen produced in female organism together with estrone, but is more active; has a prolonged action and is administered IM once every 3–5 days; has the indications similar to the indications of estrone.

Estriol is a low active natural estrogen used orally and intravaginally to treat the atrophy of the mucous membrane in the lower urinary tract due to estrogen deficiency, pre- and postoperative therapy in postmenopausal women with operative interventions by vaginal access, climacteric syndrome; infertility caused by cervical factor; dryness of the vagina and frequent urination.

Ethinylestradiol is a synthetic estrogen similar to estradiol by its structure; is taken orally, has slow metabolism, a prolonged action, and higher potency; is used for primary amenorhea, the hyhofunction of ovaries and secondary amenorrhea, climacteric disturbances in women, breast cancer in women after 60, prostate cancer in men; may cause feminization in men, nausea, vomiting or vertigo.

Synoestrol is a synthetic compound, a stilben derivative; has not a steroidal structure, but has estrogenic pharmacological properties and indications; is administered orally, IM, SC.

Diethylstilbestrol is a synthetic non-steroidal compound with estrogenic activity, may be administered orally, IM; is more active than estrone and synoestrol.

Klimonorm contains estradiol valerate which in the human body is converted to natural 17β-estradiol as well as progesterone derivative levonorgestrel adding of which within 12 days of each cycle prevents the development of hyperplasia and endometrial cancer. Due to the composition and the cyclic schedule of administration, the drug can restore the menstrual cycle in postmenopausal women. Estradiol replenishes the estrogen deficiency in the female body after the onset of menopause and provides effective treatment of psychoemotional and vegetative climacteric symptoms; involution of the skin and mucous membranes, reduces the risk of atherosclerosis and IHD, inhibits proliferative processes in the endometrium (Fig. 26.8). Estradiol also prevents bone loss caused by estrogen deficiency mainly due to the suppression of osteoclast function and stimulation of the bone remodeling process and in such a way can reduce the risk of fractures of peripheral bones in women after menopause. The drug is used for hormone replacement therapy in pre- and postmenopause, for the treatment of climacteric syndrome, postclimacteric dysfunction of urinary bladder and for prevention of postmenopausal osteoporosis in women.

ANTIESTROGENS

Antiestrogens (estrogen antagonists or estrogen blockers) are the drugs which prevent estrogens' biological effects in the body. They include selective estrogen receptor modulators ***(Tamoxifen, Clomifene)***, selective estrogen receptor degrader ***(Fulvestrant)***, aromatase inhibitors ***(Anastrozole)***. Androgens, anabolic steroids, progestogens, and GnRH analogues also have an antiestrogen effect.

Antiestrogens are mainly used as estrogen deprivation therapy in the treatment of estrogen-positive breast cancer, for infertility, male hypogonadism, and gynecomastia and as a component of hormone replacement therapy for transgender men.

Clomiphene interacts with estrogen receptors; by a feedback mechanism it stimulates the secretion of gonadotropins, leading to ovulation; is used to treat infertility on the ground of anovulatory cycles.

Tamoxifen inhibits estrogens action by interfering with their access to receptor sites; is used to treat breast cancer in postmenopausal women.

PROGESTINS

Progestins are female gonadal hormones produced by *corpus luteum* or their synthetic analogues.

PROGESTERONE

- is a native progestine;
- is given IM, orally (as a micronized form), intravaginally (vaginal cream);
- takes part in the development of sex characteristics, maintains the luteal phase of a menstrual cycle, stimulates maturation of the uterus endometrium and provides implantation, decreases uterus sensitivity to oxytocin and supports the normal development of pregnancy, promotes the development of breast secretory tissue, acts on the carbohydrate metabolism and stimulates fat deposition;
- is used for the prevention of spontaneous abortion, dysfunctional uterine bleeding, dysmenorrhea, endometriosis, suppression of postpartum lactation and the therapy of endometrial carcinoma;
- may cause side effects, such as uterine bleeding, dyspepsia, edema, depression, an increase in the cholesterol level, an increase in blood coagulation, acne, hirsutism and weight gain.

PECULIARITIES OF OTHER PREPARATIONS

Oxyprogesterone caproate is a synthetic analogue of progesterone, is more stable in the body and has prolonged action during 7–14 days; is administered IM; is more suitable for a long-term therapy.

Allilestrenol is a synthetic progestin; is administered orally, is more stable to first-pass metabolism; is used for the prevention of spontaneous abortion.

Dydrogesterone is a progestin, an agonist of the progesterone receptor. The drug is atypical progestogen and does not inhibit ovulation, has weak antimineralocorticoid activity and no other important hormonal activity. It is used orally for miscarriage during pregnancy, dysfunctional bleeding, infertility due to luteal in-

sufficiency, dysmenorrhea, endometriosis, secondary amenorrhea, irregular cycles, premenstrual syndrome, and as a component of menopausal hormone therapy. Side effects more often include menstrual irregularities, headache, nausea, breast tenderness.

Norethisterone is a progestin, an agonist of the progesterone receptor like progesterone. It has weak androgenic and estrogenic activity at high doses, is used alone or in a combination with estrogen, is applied in birth control pills, menopausal hormone therapy, and for the treatment of gynecological disorders. Side effects are typical to progestins and include menstrual irregularities, headaches, nausea, breast tenderness, mood changes, acne, increased hair growth, etc.

ANTIPROGESTINS

Antiprogestogens (antiprogestins, progesterone antagonists) are drugs which prevent progestogens' biological effects in the body. They act by blocking the progesterone receptor or inhibiting progesterone production. They are used as abortifacients and emergency contraceptives and in the treatment of uterine fibroids. Between many compounds of this class, only mifepristone has been approved and introduced for clinical use.

Mifepristone is a progestine antagonist, has antiglucocorticoid activity, is used for the termination of gestation and for contraception.

ORAL AND INPLANTABLE CONTRACEPTIVES

Hormonal contraceptives are hormonal preparations for the prevention of pregnancy.

There are 4 main classes of oral contraceptives (Fig. 26.9).

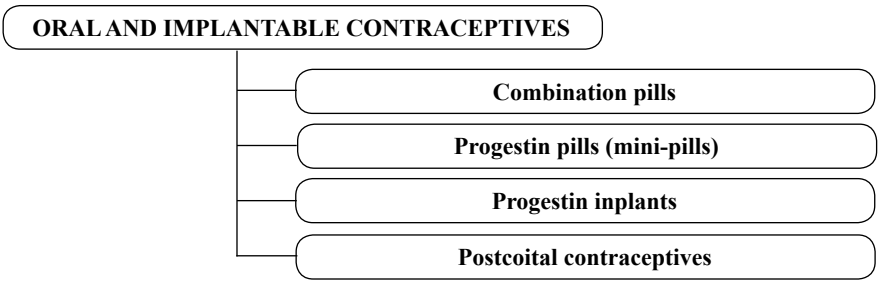

Fig. 26.9. Classes of oral contraceptives

- **Combination pills** contain estrogen and progestin. The estrogen suppresses ovulation. The progestin prevents implantation and makes the cervical mucus impenetrable to sperm. They are taken in mono-, bi- or triphase regimen. Monophasic drugs are ***Logest*** and ***Marvelon***. Biphasic preparation is ***Anteovin***, Triphasic preparations are ***Tri-regol, Triquilar, Trisiston***.
- **Progestin pills** contain progestin only ***(norethindrone*** or ***norgestel)***. They are less effective than the combination pills.
- **Progestin inplants** are subdermal capsules containing ***levonorgestrel*** for a long-term contraception (5 years) (e.g., ***Depo-provera***).
- **Postcoital contraceptives** contain a high dose of estrogen (ethinylestradiol, diethylstilbestrol) or estrogen ***(ethinylestradiol)*** and progestin ***(norgestrel)*** administered within 72 hrs of coitus (e.g., ***Postinor***).

Side effects of oral contraceptives

Breast fullness, depression, dizziness, nausea, vomiting, thromboembolism, thrombophlebitis, hypertension, increased incidents of myocardial infarction and cerebral thrombosis, abnormal glucose tolerance tests, changes in the serum lipoprotein profile, cholestatic jundice, skin pigmentation, acne, hirsutism, amenorrhea and uterine bleeding.

TESTS FOR SELF-CONTROL

1. The hormonal preparation with mineralcorticoid activity is:
A. Prednisolone
B. Dexamthasone
C. Testosterone propionate
D. Desoxycorticostrone acetate
E. Estradiol caproate.

2. Glucocorticoids may cause all the following side effects, except:
A. Hypertension
B. Bronchospasm
C. Thromboembolism
D. Hypokalemia
E. Osteoporosis.

3. Regular insulin:
A. Is produced by genetically modified *Escherichia coli*
B. Is administered SC, IV

C. Is used for replacement therapy of type I diabetes mellitus
D. Is taken orally in II type diabetes mellitus
E. May cause hyperglycemia.

4. Anabolic steroids:
A. Have high androgenic activity
B. Have high anabolic activity
C. May cause feminization in men
D. May cause masculinization in women
E. Are contraindicated to sportsmen.

5. A patient suffering from the hypofunction of the thyroid gland was treated by hormonal preparation. An overdose of this preparation causes restlessness, insomnia, fever, headache, tachycardia, pain in the heart, palpitation and tremor. What drug was used by this patient?
A. Insulin
B. Methimazole
C. L-thyroxine
D. Triamcinolone
E. Retabolil.

Answers

1 – D; 2 – B; 3 – A, B, C; 4 – B, D, E; 5 – C.

Chapter 27 VITAMINS PREPARATIONS

VITAMINS AND THEIR PREPARATIONS

Vitamins are organic substances essential for normal metabolism. They are the normal components of diet and must be supplied in very small quantities.

History of vitamins. A russian scientist N. Lunin discovered vitamins (1880). Holand Ch. Echman supposed that rice husk contained substance for the prevention and treatment of disease beri-beri (vitamin B_1) (1897). A polish scientist K. Funk separated this substance from rice husk and proposed the name "vitamin".

Vitamins preparations are medicinal forms of vitamins used for the prophylaxis and treatment of diseases.

Distinguishes between membranetropic and enzymetropic vitamins

Division of vitamins into groups is based on their biochemical properties and participation in the biological processes. Some common characteristics make it possible to speak about membranetropic and enzymetropic vitamins (Table 27.1).

Table 27.1. **Distinguishes between groups of vitamins**

Membranetropic vitamins	***Enzymetropic vitamins***
1. Are fat and water-soluble substances 2. Have a requirement of 100 mg per day 3. Are components of cell membranes 4. Are not phosphorilized 5. Take part in the forming and protection of cells membranes 6. May cause hypervitaminosis	1. Are only water-soluble substances 2. Have a requirement of 1–10 mg per day 3. Are components of enzymes (coenzymes) 4. Are phosphorilized 5. Take part in biochemical reactions 6. Don't cause hypervitaminosis

Vitamin deficiency

Avitaminosis is a specific deficiency syndrome caused by the absence of particular vitamin. It is occurred very rarely.

Hypovitaminosis is a specific deficiency syndrome caused by the deficit of particular vitamin. It is often occurred. There are two types of hypovitaminoses: exogeneous and endogeneous (Fig. 27.1). Exogeneous hypovitaminosis is caused by factors outside the body, e.g., deficit of vitamin in the diet or poor nutrition. Endogeneous hypovitaminoses is caused by factors inside the organism and are divided into physiological and pathological.

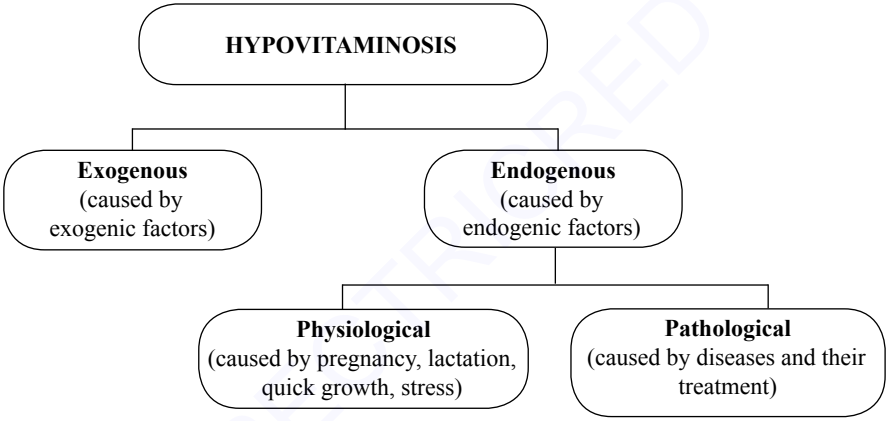

Fig. 27.1. Types of hypovitaminoses

Antivitamins

Antivitamins are substances which decrease a vitamins action.

There are three groups of antivitamins:

- antimetabolites which are chemical analogues of vitamins (e.g., warfarin is an antivitamin of naphthoquinon; isoniazid is an antivitamin of pyridoxine; methotrexate is an antivitamin of the folic acid)
- enzymes which destroy vitamins (e.g., thiaminase or ascorbinase)
- substances which increase the utilization of vitamin (e.g., antiatherosclerotic drug linethol increases the utilization of vitamin E).

Hypervitaminosis

Hypervitaminosis is an overdose of the vitamin preparation.

Most of vitamins are comparatively safe, but vitamins A and D can cause serious toxic effects. Hypervitaminosis may be acute and chronic.

Vitamins therapy

Vitamins therapy is a therapy by vitamins preparations.

Vitamins therapy is divided into three types (Fig. 27.2):

- specific replacement therapy which is the use of vitamins for the treatment of hypo- and avitaminosis (e.g., the ascorbic acid is for the treatment of scurvy; thiamine – for beri-beri)
- pharmacodynamic therapy which is the use of vitamins for diseases non-connected with vitamins deficit (e.g., the use of the ascorbic acid to treat wounds and infections)
- adaptation therapy which is the use of vitamins for the improvement of non-specific resistance and adaptation (e.g., the use of the ascorbic acid, α-tocopherol acetate, and multivitamins preparations in healthy persons under the conditions of stress or physical overstrain).

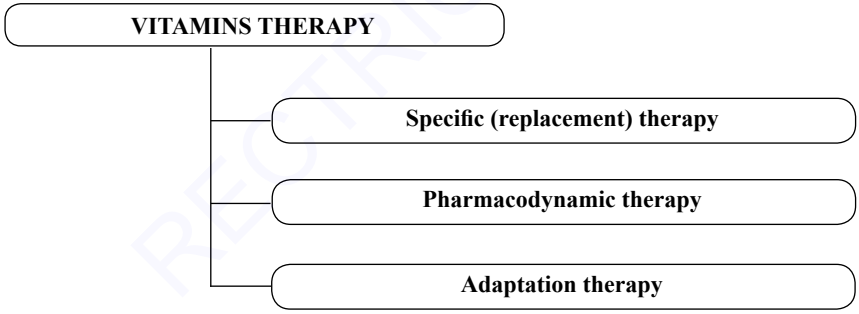

Fig. 27.2. The types of vitamins therapy

CLASSIFICATION

According to the solubility

1. Water-soluble vitamins:
   - Thiamine chloride (B_1)
   - Riboflavin (B_2)
   - Nicotinic acid (B_3 or PP)
   - Calcium pantothenate (B_5)
   - Pyridoxine hydrochloride (B_6)
   - Cyanocobalamin (B_{12})

According to the biological activity

1. Membranetropic vitamins:
   - Vitamin A
   - Vitamin E
   - Vitamin D
   - Vitamin K
   - Vitamin C
   - Vitamin P

- Folic acid (B_c)
- Calcium pangamate (B_{15})
- Ascorbic acid (C)
- Rutin (P)

2. Fat-soluble vitamins:
   - Retinol acetate (A) and related substances
   - Ergocalciferol (D) and related substances
   - α-Tocopherol acetate (E)
   - Naphthoquinon (K)

2. Enzymetropic (coenzyme) vitamins:
   - Vitamin B_1
   - Vitamin B_2
   - Vitamin PP
   - Vitamin B_5
   - Vitamin B_6
   - Vitamin B_{12}
   - Vitamin B_c

MEMBRANETROPIC VITAMINS PREPARATIONS
RETINOL ACETATE

Retinol has a polyenic structure (Fig. 27.3). It is a fat-soluble vitamin.

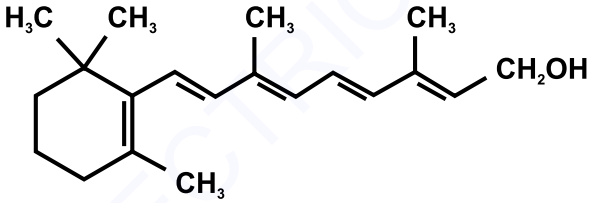

Fig. 27.3. Chemical structure of retinol

Pharmacokinetics

- is taken orally, rarely IM, is applied topically;
- is absorbed in the intestine in the presence of bile acids;
- binds to proteins in the blood plasma that protects retinol from renal excretion;
- concentrates in the liver;
- exists in the body in such forms as retinol, retinal, and retinoic acid;
- is metabolized in the liver and excreted with bile and urine, has durative elimination.

Mechanism of action

- active form of retinol is a constituent of visual purple (rhodopsin);
- it takes part in the synthesis of keratohyalin;

- it takes part in the forming of bones and teeth;
- retinol activates synthesis of immunoglobulins, antibodies and lysosome enzyme;
- it activates glycogen deposition in the muscles, heart, and liver;
- retinol activates release of STH and thyroid hormones;
- it is an antioxidant.

Pharmacodynamics

- supporting of the normal function of the retina (night vision);
- stimulation of the proliferation and regeneration of the epithelium;
- the promotion of growth of the organism, prevention of bones' epiphyses calcification;
- an increase of immunity;
- the improvement in the trophy of the myocardium, skeletal muscles, liver, and nervous system;
- supporting of the reproductive function.

Indications

- hypovitaminosis (hemeralopia). A therapeutic dose for adult patients is up to 10000 IU per day, a prophylaxis dose is 5000 IU per day (1 drop of 3.44% oil solution contains 5000 IU);
- eye diseases (cornea and retina diseases);
- hyperkeratosis, leukoplacia;
- skin diseases, burns, frostbites;
- chronic inflammations of the bronchi, urinary or bile pathways;
- rickets (a complex therapy and prophylaxis);
- pregnancy;
- diseases of the mucous membrane of the oral cavity, a complex therapy of severe caries.

Side effects and overdose

***Acute hypervitaminosis*:** fatigue, headache, sleepiness, nausea, vomiting, photophobia, convulsions (resulting from an increase in intracranial pressure).

***Chronic hypervitaminosis*:** weakness, fatigue, sleepiness, nausea, skin pigmentation, hyperkeratosis, bone pains, the liver and spleen enlargement.

Contraindications

1. Acute diseases of the liver and kidney.
2. Heart failure.

RETINOIDS

- are a class of chemical compounds that are vitamers of vitamin A or are chemically related to it;
- have many important functions throughout the body including roles in vision, regulation of cell proliferation and differentiation, growth of bone tissue, immune function, and activation of tumor suppressor genes;
- there are three generations of retinoids: the 1st generation ***(Tretinoin (Retinoic acid)***, ***Isotretinoin,*** and ***Alitretinoin***); the 2nd generation (***Etretinate*** and its metabolite ***acitretin***); the 3rd generation (***Adapalene, Bexarotene***, and ***Tazarotene***);
- are used in the treatment of many dermatological conditions, such as inflammatory skin disorders, skin cancers, psoriasis, acne or photoaging. They reduce the risk of head and neck cancers. Isotretinoin is used as chemotherapy for leukemia;
- toxic effects occur with prolonged high intake and are characterized by painful tender swellings on the long bones, anorexia, skin lesions, hair loss, hepatosplenomegaly, papilloedema, bleeding, general malaise, *pseudotumor cerebri* (hypervitaminosis A syndrome);
- systemic retinoids (isotretinoin, etretinate) are contraindicated during pregnancy as they may cause CNS, cranio-facial, cardiovascular and other defects.

ERGOCALCIFEROL

Vitamin D is a family of substances with an antirachitic effect. They have steroid structure and are fat-soluble. ***Ergocalciferol*** is vitamin D_2. Cholecalciferol is vitamin D_3. Cholecalciferol is synthesized in the skin under the influence of ultraviolet rays (Fig. 27.4).

Pharmacokinetics

- is taken orally;
- is absorbed in the intestine with the participation of bile acids;
- is transported to the liver by lymph;
- is transported in connection with transcalciferrine in the blood plasma;
- is transformed into calcidiol in the liver and into calcitriol in the kidneys (Fig. 27.4);
- is deposited in the liver, mucosa of intestines, and bones;
- is excreted with bile and then is absorbed again;
- finally, is excreted with urine and feces;

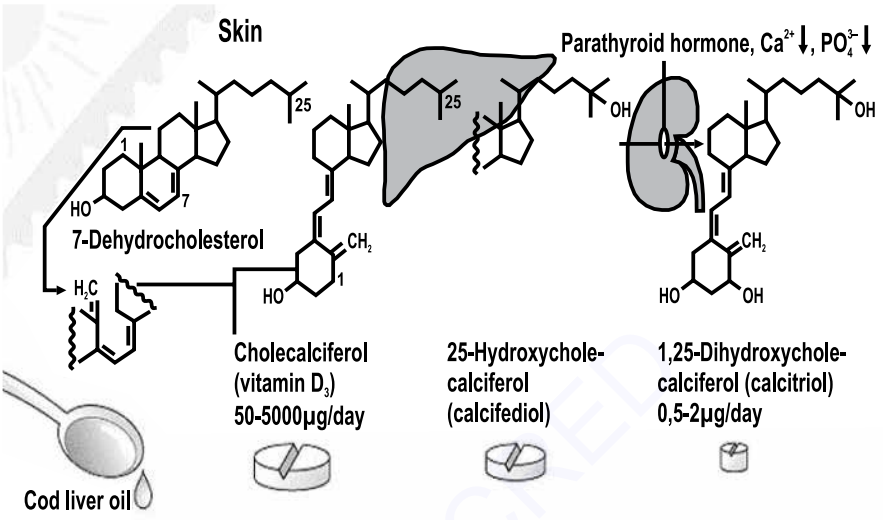

Fig. 27.4. Vitamin D and its active forms *(by H. Lüllmann, 2000)*

- stays in the body for a long time;
- accumulates.

Mechanism of action

- vitamin D penetrates cell membrane, binds to the receptor in cytoplasma and forms the complex "vitamin D–receptor" (Fig. 27.5);
- it is transported to the nucleus and changes genes expression;
- as a result, the synthesis of proteins concerning calcium and phosphate metabolism is increased;
- such events are similar to the mechanism of action of steroid hormones.

Pharmacodynamics

Main task of vitamin D is to regulate calcium-phosphor homeostasis and to support calcium level in the blood (Fig. 27.6). According to this purpose, it causes:

- an increase in calcium and phosphates absorption from the intestine;
- an increase in calcium and phosphates reabsorption in the kidney;
- an elevation of the level of calcium in the blood plasma;
- an increase in fixation of calcium in bone tissue under the conditions of the normal calcium level in the blood plasma, but stimulation of calcium mobilization from bones if the plasma calcium level is low;

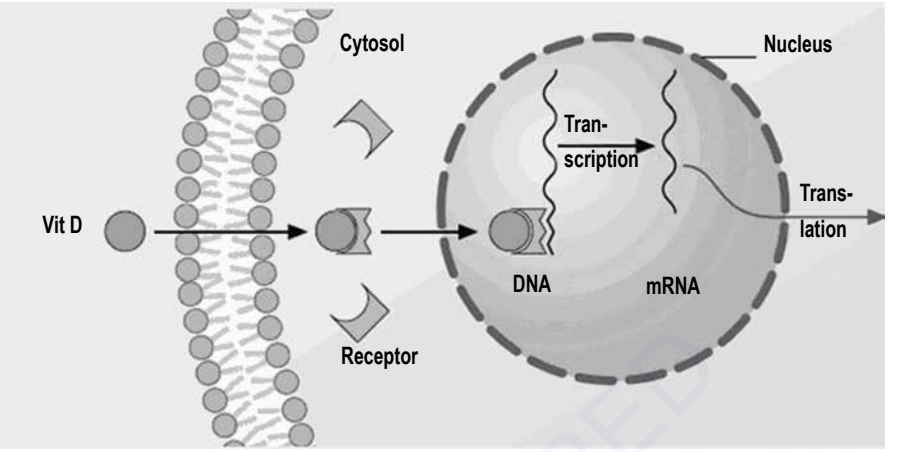

Fig. 27.5. Vitamin's D mechanism of action *(by H. Lüllmann, 2000)*

- an increase in the calcium influx into the nervous cells;
- an increase in the calcium influx into the cells of skeletal muscles;
- the stimulation of immunity and regeneration.

Indications

- hypovitaminosis: the prophylaxis and treatment of rickets. A prophylactic dose is 500–1000 IU per day; a therapeutic dose is 10000 IU and more per day and depends on the severity of vitamin deficiency (1 drop of 0.125% oil solution contains 1250 IU; 1 drop of 0.5% alcohol solution – 5000 IU of vitamin D);
- osteoporosis;
- bone fractures;
- caries, disturbances of teeth forming;

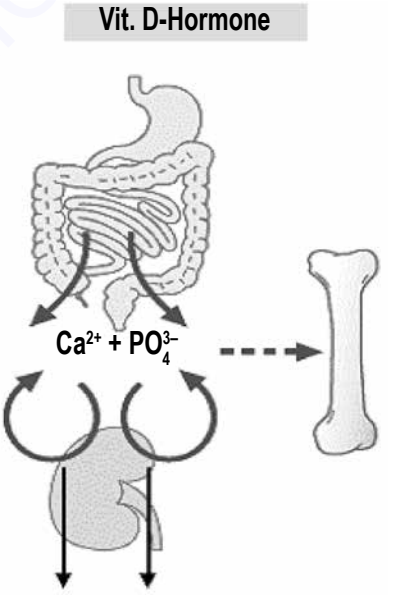

Fig. 27.6. Vitamin D and regulation of calcium homeostasis in the body *(by H. Lüllmann, 2000)*

- Skin diseases
- Tuberculosis.

Side effects and overdose

***Acute hypervitaminosis*:** weakness, sleepiness, nausea, vomiting, dyspepsia, hypotension, arrhythmia, an increase in body temperature, an increase in the calcium concentration in the blood plasma, changes in urine (protein, cylinders, calcium salts, erythrocytes, and leukocytes).

***Chronic hypervitaminosis*:** bone demineralization, calcium deposition in the blood vessels, kidney, and other organs (calcinosis), CNS damage, heart insufficiency, an increase in BP, an increase in the calcium level in the blood plasma and urine.

Treatment of D hypervitaminosis

– abolishing of the drug;
– antioxidants (vitamins E, C, A);
– glucocorticoids;
– other medications: phenobarbital for the intensification of vitamin D biotransformation; solution of sodium bicarbonate for acidosis; preparations of potassium and magnesium; calcitrin for the prevention of bone demineralization.

Contraindications

1. Severe atherosclerosis.
2. Elderly age.

OTHER VITAMINE D PREPARATIONS, ITS ANALOGUES AND ACTIVE METABOLITES

Cholecalciferol (D_3) is a type of vitamin D which is made by the skin, found in some foods, and taken as a dietary supplement. It is used to treat and prevent vitamin D deficiency and associated diseases, including rickets. It is also used for familial hypophosphatemia, hypoparathyroidism, Fanconi syndrome. There are conflicting data concerning the relative effectiveness of cholecalciferol (D_3) versus ergocalciferol (D_2), with some studies suggesting less efficacy of D_2, and others showing no difference. There are differences in absorption, binding and inactivation of the two forms, with evidence usually favoring cholecalciferol in raising levels in blood.

Dihydrotachysterol (DHT) is a synthetic vitamin D analogue activated in the liver that does not require renal hydroxylation like ergocalciferol and cholecalciferol. DHT has a rapid onset of action (2 hrs), a shorter half-life, and a greater effect on mineralization of bone tissue than vitamin D does.

Calcitriol is an active metabolite of vitamin D which has three hydroxyl groups. It does not need metabolic activation and is preferable in the patients with low synthesis of endogenous calcitriol in the kidneys (chronic kidney disease, renal osteodystrophy). Calcitriol is prescribed for the treatment of hypocalcemia, hypoparathyroidism, osteomalacia, rickets, treatment of osteoporosis and prevention of corticosteroid-induced osteoporosis. It is used topically for the treatment of psoriasis.

Alfacalcidol is an active metabolite of vitamin D. The drug has a weaker impact on the calcium metabolism and parathyroid hormone levels than calcitriol however it has significant effects on the immune system. Alfacalcidol is more useful form of vitamin D supplementation due to much longer half-life and lower kidney load. It does not require hydroxylation in the kidney that is why is the most commonly prescribed vitamin D metabolite for patients with end stage renal disease.

α-TOCOPHEROL ACETATE

It belongs to quinons (Fig. 27.7), is fat-soluble.

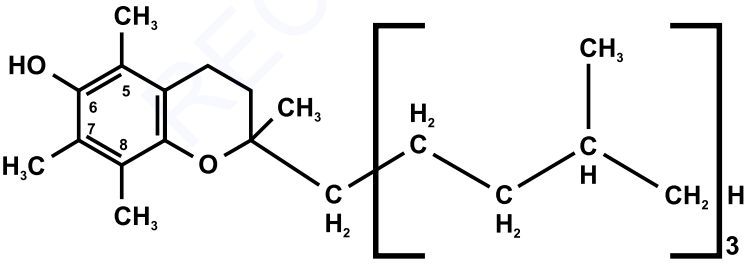

Fig. 27.7. Chemical structure of tocopherol

Pharmacokinetics

- is taken orally and administered IM; is applied topically;
- is absorbed in the small intestine in the presence of bile acids;
- enters lymph, then blood and is transported with lipoproteins;
- is located in the membranes of cells, the membranes of mitochondria and microsomes;

- concentrates in the adrenal glands and fat tissue;
- is excreted in non-transformed status with feces (more than 80% of a dose).

Mechanism of action

- α-tocopherol is the strongest bioantioxidant and protects cell membranes from free radicals and peroxides;
- it increases the activity of creatinphosphokinase, cytochrome-C oxidase and some other enzymes, stimulates the synthesis of ubiquinon, improves tissue respiration;
- α-tocopherol increases the secretion of gonadotropines and gonadal hormones;
- it increases iron absorption, the synthesis of hem and surphactant in the lungs.

Pharmacodynamics

- the regulation of reproduction (the promotion of follicles formation and normal development of pregnancy in females; the stimulation of spermatogenesis in males);
- the improvement of skeletal muscles trophy;
- a cardioprotective action;
- an increase in the stability to hypoxia;
- the stimulation of erythropoiesis;
- the improvement of reological properties of the blood;
- an antiatherosclerotic action;
- a stressprotective action;
- a hepatoprotective action;
- the stimulation of regeneration.

Indications

- spontaneous abortions, sexual glands function impairment, climax;
- myodystrophy;
- angina pectoris, a complex therapy of myocardial infarction;
- atherosclerosis;
- liver diseases;
- complex therapy of anemia;
- diseases of blood vessels;
- radiation sickness;
- stress;
- paradontitis, diseases of the mucous membrane of the oral cavity;
- hypervitaminosis D.

Side effects

- creatinuria;
- very rarely: hepatic disturbances, nausea, headache and an increase in BP (in bigger doses).

PHYTOMENADIONE

- is known as vitamin K_1 or phylloquinone, belongs to fat-soluble vitamins;
- is typically recommended by mouth or SC injection, rarely IV or IM. When taken orally, the effect manifests itself after 6–10 hrs (IM for 1 hr) and persists for 3–6 hrs;
- stimulates hepatic biosynthesis of prothrombin (factor II), proconvertin (factor VII), plasma thromboplastin component (IX, or Christmas factor), Stuart-Prower factor (factor X). It is a cofactor of the microsomal enzymes of hepatocytes which catalyze γ -carboxylation of the pro-clotting factors II, VII, IX, X, protein C (coagulation inhibitor) and calcium-binding proteins (osteocalcin). After the γ-carboxylation of glutaminic acid, functionally inactive progenitors acquire antihemorrhagic properties and are secreted into the blood. Vitamin K participates in biosynthesis of ATP and creatine phosphate, activation of ATPase, creatine kinase, aminotransferases, pancreatic and intestinal enzymes;
- is used in hemorrhagic syndrome associated with a deficiency of vitamin K_1 or violation of its absorption in the gut; an overdose of anticoagulants of indirect action (coumarin and indanedione derivatives), salicylates, sulfonamides, and broad-spectrum antibiotics; hemorrhagic disease of newborns; prevention of bleeding before operations;
- can cause such side effects as feeling of heat and redness of the skin, altered taste, weakness, tachycardia, sweating, short-term hypotension, dyspnoea, cyanosis, allergic reactions and hyperbilirubinemia (in children).

ASCORBIC ACID

Ascorbic acid is a hexose, easily losses the atom of hydrogen and transforms into the dehydroascorbic acid (Fig. 27.8). It is water-soluble vitamin.

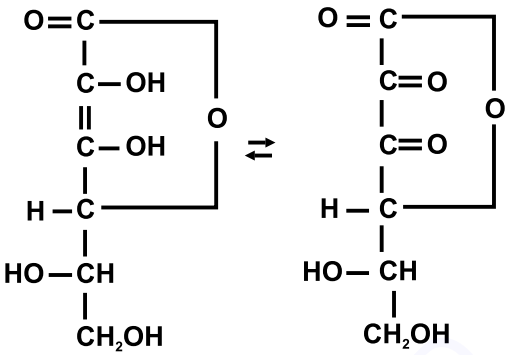

Fig. 27.8. Chemical structure of ascorbic acid

Pharmacokinetics

- is administered orally, IM, IV;
- is well absorbed in the intestine;
- vitamin C concentration in erythrocytes and leukocytes is more than that in the blood plasma;
- concentrates in the gland tissue, especially in the adrenal glands;
- is excreted with urine if the depot is complete.

Mechanism of action

Ascorbic acid is a donator and an acceptor of hydrogen. That is why it takes part in oxidation-reduction systems, is a direct-acting antioxidant.

Pharmacodynamics

- participation in the synthesis of procollagen and collagen;
- providing of the growth of bones, the formation of cartilages and dentine;
- the stimulation of regeneration;
- participation in the transformation of folic acid into the tetrahydrofolic acid;
- an increase in the absorption of iron and synthesis of hem;
- participation in the synthesis of adrenal steroids and thyroid hormones;
- participation in the synthesis of catecholamines and activation of sympathetic nervous system;
- the improvement of immunity and phagocytosis;
- a decrease in the permeability of blood vessels;
- participation in the cholesterol metabolism and the inhibition of the development of atherosclerosis;

- detoxification of xenobiotics in the liver;
- an increase in the resistance to stress and radiation;
- the improvement of adaptation.

Indications

- hypovitaminosis (scurvy);
- collagenoses;
- rheumatism;
- wounds, bone fractures;
- hemorrhagic diathesis;
- atherosclerosis;
- radiation sickness;
- complex therapy of anemia;
- infections;
- acute and chronic intoxications;
- the stimulation of protective powers of the organism and the improvement of adaptation;
- bleeding gums, paradontitis, a complex therapy of severe caries.

Side effects

Side effects only occure in bigger doses of vitamin C:

1. A decrease in the secretion of insulin.
2. Renal concrements.
3. An increase in BP.
4. A decrease in permeability of blood-tissue barriers.
5. Hypercoagulation of the blood.

RUTIN

- is a water-soluble membranetropic vitamin, a flavonoid;
- is taken orally;
- is an antioxidant; protects the ascorbic acid and epinephrine from oxidation, participates in the oxidation-reduction processes, inhibits hyaluronidase activity, decreases the permeability of the blood vessels wall;
- is used together with the ascorbic acid in vasculitis, hemorrhagic diathesis, rheumatism, collagenosis, radiation sickness, atherosclerosis, infections or paradontitis.

CALCIUM PANGAMATE

- is a water-soluble membranetropic vitamin, a derivative of the gluconic acid and dimethylglycine;
- is taken orally;
- has the mechanism of action relating to the ability to be a donator of active methyl groups;
- improves lipids metabolism; enhances oxygen utilization in the tissues; increases the concentration of creatin phosphate and glycogen in the skeletal muscles and liver; decreases hypoxia; has neuroprotective, cardioprotective, antihypoxic, antidystrophic and hepatoproptective effects; decreases side effects of sulfa drugs and corticosteroids;
- is used to treat atherosclerosis, especially atherosclerosis of arteria in the lower extremities, emphysema of the lungs, pneumosclerosis, chronic hepatitis, chronic alcoholism and skin diseases; may be applied to improve the tolerance to sulfa drugs and adrenal steroids;
- may cause allergy, abdominal pain.

COENZYME VITAMINS PREPARATIONS

Coenzyme vitamins preparations are water-soluble ones. They are also named "complex B vitamins" (Fig. 27.9).

The main hypovitaminoses and avitaminoses caused by deficit of coenzyme vitanins are:

- thiamine deficiency – beri-beri (polyneuritis, CHF, psychic disturbances; in babies – heart failure, tachycardia, seizures, vomiting, anorexia and nervous excitement);
- riboflavin deficiency – ariboflavinosis (cheilosis, angular stomatitis, perioral dermatitis, photophobia and conjunctivitis);
- nicotinic acid deficiency – pellagra (dermatitis, diarrhea, dementia and dystrophy);
- pyridoxine deficiency – microcytic anemia, may be secondary pellagra, neuropathy, depression, in babies – anemia, hypotrophy, seizures, meteorism;
- cyanocobalamin deficiency – megaloblastic anemia (hyperchromic anemia, crimson tongue, atrophic glossitis, parasthesia and ataxia).

THIAMINE CHLORIDE

It is a coenzyme water-soluble vitamin from B complex.

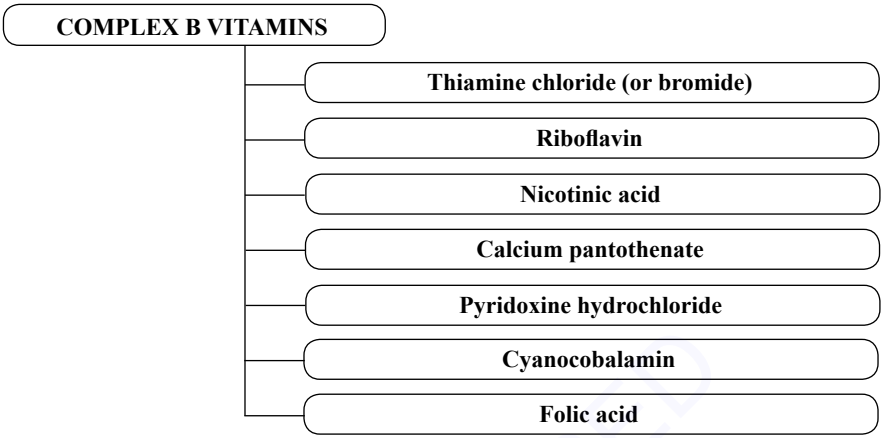

Fig. 27.9. Vitamins preparations of B complex

Pharmacokinetics

- is administered orally, IM, SC, IV;
- is absorbed in the small intestine;
- is phosphorilized in the liver and transformed into cocarboxylase;
- concentrates in the liver, heart, brain, and kidney;
- is excreted with urine.

Mechanism of action

- active form of vitamin B_1 is a coenzyme of decarboxylase and takes part in the oxidative decarboxilation of α-ketoacids (Fig. 27.10);
- in such a way it stimulates the forming of piruvic acid and decreases the lactate level;
- it is a coenzyme of transketolase and takes part in a pentosophosphate way of glucose metabolism;
- B_1-stimulates synthesis of acetylcholine.

Pharmacodynamics	Indications
Neurotropic effect: it improves impulses conduction in the nervous fibers, decreases pain, has ganglia blocking action, decreases the action of depolarized myorelaxants	Hypovitaminosis (beri-beri) Polyneuritis, radiculitis, neuralgia

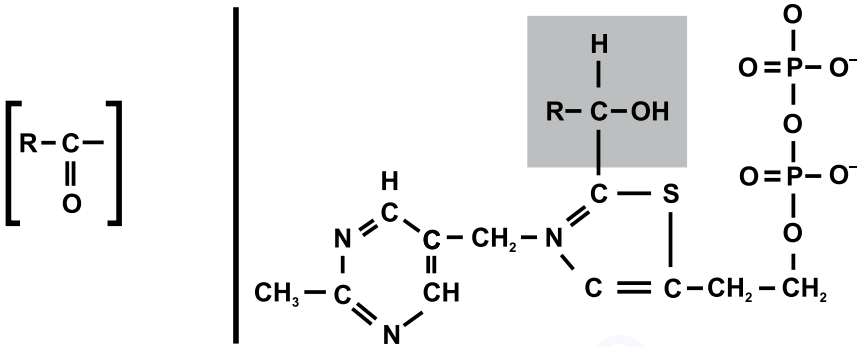

Fig. 27.10. Active form of thiamine is for oxidative decarboxilation of α-ketoacids: acid residue is shown at left *(by J. Musil et all, 1980)*

Cardiotropic effect: it widens coronary vessels, improves the trophy of the myocardium, increases contractility, normalizes the heart rate, improves the oxygenation of the heart muscle, increases the action of cardiac glycosides
Hypoglycemic effect: it improves the utilization of glucose, is a synergist of insulin.

Chronic heart failure, arrhythmia
Diabetes mellitus
Ulcer of the stomach and duodenum
Skin diseases.

Side effects

1. Allergic reactions, anaphylactic shock.
2. Lethargy, ataxia, nausea and hypotension (in overdose).

Contraindications

Should not be used in allergy to vitamin B_1 as well as together with pyridoxine (resulting in disorders of phosphorilizing) or cyanocobalamin (resulting in allergy).

COCARBOXYLASE

Cocarboxylase is an active form of vitamin B_1; is a dry substance in ampoules for IM and IV administration; is used for the treatment of acidosis, diabetes mellitus, diabetic coma, hepatic coma, renal failure, chronic heart failure, arrhythmia and diseases of the CNS.

RIBOFLAVIN

It is a coenzyme water-soluble vitamin from B complex.

Pharmacokinetics

- is taken orally and applied topically as eye drops
- is absorbed in the small intestine
- is phosphorilized in the intestine, liver, and erythrocytes
- concentrates in the liver and kidneys
- is excreted with urine and colored urine in light yellow color.

Mechanism of action

Active forms are FAD (flavin adenine dinucleotide) and FMN (flavin mononucleotide). They are coenzymes of flavin enzymes which take part in the H^+ transport chain in the tissue respiration (Fig. 27.11).

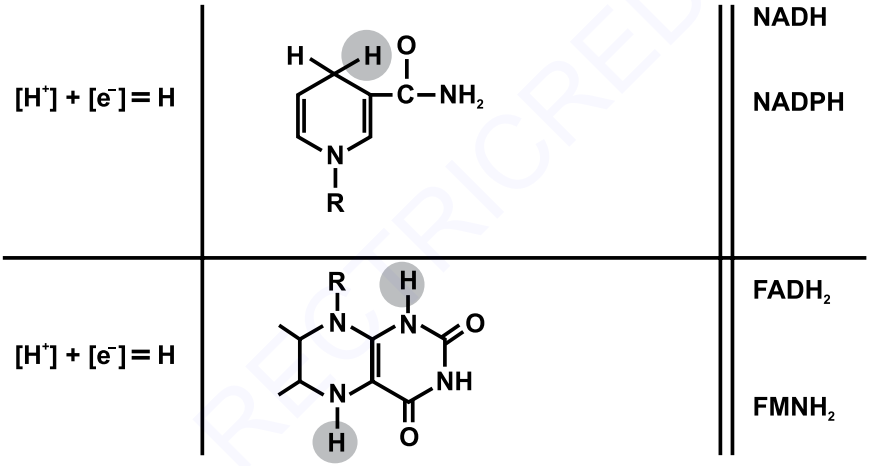

Fig. 27.11. Active forms of vitamins B_2 and PP participate in tissue H^+ and e^- transport *(by J. Musil et all, 1980)*

Pharmacodynamics	Indications
The improvement of trophy of the eye and function of vision	Hypovitaminosis (heilosis, glossitis, photophobia)
The stimulation of epithelium regeneration	Eye diseases (keratitis, conjunctivitis)
	Skin diseases
The stimulation of hemopoesis	Radiation sickness
An increase in stability to hypoxia	Anemia
The stimulation of gastric secretion	Asthenia
A decrease in cardiac glycosides toxicity	Liver diseases
	Heilosis, angular stomatitis

Side effects

None recorded.

NICOTINIC ACID

It is a coenzyme water-soluble vitamin from B complex.

Pharmacokinetics

- is taken orally and administered IM, SC, IV;
- is absorbed in the small intestine;
- is transformed into the active forms in the liver;
- is metabolized in the liver;
- is excreted with urine.

Mechanism of action

The active forms are NAD (nicotine amide dinucleotide) and NADP (nicotine amide dinucleotide phosphate). They take part in the electron transport chain in the tissue respiration (Fig. 27.11), are the acceptors of H^+

Vitamin PP active forms participate in the synthesis of amino acids, neurotransmitters, cholesterol, bile acids, steroid hormones, etc.

Pharmacodynamics	Indications
Neurotropic effect: it inhibits CNS activity, interacts with benzodiazepine receptors, stimulates the synthesis of neurotransmitters, has sedative and antiepileptic properties	Hypovitaminosis (pellagra) Diseases of the skin and mucous membranes Liver diseases
Cardiotrophic effect	
The improvement of the skin trophy	Atherosclerosis
The improvement of the liver function	Spasms of blood vessels
Hypolipidemic action: it decreases triglycerids, cholesterol, and LDL level in the blood (in a bigger dose)	Gastritis, gastric ulcer Radiation sickness
Vasodilation (in a bigger dose)	
Activation of fibrinolysis and an antiplatelet action (in a bigger dose)	
Stimulation of the gut's activity	

Side effects

1. Skin hyperemia, itch, hypotension (flush syndrome).
2. A loss of appetite, nausea and vomiting.
3. Lipid liver infiltration.

CALCIUM PANTOTHENATE

- is administered orally, parenteraly and applied topically;
- takes part in the formation of coenzyme A and acyl carrier protein. In such a way it participates in the synthesis of acetylcholine and corticosteroids, in the metabolism of fatty acids and the citric acid;
- improves neurotransmission, increases skin trophy and regeneration, stimulates the activity of the intestine, increases the effectiveness of cardiac glycosides, decreases the toxicity of streptomycin;
- is indicated in neuritis, neuralgia, skin diseases, wounds, burns, allergic reactions, bronchial asthma, diseases of the upper respiratory pathways, heart failure, atonia of the intestine and toxicosis of pregnancy;
- has minimal side effects (nausea, vomiting).

PYRIDOXINE HYDROCHLORIDE

It is a coenzyme water-soluble vitamin from B complex.

Pharmacokinetics

- is administered orally, SC, IM;
- is absorbed in the jejunum and ileum by passive diffusion, which is driven by trapping of the vitamin as 5′-phosphates through the action of phosphorylation in the jejunal mucosa. The trapped pyridoxine and pyridoxamine are oxidized to pyridoxal phosphate in the tissue;
- is excreted in the urine as the products of metabolism, the major of which is 4-pyridoxic acid.

Mechanism of action

- vitamin B_6 exists in three forms: pyridoxine, pyridoxamine, pyridoxal. Pyridoxalphosphate is an active form (Fig. 27.12);
- it takes part in the transamination, desamination, and decarboxylation of amino acids;
- vitamin B_6 participates in the synthesis of dopamine, histamine, aminolevulinic acid, serotonin, GABA and glutaminic acid;
- it promotes the transition of linoleic acid into the arachidonic acid.

Pharmacodynamics	Indications
Neurotropic effect: it increases synthesis of neurotransmitters in the CNS, improves	Hypovitaminosis (normochromic microcytes anemia)

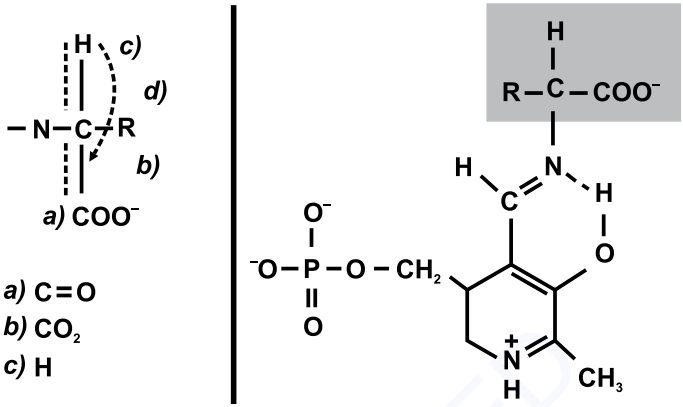

Fig. 27.12. Active form of pyridoxine and groups which are transported by it (at left) *(by J. Musil et al. 1980)*

functions of the brain, decreases epileptic activity, interacts with anti-parkinsoian drugs

Cardiotrophic effect: it improves the trophy of the myocardium, has positive inotropic and negative chronotropic effect

Hepatotrophic effect: it activates the secretion of bile, biosynthesis of glycogen and proteins, improves detoxification in the liver

The stimulation of hemopoiesis: it activates the synthesis of hem and forming of leukocytes.

Neuritis, radiculitis

Chorea, Parkinson's disease, epilepsy

Myocardiodystrophy, chronic heart failure

Liver diseases

Chronic alcoholism

Gestational toxicosis

Anemia, leukopenia, aplastic anemia

Radiation sickness

Prophylaxis and the treatment of side effects of antimycobacterial drugs, hormonal contraceptives, and some other drugs.

Side effects

1. Allergy.
2. A reduce of prolactin secretion.
3. Damage of sensor nerves and the liver.

CYANOCOBALAMIN

It is a water-soluble coenzyme vitamin of B complex.

Pharmacokinetics

- is taken orally, administered IM, IV;
- after the oral administration, binds to the intrinsic Castle factor in the stomach and is absorbed in the intestine by endocytosis;
- concentrates in the liver;
- is biotransformed to deoxyadenosylcobalamine and methylcobalamine.

Mechanism of action

Active form of cyanocobalamin is a cofactor of the folic acid reductase (Fig. 27.13).

It takes part in the synthesis of purine and pyrimidine nucleotides and transforms megaloblastic hemopoiesis into the normoblastic one.

It takes part in the synthesis of myeline and acetylcholine.

Cyanocobalamin participates in the synthesis of thiol compounds, methionine, choline as well as in the lipid metabolism (it increases lipids fixation in children and promotes lipids mobilization in adults).

Pharmacodynamics	Indications
The regulation of hemopoiesis, the transformation of megaloblastic hemopoiesis into the normoblastic one; the improvement of the formation of erythrocytes, leukocytes, and thrombocytes	Hypovitaminosis (megaloblastic anemia, glossitis, myelosis) Radiation sickness Neuritis, neuralgia, radiculitis, neurological diseases of the spinal cord and brain
The regulation of the epithelium forming The improvement of neurotransmission and functions of the nervous system The stimulation of regeneration and growth.	Liver diseases Hypotrophy in children Glossitis, stomatitis.

Side effects

1. Allergy.
2. Hypercoagulation.
3. Tachycardia, pain in the heart and the aggravation of angina pectoris.

Contraindications

Hypersensitivity, thrombosis, thromboembolism.

The drug should not be administered together with vitamins B_1 and B_6 due to an increase in allergy.

Fig. 27.13. Active form of cyanocobalamin and methyl group transported by it (at left) *(by J. Musil et al. 1980)*

FOLIC ACID

- is a water-soluble vitamin;
- is taken orally;
- takes part in the synthesis of purine and pyrimidine nucleotides, amino acids and proteins;
- is an additional remedy in the treatment of hyperchomic megaloblastic anemia; is used together with cyanocobalamin; is also indicated in chronic gastroenteritis, sprue, in pregnancy for the prophylaxis of neurological pathology of the fetus and newborn.

MULTIVITAMIN DRUGS

- are complexes of fat- and water-soluble vitamins for the oral administration;
- contain doses of vitamins which are equal their day requirement;
- are used for the prophylaxis of hypovitaminosis and for the adaptation therapy;
- may cause an overdose due to the presence of vitamins A and D in multivitamin drugs if they are used uncorrectly.

TESTS FOR SELF-CONTROL

1. All the statements regarding vitamins preparations are correct, except:
A. Ascorbic acid and tocopherol acetate are antioxidants
B. Riboflavin and a nicotinic acid take part in the tissue respiration
C. Thiamine chloride regulates calcium homeostasis
D. Cyancobalamin and the folic acid transform megaloblastic hemopoiesis into the normoblastic one
E. Calcium panthotenate improves regeneration and skin trophy.

2. Rutin is:
A. A multivitamin drug
B. A fat-soluble vitamin
C. A stimulant of bone mineralization
D. An antioxidant which decreases blood vessels wall permeability
E. A constituent of rhodopsin.

3. Ergocalciferol has following effects:
A. Stimulates calcium absorption in the GI tract
B. Stimulates calcium reabsorption in the kidney
C. Stimulates resorption of bones
D. Inhibits bones resorption
E. Maintains calcium level in blood.

4. Processes with the participation of the ascorbic acid are:
A. The synthesis of glucocorticoids
B. The synthesis of catecholamines
C. The absorption of calcium
D. The synthesis of procollagen
E. The resorption of the bone tissue.

5. A patient has disturbances of vision (hemeralopia), xerophthalmia, xerostomia, dry skin, and hypochromic anemia. Point a correct diagnosis and basic preparation for the therapy.
A. Rickets and ergocalciferol
B. Megaloblastic anemia and cyanocobalamin
C. Malaria and chloroquine
D. Hyperthyroidism and methimazole
E. Hypovitaminosis of vitamin A and retinol acetate.

Answers:

1 – C; 2 – D; 3 – A, B, D, E; 4 – A, B, D; 5 – E.

Chapter 28 ACIDS, ALKALIS, SALTS. DRUGS FOR TREATMENT OF OSTEOPOROSIS. ENZYMES AND ENZYME INHIBITORS. GLUCOSE. PREPARATIONS FOR TRANSFUSION THERAPY

ACIDS

Acids are electrolytes which dissociate with the formation of H^+ ions. They are non-organic and organic acids.

PECULIARITIES OF PREPARATIONS

Hydrochloride acid (HCl) is a normal constituent of gastric juice. It is necessary for a normal function of pepsin, for the absorption of iron, and the supporting of normal microbial status in the stomach. 2% solution of HCl is used orally as a replacing therapy in hypoacidic gastritis, achilia and together with iron preparations.

Boric acid is an antiseptic. It is used topically to treat purulent wounds, burns, skin diseases or eye infections.

Salicylic acid is also an antiseptic. In high concentration, it has a keratolytic action, in low concentration – a keratoplastic one; is used to treat skin diseases.

Acute poisoning with acids

Signs: coagulation necrosis of the skin or mucous membrane, acute pain in the mouth, gullet, and stomach, vomiting with admixtures of blood, acidosis, shock.

Emergency help:

– lavage of the stomach with cold water;

– neutralization of the acid and protection of the gastric mucosa (magnesium oxide, egg albumin or milk);
– neutralization of the acid on the surface of the skin or mucous membrane by weak solution of the alkali;
– IV administration of sodium bicarbonate;
– narcotic analgesics.

ALKALIS (BASES)

Bases are electrolytes dissociating with the formation of OH^- ions. They include solution of ammonia, sodium bicarbonate, and magnesium oxide.

SODIUM BICARBONATE

- is administered orally, by IV infusion, by inhalation, rectally, or topically;
- causes the alkalinization of body fluids, decreases the acidity of gastric juice (after the oral administration), decreases acidosis, has expectorant, antiarrhythmic and antihypertensive actions, antiseptic and osmotic effects (locally);
- is used to treat acidosis, hyperacidic gastritis, bronchitis, purulent diseases in the oral cavity and throat, hypersensitivity of the teeth enamel;
- may cause side effects, such as alkalosis, the formation of CO_2 during an antacid action in the stomach that may produce a secondary stimulation of gastric secretion and a rupture of the stomach wall in patients suffering from peptic ulcer disease.

PECULIARITIES OF OTHER PREPARATIONS

Magnesium oxide is taken orally for an antacid action in the stomach (the antacid effect is without CO_2 formation); is used to treat hyperacidic gastritis, may cause a weak laxative action.

Solution of ammonia is an antiseptic used for the processing of surgeon's hands. It is an irritant agent and may cause the reflexive stimulation of respiration in syncope. High concentration of the vapor of ammonia causes the irritation and burn of the upper respiratory pathways, provokes a respiratory arrest.

Acute poisoning with alkalis

Signs: colliquation necrosis of the skin or mucous membrane, acute pain in the mouth, gullet, and stomach, vomiting with admixtures of blood, excitation, shock.

Emergency help:

– lavage of the stomach with cold water;

– coverings (egg albumin, milk);
– narcotic analgesics;
– neutralization of the alkali on the surface of skin or mucous membrane by the weak acid.

SALTS OF ALKALINE AND ALKALINE-EARTH METALS

Salts are electrolytes which dissociate into the ions of metal and acid (Fig. 28.1).

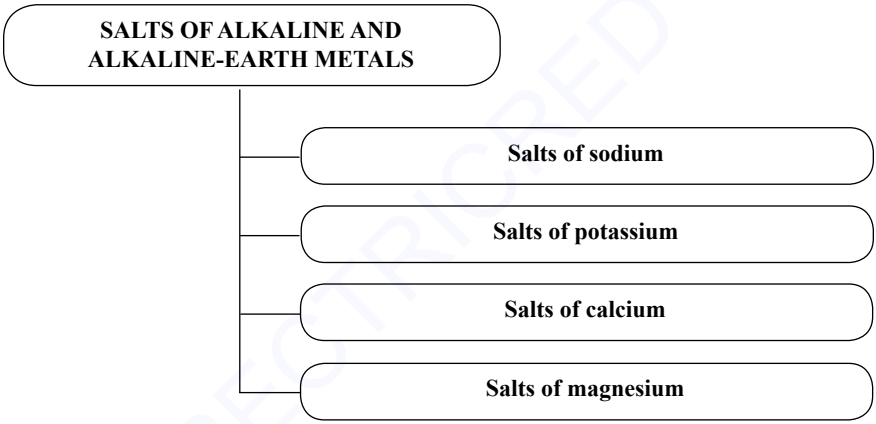

Fig. 28.1. Main groups of salts used in clinic

SODIUM CHLORIDE

- ions of Na^+ are the main extracellular ions in the body which influence osmotic pressure, electrolyte balance, and volume of circulating blood, take part in the polarization and depolarization of cell membranes, participates in the neurotransmission, contractions and tone of the muscles, synthesis of hormones;
- isotonic (0.9%) solution of sodium chloride is administered by IV infusion for the treatment of dehydratation in cases of vomiting, diarrhea, intoxications or hemorrhages, for forced diuresis; is used to dissolve other drugs and to irrigate wounds, cavities and eyes;

- hypertonic (2–10%) solution of sodium chloride has an antiseptic and osmotic action; is used topically for the treatment of purulent wounds or administered IV for the stopping of the lung and stomach bleeding.

POTASSIUM CHLORIDE

- ions of K^+ are the main intracellular ions which take part in the polarization/depolarization processes in cell membranes, neurotransmission, supporting of the heart rhythm and normal function of skeletal muscles;
- is administered IV or by mouth, has a short duration of action;
- is used to treat hypokalemia, arrhythmia, myastenia gravis, acute poisoning with cardiac glycosides; to prevent hypokalemia caused by some drugs (cardiac glycosides, glucocorticoids or diuretics);
- may cause hyperkalemia.

Asparkam (Panangin) is a combined potassium preparation which contains asparaginates of potassium and magnesium; its properties and indications are the same as the properties of potassium chloride.

CALCIUM CHLORIDE

- Ca^{++} ions regulate functions of the CNS and autonomic nervous system, stimulate sympathetic activity, participate in the blood coagulation, decrease blood vessels permeability, inhibit allergic reactions and inflammation, take part in the formation of bones and teeth;
- is administered IV, rarely is taken by mouth in the form of solution, in dentistry is used topically (applications, electrophoresis);
- is used for hypocalcemia, tetania and spasmophylia, allergic reactions, inflammations, bleedings and their prophylaxis, vasculitis, acute intoxications with fluorides, oxalates or magnesium salts;
- may cause necrosis of the soft tissues if is administered SC or IM, irritates the gastric mucous membrane.

PECULIARITIES OF OTHER CALCIUM PREPARATIONS

Calcium gluconate is similar to calcium chloride in its pharmacological activity, but is administered IV, IM, and orally (in the form of tablets), is often used to treat bone fractures, osteoporosis, to prevent rickets and osteoporosis under the conditions of immobilization.

Calcium glycerophosphate contains calcium and phosphor, improves the mineralization of bones and teeth, has an anabolic action, is used orally for the treatment of bone fractures and osteoporosis.

MAGNESIUM SULFATE

The drug contains Mg^{++} and has a wide spectrum of effects depending on the route of administration. For details – see Chapter 19.

DRUGS FOR TREATMENT OF OSTEOPOROSIS

Osteoporosis is a condition of skeletal fragility due to progressive loss of the bone mass. It is characterized by frequent bone fractures, which are a major cause of disability among the elderly, especially among postmenopausal women.

New options in the pharmacological management of osteoporosis are connected with bisphosphonates, selective estrogen-receptor modulators, calcitonin and teriparatide. Preparations of calcium and strontium, salts of fluorine, vitamin D preparations also may be used in patients with osteoporosis.

PECULIARITIES OF PREPARATIONS

Bisphosphonates (Etidronate, Risedronate, Zoledronic acid) are the analogues of pyrophosphate, They decrease osteoclastic bone resorption via: 1) the inhibition of the osteoclastic proton pump necessary for the dissolution of hydroxyapatite, 2) a decrease in osteoclastic formation/activation, 3) an increase in osteoclastic apoptosis, 4) the inhibition of the cholesterol biosynthetic pathway important for osteoclast function. Bisphosphonates are preferred agents for the prevention and treatment of postmenopausal osteoporosis. They may be used for the treatment of bone metastases and hypercalcemia of malignancy. Side effects include diarrhea, abdominal, and musculoskeletal pain, esophagitis and esophageal ulcers.

Selective estrogen-receptor modulators. Estrogen replacement is an effective therapy for the prevention of postmenopausal bone loss, but it has some limitations due to serious side effects. ***Raloxifene*** is a selective estrogen-receptor modulator. It increases bone density without increasing the risk of endometrial cancer and may reduce the risk of breast cancer. Raloxifene is a first-line alternative for postmenopausal osteoporosis in women who are intolerant to bisphosphonates.

Calcitonin (intranasally) is effective and well tolerated in the treatment of postmenopausal osteoporosis. The drug reduces bone resorption, but it is less ef-

fective than the bisphosphonates. A unique property of calcitonin is the relief of pain associated with osteoporotic fracture.

Teriparatide is a recombinant segment of human parathyroid hormone. This hormone given continuously leads to the dissolution of bone, but when it is given SC once daily, bone formation is a predominant effect. The safety and efficacy of this agent have not been evaluated beyond 2 years. Teriparatide is an alternative preparation for patients who cannot tolerate other osteoporosis therapies.

ENZYMES AND INHIBITORS OF ENZYMES

ENZYMES

Enzymes are preparations which play a role of the biological catalyzers of metabolism in the organism. Enzymes catallyzing the restriction of different substrates (Fig. 28.2) are of great importance for clinic.

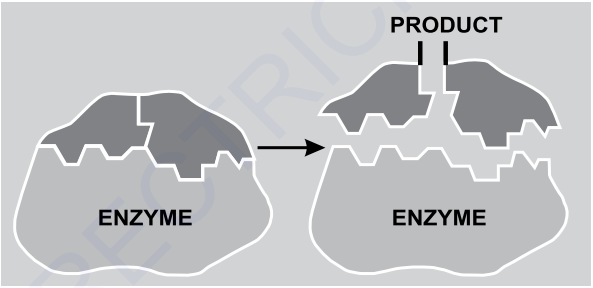

Fig. 28.2. Restriction of substrate by enzyme *(http://www.picsearch.com)*

CLASSIFICATION

1. Peptidases and proteases:
   - Pepsin;
   - Trypsin;
   - Chymotrypsin.
2. Nucleases:
   - Ribonuclease;
   - Desoxyribonuclease.
3. Preparations of hyaluronidase:
   - Lydase;
   - Ronidase.

4. Fibrinolytic enzymes:
   – Fibrinolysin;
   – Streptolyase.
5. Enzymes of another action:
   – L-asparaginase;
   – Penicillinase.
6. Combined polyenzyme preparations:
   – Pancreatin;
   – Creon;
   – Festal;
   – Wobenzym.

PECULIARITIES OF PREPARATIONS

Pepsin is a normal constituent of gastric juice; is active in the acidic pH and tears peptide connections; is taken orally together with hydrochloride acid to treat hypoacidic and anacidic gastritis, achilia, dyspepsia.

Trypsin is obtained from the pancreas of horned cattle, is administered IM, in cavities, by inhalation, or topically; splits peptones, that's why decreases the density of pus and exudation, improves the clean of wounds and bronchi, decreases edema and inflammation; is used to treat purulent wounds, purulent diseases of the lungs, bronchi, and pleura, osteomyelitis; may cause an allergic reaction, fever and chill.

Chymotrypsin is a protease similar to trypsin; is more stable in the body.

Ribonuclease is a nuclease obtained from the pancreas of horned cattle; the mechanism of action is connected with the restriction of RNA to oligonucleotides; in such a way it decreases the viscosity of pus and exudation, improves the clean of wounds, cavities, and bronchi; has indications similar to the indications of trypsin.

Desoxyribonuclease is also a nuclease, but its action is connected with the depolymerization and restriction of DNA.

Lydase contains hyaluronidase; depolimerazes hyaluronic acid and decreases the viscosity of connective tissue, increases tissues permeability and the penetration of other drugs; is used to treat contractures of joints, scars after burns and surgeries, hematomas and chronic inflammation; may cause allergy.

Ronidase is a hyaluronidase preparation; its pharmacological properties are close to lydase, but it has a lower degree of purification and is used only locally in the form of wet bandages for the treatment of contractures of joints, scarring, hematoma, chronic tendovaginitis or wounds that do not heal for a long time.

Pancreatin is a polyenzyme preparation that improves digestion. It contains trypsin, amylase, and lipase. In diseases of the pancreas, the drug compensates for

the lack of its external secretory function and improves digestion. Pancreatin is prescribed for chronic pancreatitis, cystic fibrosis, chronic inflammatory-dystrophic diseases of the stomach, intestine, liver and gall bladder. The drug can be used in people with normal function of the GI tract in the case of errors in nutrition.

Creon is an original form of pancreatin. Its capsules contain pancreatin in mini-microspheres resistant to gastric juice. The drug provides physiological digestive process and avoids loss of enzyme activity. Indications for the use of creon as well as for pancreatin, are diseases that are accompanied by exocrine pancreatic insufficiency.

Festal is a polyenzyme drug for improving digestion. It contains pancreatic enzymes (protease, amylase, lipase) and bile components. The presence of bile components stimulates the secretion of bile and promotes emulsification of fats making them more accessible to pancreatic lipase. Festal has advantages in cases where the lack of external secretory function of the pancreas is combined with biliary disorders.

Wobenzym is a polyenzyme drug for systemic enzymotherapy, that is a resorptive action of the complex of hydrolytic enzymes of plant and animal origin on pathophysiological processes. It contains pancreatin, papain, bromelain, lipase, amylase, trypsin, and chymotrypsin. After an oral administration, a part of the enzymes is absorbed in the small intestine and enter the blood, the rest is involved in digestion. In the blood, the proteolytic enzymes bind to α_2-macroglobulin and are transported to damaged tissues, where they realize their therapeutic effect. The drug has anti-inflammatory, immunomodulatory and fibrinolytic properties. It is used as a non-specific component of the therapy for cronic inflammations of the respiratory system, pancreatitis, ulcerative colitis, multiple sclerosis, coronary heart disease, rheumatoid arthritis, rheumatism, etc. During the treatment, dyspeptic phenomena and allergic reactions are possible.

INHIBITORS OF ENZYMES

Inhibitors of enzymes are drugs inhibiting the activity of different enzymes. Among them there are inhibitors of proteolysis and fiibrinolysis ***(Aprotinin, Contrykal, Aminocaproic acid)*** and inhibitors of lipases ***(Orlistat)***.

PECULIARITIES OF PREPARATIONS

Contrykal is a natural substance with short time of action; is administered IV, by IV infusion, or applied topically (in dentistry); inhibits the activity of trypsin and plasmin, has a direct action on proteolytic enzymes, decreases proteolysis and

fibrinolisis, has anti-inflammatory properties; is indicated in acute pancreatitis, surgeries on the pancreas, lungs, and glands, bleeding due to an increased fibrinolysis, obstetrics pathology.

Aminocaproic acid is used orally, by IV infusion, and topically (in dentistry); inhibits the activity of trypsin and plasmin; has a direct and indirect action, decreases proteolysis and fibrinolisis, has anti-inflammatory properties, decreases allergy and intoxication; has the indications similar to the indications of contrykal. Both preparations are also described in Chapters 22, 28.

Orlistat is a pentanoic acid ester that inhibits gastric and pancreatic lipases, thus decreasing the breakdown of dietary fat into smaller molecules that can be absorbed. Fat absorption is decreased that leads to weight loss. Orlistat is used as anti-obesity drug. Side effects are gastrointestinal symptoms, such as oily spotting, flatulence with discharge, fecal urgency, and increased defecation. It interferes with the absorption of fat-soluble vitamins. Orlistat is contraindicated in patients with malabsorption syndrome and cholestasis. It is also mentioned between the gastrointestinal drugs (Chapter 24).

GLUCOSE

- is administered IV, SC, orally;
- isotonic 5% solution of glucose is used for an increase of fluids volume, as a source of energy or as a solvent for other drugs;
- hypertonic 40% solution of glucose increases osmotic pressure, improves antitoxic liver function, and contractility of the myocardium, decreases the permeability of blood vessels; is used to treat hypoglycemia, hypotension, asthenia, liver diseases, heart failure and to dissolve some other drugs;
- is an ingredient of many tablets and dosed powders;
- may cause hyperglycemia;
- is contraindicated in diabetes mellitus.

DRUGS FOR TRANSFUSION THERAPY

Drugs for transfusion therapy are solutions for IV infusions.

CLASSIFICATION

1. Low molecular weight solutions:
   – 0.9% solution of sodium chloride;
   – 4% solution of sodium bicarbonate;

- 5% solution of glucose;
- Ringer-Lock solution;
- Trisol;
- Trasamine.

2. Plasma substitutes and hemodynamic solutions:
   - Albumin;
   - Rheopolyglucin;
   - Refortan.
3. Detoxification drugs:
   - Neohemodez.
4. Drugs for IV nutrition:
   - Aminosteril;
   - Lipofundin.

PECULIARITIES OF PREPARATIONS

Low molecular weight solutions (Crystalloids) are used for rehydratation, the restoration of the acid-base balance, hemodilution under the conditions of acute poisoning, diabetic coma, etc.

Ringer-Lock solution is a multicomponent physiological solution of sodium chloride (9 g/L), potassium chloride (0.2 g/L), calcium chloride (0.2 g/L), sodium bicarbonate (0.2 g/L), and glucose (1 g/L). It compensates for losses of extracellular fluid and basic electrolytes; is administered by IV infusion from 500 to 1000 ml per day. The drug is used for dehydration of various genesis, hyponatremia, hypovolemic shock or metabolic acidosis with loss of fluid. Indications for the use are shock, collapse, burns, prolonged vomiting, and diarrhea.

Trisol is a multicomponent physiological solution. It contains sodium chloride (5 g), potassium chloride (1 g), sodium bicarbonate (4 g), and water for injection (up to 1 l) and is used by IV infusion to reduce dehydration and intoxication similar to Ringer-Lock solution.

Trisamine is 3.66% solution of tris-hydroxymethyl aminomethane. It has buffer properties, reduces the concentration of hydrogen ions and increases the alkaline reserve of blood, eliminates acidosis; unlike sodium bicarbonate, does not increase the concentration of CO_2 in the blood. Penetrating through cell membranes, it is able to eliminate intracellular acidosis, has a hypoglycemic and osmotic diuretic effect. Indications for use include diseases accompanied by metabolic and mixed acidosis (in shock, massive blood transfusion, extracorporeal blood circulation, burns, peritonitis and acute pancreatitis), diabetic ketoacidosis, poisonings with salicylates, hypnotics, derivatives of barbituric acid, or methyl alcohol. The drug can cause inhibition of the respiratory center, lowering of BP, hypoglycemia, hypona-

tremia, hypokalemia, dyspeptic disorders, local reactions in the site of administration (venous spasm, phlebitis).

Plasma substitutes and hemodynamic solutions (Colloids) restore the volume of circulating blood, support colloid-osmotic pressure, increase BP, improve reological blood properties; are used in shock.

Refortan is a colloidal plasma substitute with hydroxyethyl starch in the isotonic solution of sodium chloride. The maximal level in the blood plasma is halved after 5–6 hrs after the end of the infusion. Refortan is continuously cleaved with serum amylase and excreted by the kidneys. It is used to treat hypovolemia caused by acute blood loss, in cases where the use of only crystalloids is considered insufficient. The drug has numerous contraindications: hypersensitivity, sepsis, burns, renal failure, intracranial hemorrhage, critical state of patients, hypervolemia, severe coagulopathy, hypokalemia, severe disturbances of water-electrolate balance, CHF, severe violations of the liver function, condition after the organ transplantation. Possible side effects are a decrease in hematocrit and protein level in the blood, liver damage, itching of the skin, pain in the kidney area, and anaphylactic reactions.

Rheopolyglucin is 10% colloidal dextran solution with the addition of isotonic sodium chloride solution or 5% glucose solution (two medicinal forms). It is plasma substitute solution, the effect of which is to promote the entering of water into the blood vessels, reducing the viscosity of the blood, restoring blood flow in small capillaries, preventing and eliminating the aggregation of blood cells. With a rapid transfusion, the volume of plasma can increase almost 2 times compared with the volume of the injected drug. Half-life is about 6 hrs; the main part of the drug is excreted by the kidneys. Rheopolyglucin is used for the prevention and treatment of shock, thrombosis, thrombophlebitis and endarteritis, for addition to perfusion fluid in cardiopulmonary bypass in cardiac surgery, to improve microcirculation and reduce the tendency to thrombosis in the transplant in vascular and plastic surgery. It may cause allergic reactions, anaphylaxis and is contraindicated in hyperhydration, disseminated vascular coagulation, thrombocytopenia, anuria, and heart failure.

Detoxification drugs increase the transport of toxic substances from tissues into the blood and their excretion, improve microcirculation. They are used to treat sepsis, severe burns, endotoxic reactions, and acute poisonings.

Neohemodez has an effect due to ability of low molecular weight polyvinylpyrrolidone to bind toxins circulating in the blood and quickly remove them from the body. The drug contributes to the elimination of stasis of erythrocytes in capillaries, improves microcirculation, increases renal blood flow, glomerular filtration and diuresis. It is not metabolized in the body and quickly excreted by the

kidneys. Indications are: shock, toxic diseases of the digestive tract (dysentery or dyspepsia, salmonellosis); burns, radiation and hemolytic disease, peritonitis, intestinal obstruction, thyrotoxicosis, liver diseases, sepsis, pneumonia; acute phase of myocardial infarction, toxemia of newborns, and gestosis. Side effects include lowering of BP, tachycardia, difficulty breathing and allergic reactions of varying severity.

Drugs for IV nutrition contain amino acids, essential fatty acids and are used for parenteral nutrition in patients after surgeries, unconscious patients, etc. ***Aminosteril*** and ***lipofundin*** are preparations of this group.

TESTS FOR SELF-CONTROL

1. The following statements concerning lydase are correct, except:
A. It is hyaluronidase preparation
B. It is used to promote drug absorption
C. It is used for the replacement therapy
D. It is used for the treatment of joint contractures
E. It is used for the scar softening.

2. The salt drug for the treatment of purulent wounds is:
A. 0.9% solution of sodium chloride
B. 5% solution of glucose
C. 25% solution of magnesium sulfate
D. 10% solution of calcium chloride
E. 10% solution of sodium chloride.

3. The main indications for calcium chloride use are:
A. Allergic reactions
B. Vasculitis
C. Thrombosis
D. Bleeding
E. An overdose of vitamin D.

4. Aminocaproic acid:
A. Is a proteolytic enzyme
B. Is an inhibitor of proteolysis
C. Is an inhibitor of fibrinolysis
D. Has anti-allergic and antitoxic properties
E. Is used to treat purulent diseases.

5. A patient has bronchoectasia with purulent dense exudation. A physician prescribes him inhalations of an enzyme preparation. The drug suitable in this case is:

A. Lydase
B. Aprotinin
C. Trypsin
D. Parathyroidin
E. Pancreatin.

Answers

1 – C; 2 – E; 3 – A, B, D; 4 – B, C, D; 5 – C.

Chapter 29 ANTISEPTICS AND DISINFECTANTS

ANTIMICROBIAL AGENTS

Antimicrobial agents are drugs for the treatment and prevention of infectious diseases. They are divided into disinfectants, antiseptics, and chemotherapeutics (Fig. 29.1). ***Disinfectants*** realize their antimicrobial properties in the environment outside the body. ***Antiseptics*** act on the surface of the body. ***Chemotherapeutics*** produce an antimicrobial effect inside the body.

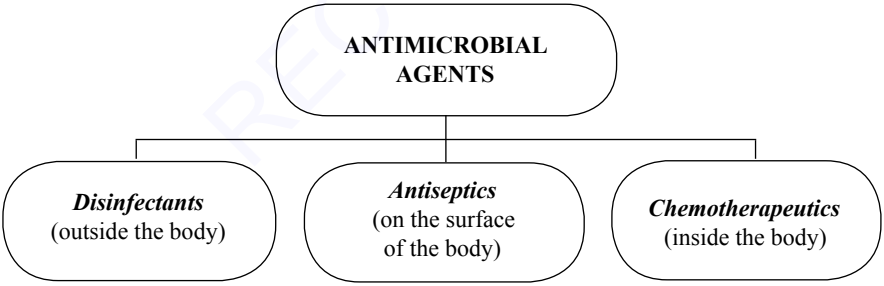

Fig. 29.1. Main classes of antimicrobial agents

Antimicrobial drugs may have a bactericidal or bacteriostatic type of action (Fig. 29.2). Antimicrobial drugs of ***bactericidal action*** produce death of microbes. ***Bacteriostatic drugs*** stop the growth and replication of bacteria and then the immune system destroys such microbes.

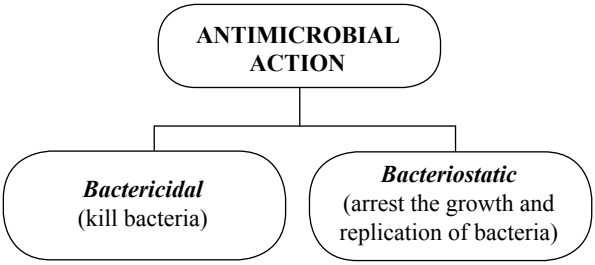

Fig. 29.2. Types of antimicrobial action

ANTISEPTICS AND DISINFECTANTS

Good antiseptic and disinfectant should meet such demands as:

- bactericidal action;
- chemical stability;
- rapid action;
- lack of absorption;
- low toxicity;
- efficacy in the presence of different organic substrates, such as pus, blood, sputum;
- the absence of allergic properties;
- the absence of irritant properties.

There are 3 main mechanisms of an antimicrobial action of antiseptics and disinfectants:

- the denaturation of bacterial proteins including enzymes;
- the oxidation of bacterial protoplasma (cytoplasma);
- changing of bacterial membrane properties and an increase in its permeability

CLASSIFICATION

A. Inorganic substances

1. Halogens:
   - Iodine alcohol solution (Iodine tincture)
   - Povidone-iodine
   - Ioddicerin
   - Chloramine B
   - Chlorhexidine (Hibitane)

B. Organic substances

1. Aldehydes:
   - Formaldehyde (Formalin)
   - Hexamethylentetramine (Urotropine)

2. Oxidizing agents:
   - Hydrogen peroxide
   - Potassium permanganate
3. Metallic salts:
   - Mercury dichloride
   - Yellow mercury oxide
   - Silver nitrate
   - Copper sulfate
   - Zinc sulfate
   - Zinc oxide
4. Acids and alkalis:
   - Boric acid
   - Salicylic acid
   - Solution of ammonia.
2. Alcohols:
   - Ethyl alcohol
3. Phenol derivatives:
   - Phenol (Carbolic acid)
   - Resorcinol
4. Dyes:
   - Methylene blue
   - Brilliant green
   - Etacridine lactate
5. Detergents (Surfactants):
   - Etonium
   - Decamethoxine
   - Miramistin
6. Tar, resins, products of petroleum:
   - Birch tar
   - Ichthyol
   - Liniment after Vishnevsky
7. Nitrofuran derivatives:
   - Nitrofurasone
8. Antiseptics from medicinal plants:
   - Chlorophylipt
   - Novoimanin
9. Combined preparations:
   - Sterillium
   - Cutasept.

OXIDIZING AGENTS

HYDROGEN PEROXIDE

Mechanism of action and effects:

The drug's effects are based on the destruction of hydrogen peroxide with the release of oxygen atoms. They produce the oxidation and denaturation of proteins. The formation of molecules of O_2 results in the foam formation and mechanical cleaning of the wound (Fig. 29.3).

Indications:

- processing of wounds (3% solution);
- processing of the impaired skin;
- gargling and mouthwash in diseases of the throat and oral cavity;

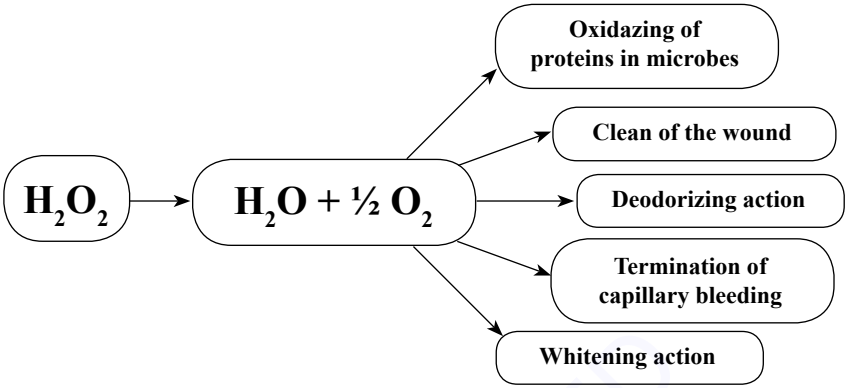

Fig. 29.3. Pharmacological effects of hydrogen peroxide

- capillary bleeding;
- whitening of teeth, the depigmentation of skin.

The drug should not be used in deep wounds and injures of bigger vessels.

POTASSIUM PERMANGANATE

Mechanism of action and effects:

The drug's effects are grounded on degradation of the molecule of potassium permanganate with the releasing of oxygen atoms and manganum oxide (Fig. 29.4). Oxygen produces the oxidation and denaturation of proteins resulting in a bactericidal action. It also oxidizes some poisons. Manganum oxide causes an astringent action on the macroorganism.

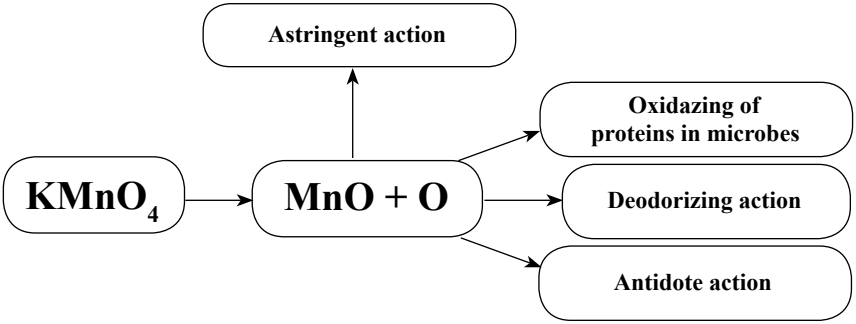

Fig. 29.4. Pharmacological effects of potassium permanganate

Indications:

- the irrigation of purulent wounds (0.1–0.5% solution);
- gargling and mouthwash in diseases of the throat and oral cavity (0.01–0.1% solution);
- syringing in gynecology and urology (0.01–0.1% solution);
- processing of burns (2–5% solution);
- lavage of the stomach in acute poisoning with morphine, alcohol and alkaloids (0.1% solutions).

HALOGENS

IODINE ALCOHOL SOLUTION

Mechanism of action and effects:

Effects of iodine are based on the interaction between atoms of halogen and proteins resulting in halogenization and oxidation of proteins (Fig. 29.5). It has bactericidal, fungicidal, and irritative actions.

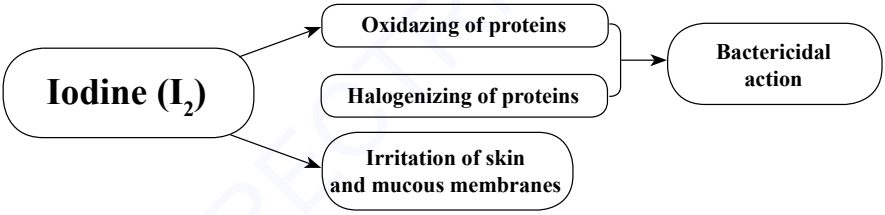

Fig. 29.5. Pharmacological effects of iodine

Indications:

- processing of small cuts of the skin;
- processing of the surgery skin area and surgeon's hands;
- dermatomycoses;
- diseases of muscles and joints (the "iodine network" on the skin).

Toxicity:

Iodine may cause the irritation of the skin, allergy or idiosyncrasy. On the surface of the skin or mucuos membrane it should be neutralized by sodium thiosulphate.

PECULIARITIES OF OTHER HALOGENS

Povidone-iodine is a chemical complex of povidone, hydrogen iodide, and elemental iodine. It works by iodine releasing with a following bactericidal effect, exhibits longer lasting antiseptic effects than tincture of iodine; has found broad application in medicine for pre- and post-operative skin cleansing; for the treatment and prevention of infections in wounds, ulcers, cuts, and burns; in gynecology for vaginitis associated with candidal, trichomonal or mixed infections; is contraindicated in patients with diseases of the thyroid gland and after the treatment with radioiodine.

Ioddicerin is a combined preparation; contains iodine, dimexide, and glycerin; due to dimexide, has an increased antiseptic activity and penetration through the skin; is used for the treatment of skin diseases, ulcers and wounds; may be used on the mucous membranes due to less irritation (in otitis, tonsillitis, chronic atrophic rhinitis, paradontosis or vaginitis).

Chloramine B is an organic compound containing chlorine; transforms into the hypoclorite acid which decays into chlorine and oxygen: chlorine exerts irreversible oxidation of SH-groups of proteins and forms toxic N-chlorocompounds, oxygen oxidizes proteins; has disinfection, antiseptic, and deodorizing actions; is used for the disinfection of the environment, clothes, non-metallic instruments (1–5%); rarely for the treatment of purulent wounds (1–2% solution) and processing of the skin (0.25–0.5% solution).

Chlorhexidine (Hibitane) is an organic chlorine containing preparation with detergent properties; has an antimicrobial and antifungal activity, improves regeneration; is used for the treatment of wounds, for gargling, for individual prophylaxis of sexually transmitted infections, for the processing of the surgeon's hands and surgical skin area, for a quick sterilization of instruments.

ACIDS AND ALKALIS

Mechanism of action:

Acids and alkalis produce changes in pH leading to the inactivation of enzymes and denaturation of microbial proteins.

PECULIARITIES OF PREPARATIONS

Boric acid can be used for minor burns or cuts, acne treatment, prevention of athlete's foot; treatment of bacterial vaginitis and candidiasis due to non-albicans candida, in alcohol solution is used to treat external otitis; is applied in the very dilute aqueous solution as eye drops in bacterial conjunctivitis.

Salicylic acid has an antimicrobial action, an anti-inflammatory effect, a keratolytic action in bigger doses (causes the reduction of the upper skin layer) and a keratoplastic action in lower doses (increases the development of the upper skin layer); is used in dermatology.

Solution of ammonia (10%) has antimicrobial, weak detergent, irritative, and reflexive actions; is used for the processing of the surgeon's hands, but the main indication is a reflexive stimulation of respiration in syncope.

METALLIC SALTS

Mechanism of action and effects:

The action of metallic salts on microbial cell results from their interaction with SH-groups of proteins which leads to the inactivation of enzymes (Fig. 29.6).

The metallic salts action on human tissues may be with the prevalence of astringent or caustic action. This phenomenon depends on chemical properties of metallic ions. On such activity, metals form Shmideberg's line. In this line, mercury salts have a caustic action, silver salts – caustic and astringent properties, salts of copper and zinc – an astringent action only.

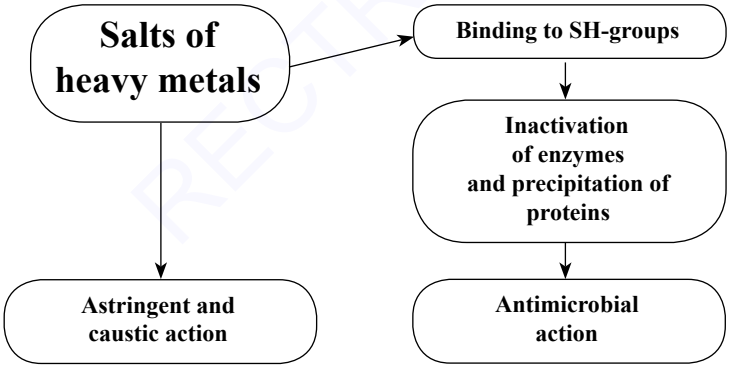

Fig. 29.6. Pharmacological effects of heavy metal salts

PECULIARITIES OF PREPARATIONS

Mercury dichloride has a bactericidal effect which is decreased at the presence of proteins; is very toxic; is used for the disinfection of clothes and non-metallic instruments.

Yellow mercury oxide is not soluble, is used in the form of ointments for the treatment of pyoderma, blepharitis, seborrhea and pediculosis.

Silver nitrate rapidly kills microbes, but the action persists for a long period because of a slow release of silver ions from silver proteinates formed by interaction with tisue proteins; is used to cauterize erosions, ulcers or surplus granulations; in past, it was used for the prophylaxis of blenorrhea in newborns. Organic silver preparations (***Protargol, Collargol***) are indicated for the treatment of conjunctivitis, diseases of the throat, urological and gynecological diseases.

Copper and zinc sulfates are used in the forms of solutions for external use, eye drops, ointments, pastes; are applied for the treatment of wounds, burns, diseases of the oral cavity, eye infections, for the washing of the urethra and urinary bladder. Copper sulfate is used in chemical burns caused by white phosphor.

Zinc oxide is an insoluble substance; has antimicrobial, astringent, and absorbting properties; is used as an ingredient of aspersions, ointments, and pastes to treat wounds, burns or skin diseases.

Toxicity:

Metallic salts can cause acute and chronic poisoning. Such poisoning is manifested by vomiting, abdominal pain, metallic aftertaste, renal failure, CNS problems, and hypochromic anemia. ***Dimercaprol (Unithiol)*** is an antidote in poisoning with salts of heavy metals. Solution of sodium chloride is used for the neutralizing of silver nitrate.

ALIPHATIC AGENTS (ALCOHOLS AND ALDEHYDES)

ETHYL ALCOHOL

Mechanism of action and effects:

The alcohol's mechanism of action is connected with the inhibition of oxido-reductases, dehydratation and precipitation of proteins. The result is a bactericidal action (an antiseptic effect and disinfection). It also has an irritating and tannic action.

Indications:

- processing of the surgeon's hands and surgical area (70%);
- processing of instruments (95%);
- compresses (40%).

FORMALDEHYDE

Mechanism of action and effects:

It acts on spores of bacteria and fungi (bactericidal and fungicidal action), dehydrates proteins and tissues (mummifying action), has deodorizing properties (Fig. 29.7). Standard 40% solution of formaldehide is called formalin.

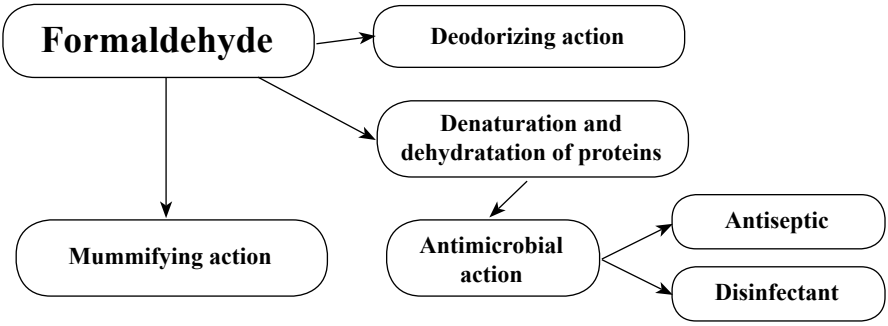

Fig. 29.7. Pharmacological effects of formaldehyde

Indications:

- feet sweating (0.5–1% solution);
- syringing in gynecology (in ratio 1:2000);
- disinfection (0.5% solution);
- the conservation of vaccines and serums;
- the conservation of anatomic preparations.

Toxicity:

Formaldehyde irritates the skin and mucous membranes of the upper respiratory pathways. It can cause acute poisoning. A weak solution of ammonia or ammonia chloride is an antidote in this case.

HEXAMETHYLENTETRAMINE (UROTROPINE)

Hexamethylentetramine is a derivative of formaldehyde; is administered IV and orally; transforms into formaldehyde in the organism; is used for the treatment of infections of urinary pathways, cholecystitis as well as for a decrease in intracranial pressure in meningitis or encephalitis.

AROMATIC COMPOUNDS (PHENOLS, TARS, RESINS)

PHENOL (CARBOLIC ACID)

Mechanism of action and effects:

It blocks dehydrogenases, denaturates proteins and damages the membranes of bacteria. Bonds between phenol and protein are not strong and one molecule of phenol can interact with few protein molecules by turn. Phenol has a bacteriostatic

action in a low concentration and bactericidal action in a bigger concentration. The action of aqueous solutions of phenol is stronger than the effect of oil solutions. It is a reference preparation for the comparison with other antiseptics.

Indications:

- disinfection (3–5% soluions);
- the conservation of serums and drugs;
- external otitis (0.5–0.1% oil solutions);
- some forms of rhinitis (e.g., ozena);
- infections of the oral mucosa and throat (spray).

Toxicity:

Phenol is very toxic. It can penetrate through the skin and mucous membranes and cause acute poisoning. A specific therapy is absent in this case.

PECULIARITIES OF OTHER AROMATIC ANTISEPTICS

Resorcinol is used for the treatment of skin diseases (eczema, seborrhea, itch and fungal diseases).

Ichthyol is a dense liquid of dark color; belongs to the group of "tars and resins"; is a product of processing of some minerals; contains aromatic compounds and sulfur; has an antimicrobial action, decreases inflammation and pain, improves regeneration; is used in burns, erysipelas.

Birch tar is a product of sublimation of birch bark; is a dense oil-like liquid of black color; contains aromatic compounds; has antiseptic properties, an insecticide action, an irritating and keratoplastic action; is used in skin diseases; is an ingredient of ***balsamic liniment after Vishnevsky.***

DYES

Mechanism of action and effects:

Dyes inhibit bacterial enzyme systems. Cations of dyes replace anions in natural compounds with the formation of insoluble complexes. By an antimicrobial action, dyes are less active than other antiseptics. The spectrum of action is not so wide as in other antiseptics: they act mainly on Gram (+) cocci.

PECULIARITIES OF PREPARATIONS

Metylene blue is used for the processing of burns, pyoderma, diseases of the mucous membrane of the oral cavity (1–2% aqueous and alcohol solutions), for the washing of the urethra and urinary bladder (0.02% water solution), is an anti-

dote in poisoning with cyanids, nitrites, and aniline derivatives (IV as the preparation ***Chromosmon***)

Brilliant green acts mainly on staphylococci; is used for pyoderma, skin pustules, small cuts, blepharitis (1–2% water and alcohol solutions).

Etacridine lactate acts mainly on streptococci; is non-toxic, does not irritate tissues; is used for the processing and treatment of wounds (0.05–0.1%), the washing of cavities (0.05–0.1%), in conjunctivitis (0.1% eye drops), and for gargling (0.1–1%).

DETERGENTS

Mechanism of action and effects:

These agents have a bactericidal action due to a decrease of the surface tension of substances and to an increase of the permeability of cell membranes (Fig. 29.8).

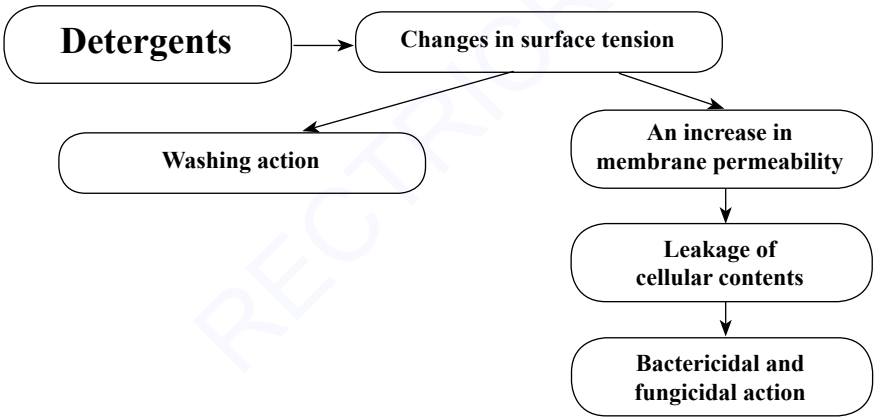

Fig. 29.8. Pharmacological effects of detergents

PECULIARITIES OF PREPARATIONS

Etonium is a quaternary ammonium compound, cationic detergent; has an antiseptic action, stimulates regeneration, causes local anesthesia and decreases intoxication; is used for the treatment of wounds, trophic ulcers, radiation injures (0.02–1% solution), eye diseases (0.1% eye drops), otitis, tonsillitis, burns and dermatitis (ointment).

Decamethoxine is a quaternary ammonium compound, cationic detergent; by its pharmacological activity, is similar to etonium; may be also used for the pro-

cessing of the surgeon's hands and surgical area, disinfection of surgical instruments and nursing items, for irrigations of the bronchi, and washing of the cavities.

Miramistin's action is based on the direct hydrophobic interaction with lipids of microorganism membranes, leading to their fragmentation, increased permeability and cytolysis. It acts on bacteria, viruses, and fungi. Indications to use include treatment of infected wounds and burns, prevention and treatment of postpartum infections; inflammatory diseases of the genital organs, treatment of skin and mucosal candidiasis, foot mycoses, individual prevention of sexually transmitted diseases, combined therapy of acute and chronic otitis media, sinusitis, tonsillitis, periodontitis, and stomatitis. In some cases, a brief burning sensation, itching, hyperemia, and dry skin are possible.

NITROFURAN DERIVATIVES

NITROFURASONE (FURACILIN)

Mechanism of action and effects:

It inhibits carbohydrates metabolism and tissue respiration in bacteria; has a bactericidal and bacteriostatic action.

Indications:

- the washing and the treatment of purulent wounds, ulcers or burns (0.02% water solution);
- the irrigation of cavities (0.02% water solution);
- gargling (0.02% water solution);
- otitis (alcohol solution 1: 1500);
- skin pustules (alcohol solution 1:1500);
- conjunctivitis (0.02% eye drops).

ANTISEPTICS FROM MEDICINAL PLANTS

PECULIARITIES OF PREPARATIONS

Chlorophyllipt is a mixture of chlorophylls from eucalypt (Fig. 29.9) used in the form of alcohol or oil solution; acts mainly on cocci, especially on staphylococci; is applied for the treatment of wounds, burns, trophic ulcers and erosions of the uterus cervix, irrigations of the cavities (alcohol solution should be dissolved before application); may be used IV in sepsis or pneumonia caused by staphylococcus; causes allergy.

Novoimanin is an antiseptic from the herb of *Hypericum* (saint John's wort), acts on Gram (+) cocci, is used topically for the treatment of wounds, burns, abscesses, etc.

Fig. 29.9. Eucalypt as a source of antiseptics

COMBINED ANTISEPTICS

PECULIARITIES OF PREPARATIONS

Sterillium contains ethanol (81–89%), moisturizing, softening and protective components for the skin, thickener, flavor and water. It has a bactericidal, fungicidal, and virulocidal action, reduces transient and resident skin microflora; keeps the action for 1 hr on the skin, 3 hrs – in gloves; provides antiperspirant action (reduces the amount of moisture under gloves), does not irritate the skin. Sterilium gel is designed for the treatment of the hands of medical personnel, workers of pharmacies, children's institutions and food industry enterprises; can be used in caring for newborns, old people, patients, during travelling, or for rapid disinfection of tools and gloves in the urgent situations.

Cutasept contains 2-propanol, benzalkonium chloride and water. It has bactericidal, fungicidal, and virulocidal action. The area of application is pre- and postoperative treatment of skin and wounds, treatment of the skin before injections, with the removal of seams, the replacement of bandages, with minor injuries and eczematous lesions.

APPLICATION OF ANTISEPTICS AND DISINFECTANTS

There are many potent antiseptics and disinfectants, but some preparations or groups of preparations are most suitable in the cases pointed at Fig. 29.10.

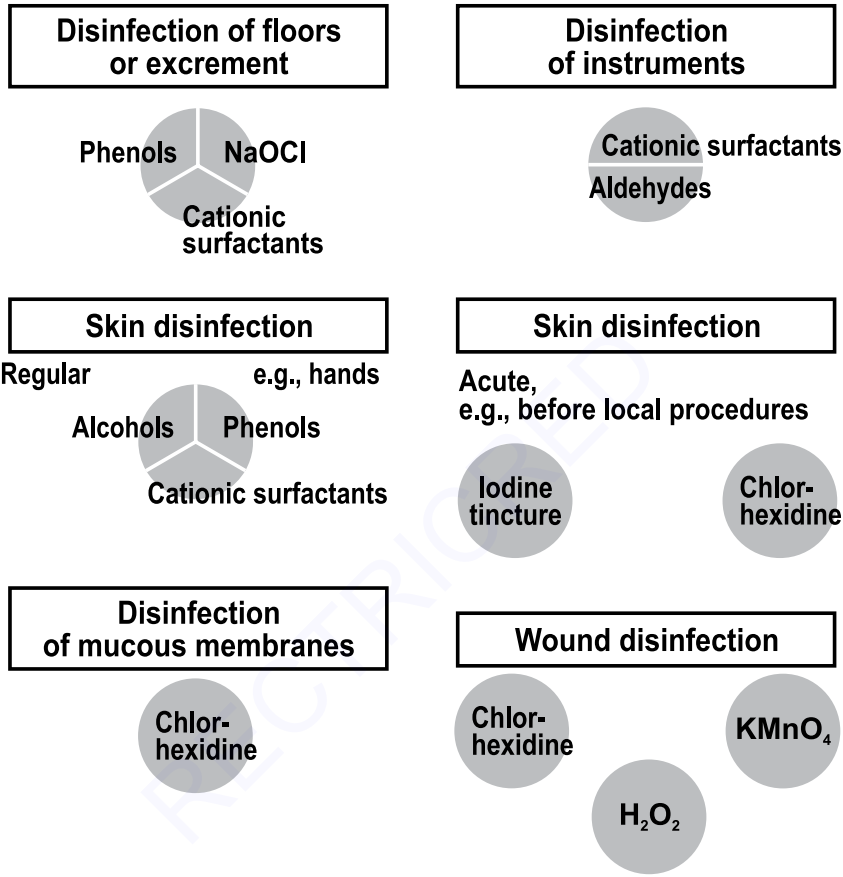

Fig. 29.10. Summary of application of antiseptics and disinfectants *(by H. Lüllmann, 2000)*

TESTS FOR SELF-CONTROL

1. An antiseptic from the oxidizers group is only:
A. Silver nitrate
B. Hydrogen peroxide
C. Etonium
D. Phenol
E. Iodine solution.

2. For the processing of surgeon's hands all the drugs are used, except:
A. Alcohol
B. Mercury dichloride
C. Chlorhexidine bigluconate
D. Solution of ammonia
E. Solution of iodine.

3. Nitrofurasone is:
A. Disinfectant
B. Antiseptic
C. Bactericidal to gram positive and gram negative pathogens
D. Inhibiting enzymes participating in carbohydrate metabolism of bacteria
E. Used for wound irrigation.

4. Phenol is:
A. An organic antiseptic
B. Used for the irrigation of wounds
C. Protoplasmic poison
D. A chemotherapeutic agent
E. A standard for comparing of other germicides.

5. A patient is admited to the clinic with severe abdominal pain and vomiting. The copper-colored shade of the mucosa in the oral cavity and metallic aftertaste are observed. Three days after that, the symptoms of acute renal failure and the defeat of CNS are appeared. What is the cause of the poisoning? What must the antidote therapy include?
A. Iodine and solution of sodium thiosulfate
B. Formaldehyde and solution of ammonia chloride
C. Mercury dichloride and unithiol
D. Strong acid and sodium bicarbonate
E. Alcohol and sodium permanganate.

Answers

1 – B; 2 – B; 3 – B, C, D, E; 4 – A, C, E; 5 – C.

Chapter 30 COMMON PRINCIPLES OF CHEMOTHERAPY. SULFONAMIDES. CHEMOTHERAPEUTICS OF DIFFERENT CHEMICAL STRUCTURE. ANTIFUNGAL DRUGS

MAIN CONCEPTS OF CHEMOTHERAPY

Chemotherapeutic drugs are anti-infective drugs realizing their action inside the body. They are divided into antibiotics, sulfonamides, fluoroquinolones and antimicrobial drugs of different chemical structure, antifungal drugs, antimycobacterial preparations, antiviral agents, antiprotozoal drugs, and antihelminthics (Fig. 30.1).

TYPES OF ANTIMICROBIAL ACTION

There are two types of antimicrobial action: bactericidal and bacteriostatic (Fig. 30.2). The drug with ***bactericidal action*** produces the death of microbes. The drug of ***bacteriostatic action*** inhibits the growth and reduplication of microbial cells and after that the immune system destroys such organisms.

SPECTRUM OF ACTION

The spectrum of action is the list of species of microbes affected by this chemotherapeutic (Fig. 30.3).

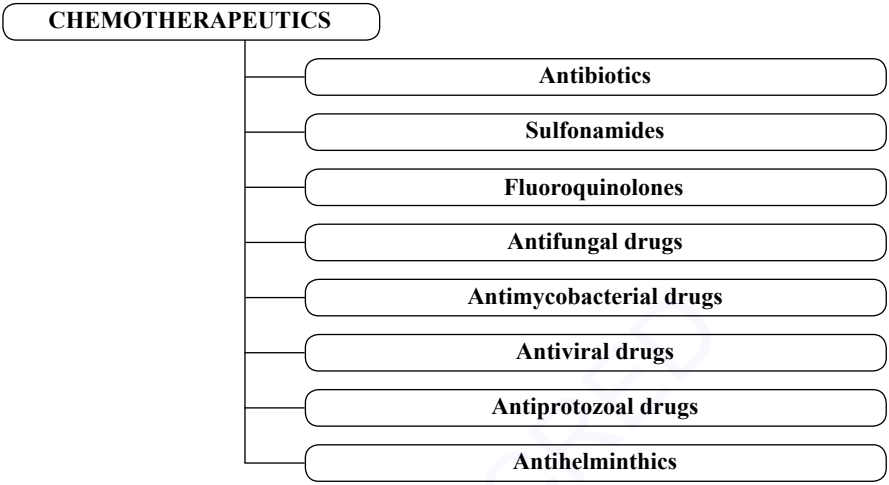

Fig. 30.1. Main classes of chemotherapeutics

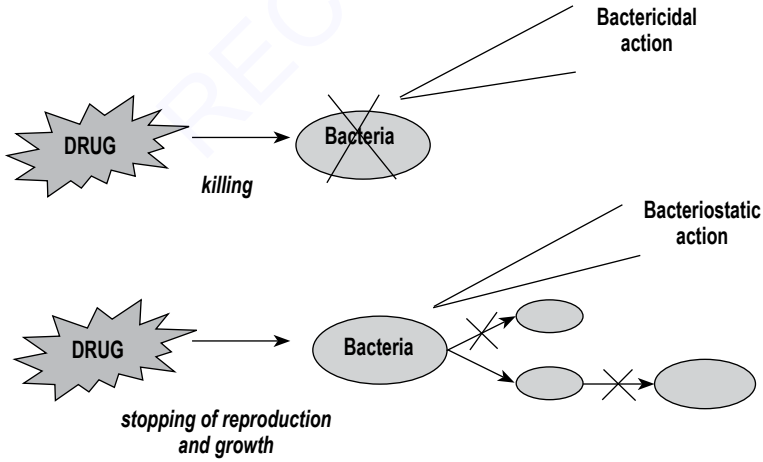

Fig. 30.2. Types of antimicrobial action

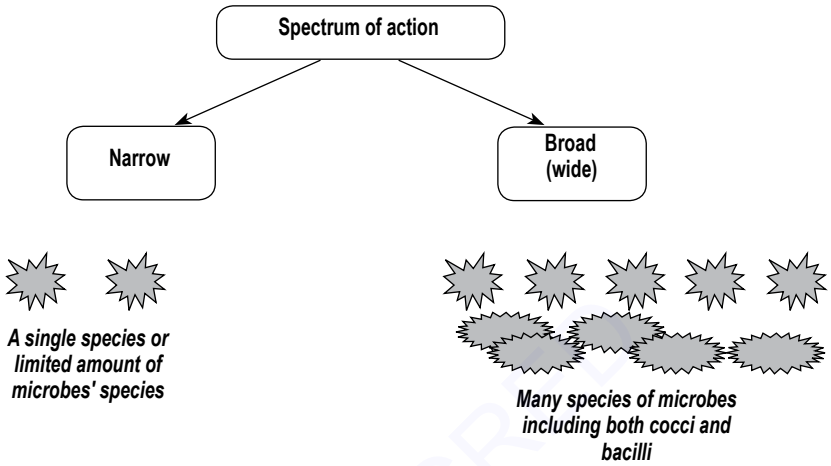

Fig. 30.3. Spectrum of antimicrobial action

GENERAL PRINCIPLES OF ANTI-INFECTIVE THERAPY

- the selection of an appropriate chemotherapeutic agent:
  1) should be grounded on the spectrum of action;
  2) should be based on the laboratory identification of the infecting microorganism;
  3) if the infecting organism is unknown, a wide spectrum drug should be used.
- the selection of the optimal route of administration and dose;
- the maintenance of a constant chemotherapeutic concentration;
- the discontinuation of chemotherapy 2–3 days after the normalization of body temperature;
- a rational combination of the drugs;
- taking into account the patient's sensitivity to the drug;
- taking into account the site of infection, immune competence, age, and physiological status of a patient;
- the clinical and laboratory monitoring of the therapeutic response to drug therapy.

SULFONAMIDES (SULFA DRUGS)

Sulfonamides and trimethoprim belong to folate antagonists. They are synthetic antimicrobial drugs inhibiting folate synthesis. Sulfonamides are sructural analogues of para-aminobenzoic acid (PABA) (Fig. 30.4). All sulfas have common pharmacological properties.

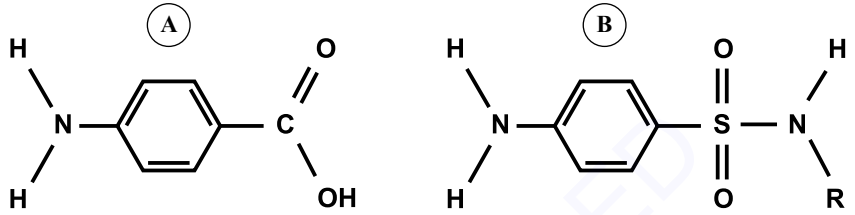

Fig. 30.4. Chemical structure of PABA (A) and sulfonamides (B)

CLASSIFICATION

A. *Highly absorbed sulfonamides:*

1. Short-acting:
   - Sulfamethazine (Sulfadimezin);
   - Sulfaethidole.
2. Intermediate-acting:
   - Sulfamethoxazole;
   - Sulfaphenoxazole.
3. Long-acting:
   - Sulfamethoxypyridazine (Sulfapyridazine);
   - Sulfadimethoxine.
4. Ultralong-acting:
   - Sulfamethoxypyrazine (Sulfalene).

B. *Poorly absorbed sulfonamides:*

- Phthalylsulfathiazole (Phthalazine).

C. *Sulfonamides for local use:*

- Sulfacetamide sodium (Sulfacyl sodium, Albucid);
- Sulfonamide (Streptocide).

D. *Derivatives of sulfonamides and the salicylic acid or silver:*

- Sulfasalazine (Salazosulfa);
- Salazopiridazine;

– Silver sulfadiazine.

E. *Combinations of sulfonamides and trimethoprim:*

– Co-trimoxazole (Bactrim).

Pharmacokinetics

- are taken orally, sometimes are administered IV or applied topically;
- are absorbed in the small intestine;
- bind to plasma albumens;
- penetrate CNS and placenta;
- are metabolized in the liver: most sulfas undergo acetylation accompanied by a decrease of their solubility that results in the crystals formation in the renal tubuli;
- are excreted with urine.

Mechanism of action

- structural similarity to PABA provides competitive antagonism of sulfonamides to PABA and the blockade of dehydropteroid synthase (Fig. 30.5);
- this leads to the inhibition of stage I of the synthesis of the folic acid active form in a microbial cell;
- the absence of tetrahydrofolate results in disturbances in the synthesis of nucleic bases and then in the synthesis of nucleic acids;

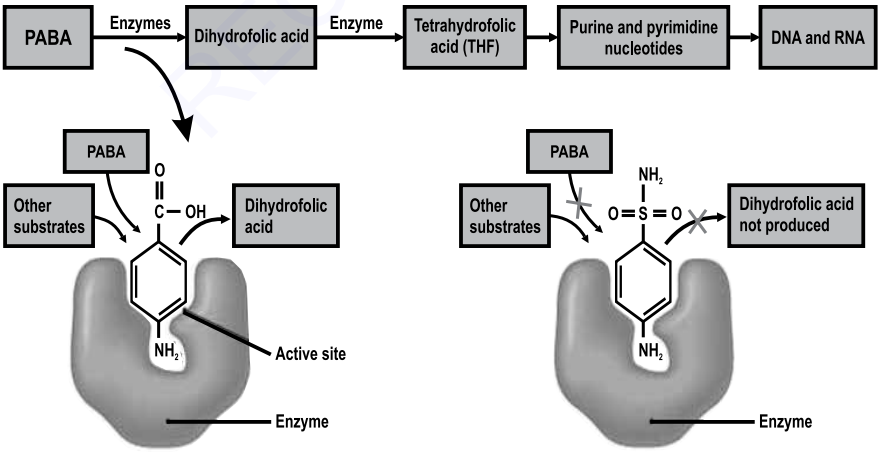

Fig. 30.5. The role of PABA in folate synthesis (at left) and its blockade by sulfonamides (at right) *(http://www.picsearch.com)*

- the reduplication and growth of microbes are inhibited (bacteriostatic action);
- sulfonamides act only on the organisms using PABA in their life cycle;
- sulfas are inactive in the purulent environment rich in PABA;
- they leak antimicrobial activity at the presence of ester local anesthetics which are hydrolyzed to PABA;
- the affinity of enzymes to sulfonamides is less than to a natural substance, that's why a strike dose of the drug is necessary at the start of treatment;
- drugs, inhibiting the second stage of folate synthesis (e.g., trimethoprim), are synergic to sulfas.

Spectrum of action

Sulfonamides have a broad spectrum of action. They are effective against Gram (+) cocci (*Streptococcus, Staphylococcus*), Gram (–) cocci (*Neisseria gonorrhoeae*), Gram (–) bacilli *(Haemophilus influenzae, Escherichia coli, Shigella, Yersenia enterocolitica, Proteus mirabilis)*, *Nocardia, Actinomycetes, Chlamidia, Toxoplasma*, *Plasmodium malariae*.

Indications

- respiratory infections;
- gastrointestinal infections;
- urinary tract infections;
- genital infections (gonorrhea);
- trachoma;
- nocardiasis;
- toxoplasmosis;
- infections of the skin and mucous membranes;
- infections of the eyes

Schemes of treatment

For short-acting drugs: 4 tablets (2 g) for the 1st administration, then 2 tablets (1 g) 4 times a day, after the normalization of body temperature 1 tablet (0.5 g) 4 times a day during 3 days. (A total dose is 20–30 g).

For long-acting drugs: 4 tablets (2 g) for the 1st administration, then 2 tablets (1 g) once a day, after the normalization of body temperature 1 tablet (0.5 g) once a day during 3 days. (A total dose is 8–10 g).

For ultra-long-acting drugs: 5 tablets (1 g) for the 1st administration, then 1 tablet (0.2) once a day (A total dose is 2 g). The total dose may be taken once a week.

Side effects

1. Crystalluria.
2. Allergy.
3. Hemopoietic disturbances.
4. Dermatitis and phototoxicity.
5. Stevens-Johnson syndrome.
6. Hepatitis.
7. Kernicterus (in newborns).
8. Idiosyncrasy (hemolytic anemia in patients with the deficiency of glucose-6-phosphate dehydrogenase).

PECULIARITIES OF PREPARATIONS

Sulfacetamide sodium is a well-soluble substance, is used as eye-drops in conjunctivitis, trauma of the eyes and for the prophylaxis of eyes gonorrhea in newborns.

Phtalylsulfathiazole is inactive *in vitro*, but active in the intestine because of norsulfazole's liberation; is used for gastrointestinal infections.

Sulfaethidole is rapidly absorbed in the gut and rapidly excreted; is used in urinary tract infections and nocardiasis.

Sulfadimethoxine is a long-acting sulfonamide, is rapidly absorbed , but slowly excreted, has a half-life of 24–48 hrs, is concentrated in bile, thus is suitable to treat cholecystitis.

Sulfalene is an ultralong-acting sulfonamide, has a half-life of more than 48 hrs due to strong bonds with plasma albumins and reabsorption in the kidney; is used orally for all infections sensitive to sulfa drugs; is suitable to treat long-durative infections.

Co-Trimoxazalole is a combined preparation containing sulfamethoxazole together with trimethoprim. Sulfamethoxazole inhibits dehydropteroide synthase (stage I of the synthesis of an active form of the folic acid). Trimetoprim inhibits dehydrofolate reductase (stage II of the synthesis of an active form of folic acid). A result is a bactericidal action. The antimicrobial spectrum of trimethoprim is similar to that of sulfonamide, however the combination is 20–50 times more potent than sulfonamide. Pharmacokinetics of trimethoprim is similar to that of sulfamethoxazole. Co-trimoxazole is used to treat *Pneumocystis carrini* pneumonia, respiratory infections, gastrointestinal infections (shigellosis, non-typhoid salmonella infections, the carrierity of *Salmonella typhi*), genital infections (gonorrhea), prostate and urinary tract infections. It may cause side effects, such as skin lesions, nausea, vomiting, stomatitis, anemia, folate deficiency and special adverse reactions in HIV infected persons.

Salazopyridazine and sulfasalazine are the combinations of sulfonamides with acetylsalicylic acid; have antimicrobial and anti-inflammatory effects; are used for ulcerative colitis.

SYNTHETIC ANTIMICROBIAL DRUGS WITH DIFFERENT CHEMICAL STRUCTURE

This group of preparations is represented by nitrofuran derivatives and quinolone derivatives.

CLASSIFICATION

A. *Nitrofuran derivatives:*
- Furozolidone;
- Nifuroxazide.

B. *Quinolones and fluoroquinolones:*
1. Quinolones:
   - Nitroxoline (5-NOK);
   - Nalidixic acid.
2. Fluoroquinolones:

a) the 1st generation:
   - Ciprofloxacin;
   - Ofloxacin.

b) the 2nd generation:
   - Lomefloxacin.

c) the 3rd generation:
   - Levofloxacin.

d) the 4th generation:
   - Gatifloxacin.

FUROZOLIDONE

- is taken orally 3–4 times a day, is metabolized in the liver and inhibits liver enzymes, is excreted with urine;
- disturbs proton transport during cell respiration;
- has a wide spectrum of action: Gram (–) bacilli, Gram (+) bacteria (against which the drug is less effective), *Trichomonas, Lamblia giardiasis;*
- is used in urinary tract infections, intestinal infections, bacillary dysentery, giardiasis, trichomoniasis, infected wounds and burns (topically);

- may cause allergy, dyspepsia, a disulfiram-like reaction, an increase in BP if the diet is reach in tyramine.

NIFUROXAZIDE

- is a nitrofuran derivative;
- is taken orally every 6 hrs, acts in the lumen of the intestine, because it is practically not absorbed from the digestive tract, is excreted with feces;
- is effective against *Staphylococcus, Streptococcus, Salmonella, Shigella, Klebsiella, Escherichia coli*, does not affect the composition of normal microflora of the large intestine, does not cause the emergency of drug-resistant strains;
- is used in diarrhea caused by gram-positive and some gram-negative bacteria, diarrhea caused by food intoxication, appendicitis, chronic autoimmune gastritis; diarrhea caused by antibiotic therapy or changes in the natural bacterial flora of the large intestine.

NITROXOLINE

- is an oxiquinoline;
- is taken orally, is excreted with urine and produces high concentration in urine;
- disturbs reduplication of nucleic acids, forms complexes with metals ions and inhibits oxidative-reductive processes;
- has a broad spectrum of action: Gram (–) cocci and bacilli, Gram (+) cocci, *Candida albicans, Trichomonas vaginale;*
- has a bacteriostatic type of action;
- is used in urological infections (so-called uroseptic) and for the prevention of infection before urological surgeries;
- may cause allergy, dyspepsia, neurological problems (ataxia, paresthesia, neuropathy) and an orange discoloration of urine.

NALIDIXIC ACID

- is a quinolone;
- is taken orally, partly is metabolized in the liver and excreted with urine;
- inhibits topoisomerase II (DNA gyrase), in such a way disturbs DNA reduplication;

- the antimicrobial spectrum is narrow (only Gram (–) bacilli) and resistance emerges rapidly;
- is used in urinary tract infections, cholecystitis, otitis media;
- may cause side effects, such as gastrointestinal irritation, glucosuria, skin rash, phototoxicity, CNS and visual disturbances.

FLUOROQUINOLONES

- are fluorine-containing quinolones divided into 4 generations;
- are administered orally or IV, are widely distributed in the body, produce high concentrations in the bones, urine, prostate, kidney, are concentrated in phagocytes and act on intracellular microbes, are excreted with urine or bile, have a half-life of from 3–8 hrs to 10–20 hrs;
- inhibit the bacterial DNA gyrase (topoisomerase II) or the topoisomerase IV enzyme, thereby inhibiting DNA replication and transcription (Fig. 30.6). First and second generation fluoroquinolones selectively inhibit the topoisomerase II ligase domain, leaving the two nuclease domains intact. This modification, coupled with the constant action of the topoisomerase II in the bacterial cell, leads to DNA fragmentation via the nucleasic activity of the intact enzyme domains. Third and fourth generation fluoroquinolones are more selective for the topoisomerase IV ligase domain, and thus have enhanced gram-positive coverage.

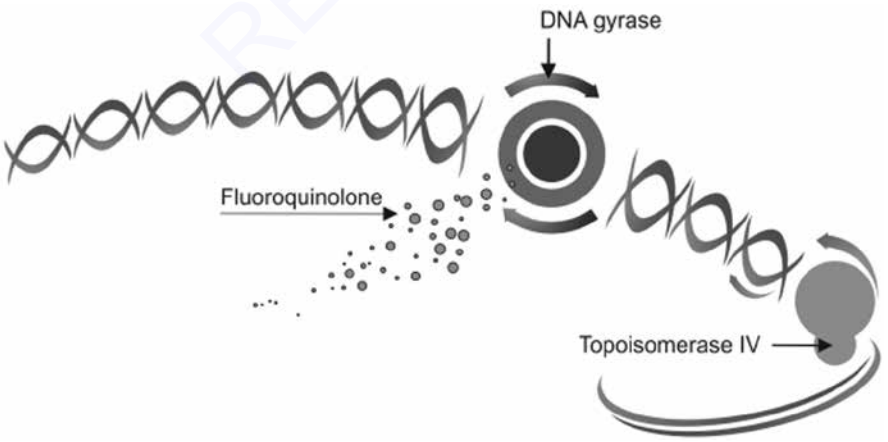

Fig. 30.6. Mechanism of action of fluoroquinolones *(http://www.picsearch.com)*

- the spectrum of action is wide: Gram (–) bacilli (*Enterobacter, Pseudomonas, Haemophilus influenzae, Moxzarella, Legionella*), *Chlamidia, Mycobacteria*, some Gram (+) cocci. Unlike the first and second generations, the third generation is active against streptococci. Fluoroquinolones can enter cells easily via porins and, therefore, are often used to treat intracellular pathogens (*Legionella pneumophila* and *Mycoplasma pneumoniae*);
- are indicated in urinary tract infections, perioperative antibiotic prophylaxis for transurethral surgery, gonorrhea, gastrointestinal infections, infections of the bones, joints, skin, and soft tissues, resistant respiratory infections, tuberculosis (ciprofloxacin, ofloxacin);
- may cause nausea, vomiting, diarrhea, pseudomembranous colitis, headache, dizziness, psychosis, seizures, crystaluria, phototoxicity, cartilage lesions and tendon damage with spontaneous tendon rupture;
- are contraindicated to pregnant women, nursing mothers, children younger than 18 years old as well as to patients with epilepsy, stroke, severe renal insufficiency, QT-prolongation in the ECG.

ANTIFUNGAL DRUGS

Antifungals are the preparations for the treatment of infections caused by pathogenic fungi (mycoses).

Like mammalian cells, fungi are eukaryotes with DNA organized into chromosomes. This homology to mammalian cells also extends to biosynthetic pathways. The similarity of fungal and mammalian cells creates a number of problems for designing drugs that are selectively toxic to fungal cells, but not the human host.

Both fungi and mammalian cells have a cell membrane. The sterol contents between mammalian cells and fungal cells is different. Ergosterol is the predominant sterol in many pathogenic fungi. This difference in sterol content has been exploited as the target of an antifungal drug action by several classes of antifungal agents

CLASSIFICATION

A. *Antibiotics:*

1. Polyenes:
   – Nystatin;
   – Amphotericin B.
2. Heterocyclic benzofurane:
   – Griseofulvin.

B. *Azoles:*

1. Imidazoles:
   - Clotrimazole;
   - Miconazole;
   - Ketoconazole.
2. Triazoles:
   - Fluconazole;
   - Itraconazole.

C. *Antimetabolites:*

- Flucirosine.

D. *Allylamines:*

- Terbinafine.

POLYENES

Polyene antifungals, such as ***amphotericin B and nystatin***, act by binding to ergosterol in the fungal cell membrane (Fig. 30.7). This results in the depolymerization of the membrane and formation of pores that increase permeability to proteins and monovalent and divalent cations, eventually leading to the cell death. Amphotericin B may also induce oxidative damage in the fungal cells and has been reported to stimulate the host immune cells.

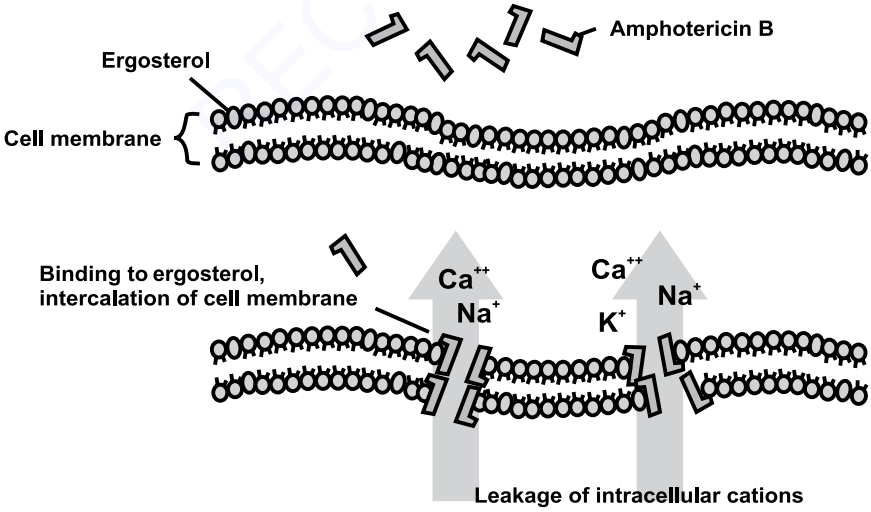

Fig. 30.7. Mechanism of action of polyenes *(http://www.picsearch.com)*

Amphoterricin B has a wide antifungal spectrum of action including *Histoplasma capsulata, Cryptococcus neoforenans, Coccidioides immitis, Blastomyces dermatitidis, Candida albicans, Aspergilus, Sporotrichum.* It is used in systemic mycoses. Toxicities of polyene antifungals are an extension of their mechanism of action. The stimulation of the host immune cells by amphotericin B causes the release of inflammatory cytokines by circulating monocytes resulting in fever, chills, rigor, nausea, vomiting, myalgias, arthralgias, and headache during IV infusions. In higher concentrations, amphotericin B binds to cholesterol in mammalian cell membranes leading to various organ toxicities.

Nystatin has a narrow antifungal spectrum. It is only effective against *Candida* fungi and is used for the treatment of *Candida* infections of the skin and mucous membranes as well as for the prevention of candidiasis under the therapy of wide-spectrum antibiotics.

Both polyenes are described in detail in Chapter 31.

GRISEOFULVIN

- is an antibiotic, heterocyclic benzofurane;
- is taken orally, is absorbed in the small intestine, concentrates in the infected newly synthesized keratin-containing tissue (skin, nails and hair), is metabolized in the liver, is the inducer of cytochrome P-450, is excreted with urine;
- interferes with the microtubule function, disturbs the mitosis of fungal cells, inhibits the synthesis of nucleic acids, has a fungistatic action;
- has a spectrum of action represented by dermatophytes *(Microsporon, Epidermophyton, Trichophyton);*
- is used for the treatment of dermatomycoses, mycoses of the scalp and nails;
- may cause headache, CNS problems, hepatotoxicity, gastrointestinal distress, leukopenia, skin rash, phototoxicity;
- is contraindicated in pregnancy, malignant diseases; should not be used in patients whose job needs a quick motor reaction.

AZOLES

- are imidazole or triazole derivatives (Fig. 30.8);
- are taken orally and applied topically; are absorbed in the gut; absorption is impaired by food, cimetidine, rifampin; are widely distributed in the body tissues; penetrates CNS poorly; are metabolized in the liver and inhibit cytochrome P-450;

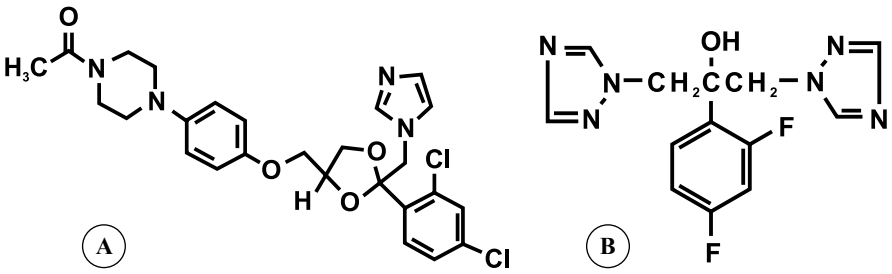

Fig. 30.8. Chemical structure of ketoconazole (A) and fluconazole (B)

- inhibit the fungal cytochrome P-450-dependent enzyme 14-α-demethylase (Fig. 30.9), thereby interrupting the synthesis of ergosterol. Inhibition of this critical enzyme in the ergosterol synthesis pathway leads to the depletion of ergosterol in the cell membrane and the accumulation of toxic intermediate sterols causing increased membrane permeability and the inhibition of fungal growth;
- have a wide antifungal spectrum of action;
- are indicated in mucocutaneous candidiasis, prophylaxis of candidiasis, dermatomycoses, cryptococcal infection, infections due to *Blastomyces, Sporotrix, Coccidioides, Histoplasma;*
- may cause side effects, such as nausea, vomiting, allergy, hepatotoxicity, blockade of the synthesis of testosterone and adrenal steroids, gynecomastia, changes in the pharmacokinetics of other drugs.

PECULIARITIES OF PREPARATIONS

Ketoconazole is used for systemic mycoses caused by *Blastomyces, Coccidioides, Histoplasma*, for dermatomycoses, and chronic candidiasis; has antihormonal activity, blocks cytochrome P-450-enzymes and changes the metabolism of co-administered drugs; may cause gynecomastia, impotence, menstrual irregularities; may accumulate in patients with hepatic dysfunction; antagonizes amphotericin B antifungal effect and should not be given together with amphotericin.

Clotrimazole (Canesten) is used to treat vaginal yeast infections, oral thrush, diaper rash, pityriasis versicolor, and types of ringworm including athlete's foot and jock itch; can be taken by mouth or applied to the skin or in the vagina; may be compounded with a glucocorticoid (betamethasone) in the topical cream. Common side effects when taken orally include nausea, itchiness, and abnormal liver func-

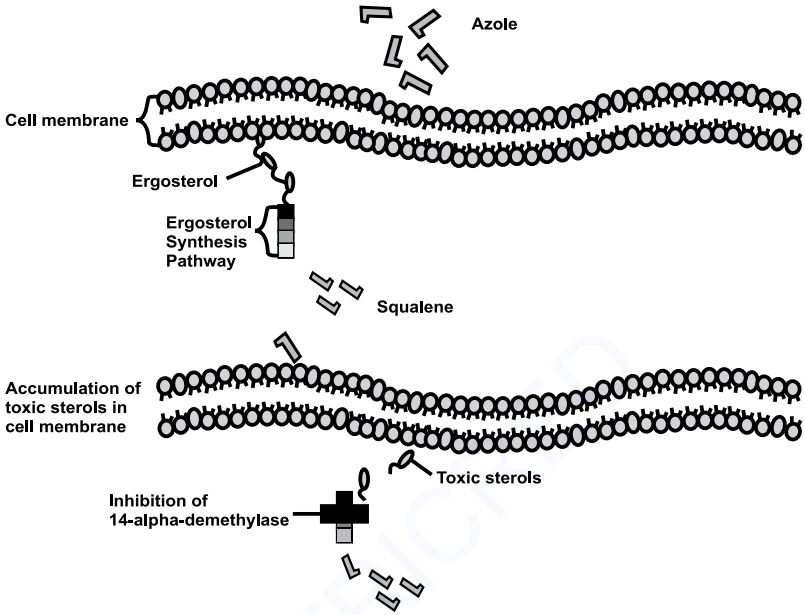

Fig. 30.9. Mechanism of action of azoles *(http://www.picsearch.com)*

tion tests; when applied to the skin – redness and burning. With oral clotrimazole, there are multiple interactions as the drug is an inhibitor of microsomal oxidation.

Fluconazole is administered orally and IV; does not bind to plasma proteins; penetrates CNS; is eliminated by the kidney in an unchanged form; is used in oropharyngeal candidiasis, *Coccidioides* infection, vaginal candidiasis, for the prevention and the treatment of cryptococcal infection; is less toxic than ketoconazole or amphotericin; has no endocrinal side effects.

Itraconazole is a drug of choice for the systemic mycoses caused by *Blastomyces* and *Sporotrix*; is an alternative drug in the treatment of aspergillosis, coccidiomycosis, cryptococcosis, and histoplasmosis; is used to treat dermatomycoses, to prevent superinfection during the therapy by wide-spectrum antibiotics.

ALLYLAMINES

Allylamines (terbinafine) work in a conceptually similar fashion to azole antifungals by inhibiting the synthesis of ergosterol. However, allylamines act at an

earlier step in the ergosterol synthesis pathway by inhibiting the enzyme squalene epoxidase.

ANTIMETABOLITES

This class has only one example, ***flucytosine*** (5-fluorocytosine, 5-FC). Flucytosine was developed as a potential anticancer agent. Although ineffective against tumors, it was later found to have antifungal activity. This small molecule is transported into susceptible fungal cells by a specific enzyme cytosine permease and converted in the cytoplasm by cytosine deaminase to 5-fluorouracil, a pyrimidine antimetabolite. A result is the inhibition of nucleic acid synthesis in the fungal cells.

TESTS FOR SELF-CONTROL

1. The following is a basis for sulfamethoxazole and trimethoprim combination:
A. Both drugs act at the same stage of folates metabolism
B. Both drugs are bacteriostatic agents
C. The combination of these drugs has less side effects
D. The combination has a long duration of action
E. Both drugs have nearly similar plasma half-life.

2. The mechanism of sulfonamides' action is:
A. Competitive antagonism with PABA
B. The inhibition of the synthesis of microorganisms' membrane
C. An increase in permeability of microorganisms' membranes
D. The inhibition of the synthesis of microorganisms' proteins
E. The blockade of the sulfhydric groups of enzymes.

3. Drugs with antifungal activity belong to:
A. Sulfonamides
B. Polyenes
C. Imidazoles
D. Fluoroquinolones
E. Allylamines.

4. The correct statements concerning antifungals are:
A. Nystatin has a narrow spectrum of action

B. Amphotericin B is never used to treat systemic mycoses
C. Griseofulvin concentrates in the skin, hair, and nails
D. Itraconazole is an antibiotic for the treatment of *Candida* infection only
E. Ketoconazole has an antihormonal activity.

5. A patient with acute cystitis was prescribed a highly active antimicrobial drug. It has a wide spectrum. The mechanism of its action is connected with the inhibition of DNA-gyrase. This drug influences negatively cartilaginous tissue. What drug was prescribed?
A. Sulfalene
B. Furozolidone
C. Ciprofloxacine
D. Nalidixic acid
E. Nystatin.

Answers

1 – E; 2 – A; 3 – B, C, E; 4 – A, C, E; 5 – C.

Chapter 31 ANTIBIOTICS

ANTIBIOTICS

Antibiotics are substances produced by microbes for their antagonism with other microorganisms. Antagonism of microbes is named antibiosis.

History of antibiotics. Antibiosis was studied by L. Paster and I. Mechnikov. The first antibiotic was penicillin. It was discovered by A. Fleming in 1928. The second antibiotic streptomycin was discovered by S. Waksman. He also proposed the name "antibiotics".

Antibiotics are divided:

1. According to the type of action:

- bactericidal;
- bacteriostatic.

2. According to the spectrum of action:

- antibiotics of wide spectrum (with Gram (+) and Gram (–) coverage including Gram (–) bacilli);
- antibiotics of narrow spectrum of action (with a limited list of microbes, Gram (+) and Gram (–) coverage without Gram (–) bacilli, only Gram (+), or only Gram (–) coverage).

3. According to the clinical use:

- basis antibiotics (antibiotics of choice) (the most effective antibiotics which are used at the start of treatment);
- alternative antibiotics (preparations which are used for the replacement of basis antibiotics in the case of microbial resistance or patient's hypersensitivity).

MAIN PRINCIPLES OF THE THERAPY BY ANTIBIOTICS

Therapy with antibiotics must be put into the practice according to some common rules concerning both microorganism and macroorganism. These rules (principles) are:

- an early beginning of the treatment;
- the choice of an antibiotic according to its spectrum of action;
- the choice of an antibiotic according to the susceptibility of microbes in a definite patient;
- the use of a wide spectrum antibiotic if the cause of infection is unknown;
- the duration of the treatment no less than 5–7 days;
- the usage of big doses of antibiotics;
- the supporting of the therapeutic concentration of the drug in the organism;
- combination of antibiotics with one another as well as with drugs from other groups;
- the discontinuation of the treatment 2–3 days after the normalization of clinical status and body temperature;
- allergy anamnesis before the start of treatment;
- attention to the age and physiological status of the patient, concomitant diseases, the location and severity of infection.

COMMON ANTIBIOTICS SIDE EFFECTS

- allergy, anaphylactic shock. For prevention – allergy anamnesis before the first administration of the antibiotic;
- a direct toxic influence;
- endotoxic reactions. They display as an increase in body temperature and intoxication resulting from the liberation of endotoxins from microbes destroyed by antibiotic;
- dysbacteriasis. It is the inhibition of normal microflora in the human body accompanied by the activation of *Candida* fungi. For prevention – to take antifungal drugs (nystatin, itraconazole) together with a wide spectrum antibiotic.

CLASSIFICATION

***A**. Inhibitors of cell wall synthesis:*

1. Penicillins.
2. Cephalosporins.

3. Carbapenems and monobactams.
4. Glycopeptides.

B. *Protein synthesis inhibitors acting on ribosomal subunits 30S:*

1. Aminoglycosides.
2. Tetracyclines.

C. *Protein synthesis inhibitors acting on ribosomal subunits 50S:*

1. Macrolides and azalides.
2. Chloramphenicols.
3. Lincosamides.

D. *Antibiotics which disturb functions of nucleic acids:*

1. Rifampicins.

E. *Antibiotics which disturb the structure and functions of cell membranes:*

1. Polyenes.
2. Cyclic polypeptides (polymyxins).

ANTIBIOTICS-INHIBITORS OF CELL WALL SYNTHESIS

The most important antibiotics of this group are the β-lactam antibiotics, named after the β-lactam ring which is essential to their activity (Fig. 31.1).

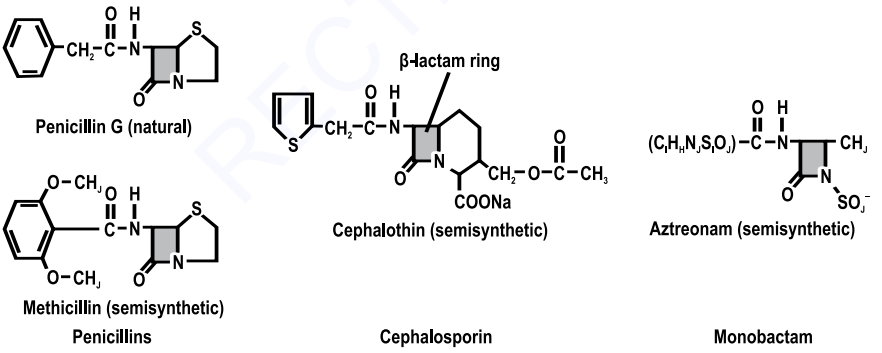

Fig. 31.1. Chemical structure of β-lactam antibiotics

PENICILLINS

Penicillins are derivatives of the 6-aminopenicillanic acid. The members of this family differs from one another in the substituent attached to the amino group of the 6-aminopenicillanic acid.

CLASSIFICATION

A. *Natural penicillins:*

1. Short-acting:
   - Benzylpenicillin sodium (penicillin G);
   - Benzylpenicillin potassium;
   - Phenoxymethylpenicillin (Penicillin V).
2. Long-acting:
   - Benzylpenicillin procaine;
   - Benzathine benzylpenicillin (Bicillin-1);
   - Benzathine benzylpenicillin + benzylpenicillin procaine + Benzylpenicillin sodium (Bicillin-3);
   - Benzathine benzylpenicillin + benzylpenicillin procaine (Bicillin-5).

B. *Semisynthetic penicillins:*

1. Penicillinase resistant:
   - Oxacillin.
2. Wide-spectrum:
   - Ampicillin;
   - Amoxicillin;
   - Carbenicillin.
3. Combined penicillins:
   - Ampiox;
   - Amoxiclav (Augmentin).

BENZYLPENICILLIN SODIUM

Benzylpenicillin sodium (***penicillin*** G) is a natural substance produced by fungus *Penicillium notatum.*

Pharmacokinetics

- is destroyed by gastric juice (Fig. 31.2), that's why is administered IM, IV, endolumbally;
- is widely distributed through the body;
- penetrates CNS only in the conditions of meningitis; penetrates placenta without negative influence on the fetus;
- is excreted with urine;
- acts during 4–6 hrs.

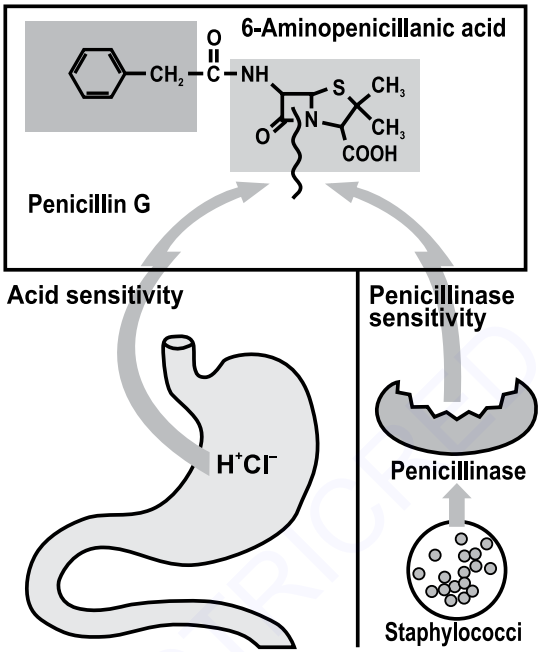

Fig. 31.2. Site of cleavage of penicillin by acid or by bacterial penicillinase *(by H. Lüllmann, 2000)*

Mechanism of action

- in bacteria, there are several integral proteins in the cell membrane that provide numerous functions: 1) transpeptidase activity – this permits cross-linking in the formation of the cell wall; 2) contribute to the shape of the bacteria; 3) contribute to septum formation during replication/division; 4) the inhibition the action of autolysin (an enzyme that causes the destruction of the bacteria). These proteins are the target for penicillin. They are referred to penicillin binding proteins or PBPs;
- penicillin G binds directly to PBPs and inhibits the enzyme transpeptidase, thus inhibiting cell wall formation. The inhibition of this action will reduce the structural and functional integrity of the cell wall. The cell bursts from osmotic pressure because the integrity of peptidoglycan is not maintained (a bactericidal action) (Fig. 31.3);
- benzylpenicillin only acts on organisms at the stage of growth and division.

- Bacteria may be resistant or develop resistance to penicillin by a variety of mechanisms: the structure of the cell wall may provide resistance to a drug effect; the PBP may undergo modification, decreasing the binding affinity for the antibiotic; the production of β-lactamase (penicillinase) provides destruction of the antibiotic before it may exert its effect.

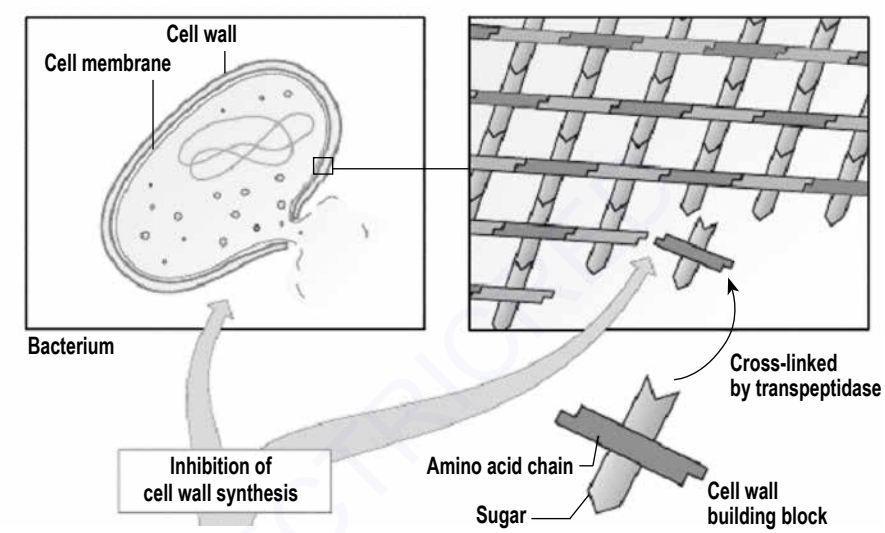

Fig. 31.3. Mechanism of bactericidal action of penicillins *(by H. Lüllmann, 2000)*

Spectrum of action

It has a narrow spectrum of action: Gram (+) and Gram (–) cocci (streptococci, some staphylococci, gonococci, meningococci), clostridia, corynebacteria, listeria, spirochetas, leptospira.

Indications

- infections caused by streptococci (angina, scarlet fever, rheumatism);
- meningitis (caused by *Meningococcus*);
- pneumonia (caused by *Pneumococcus*);
- gonorrhea;
- syphilis;
- gangrene;
- diphtheria;
- infections of the skin and soft tissues;

- listeriosis;
- leptospirosis.

Side effects

1. Allergic reactions which occur in 0.7–20% of patients taking penicillin and may range from rash, fever, through broncospasm, vasculitis, serum sickness, exfoliative dermatitis, and Steven-Johnson syndrome to anaphylaxis.
2. Neurotoxicity (in a bigger dose).

Contraindications

Hypersensitivity to penicillin.

PECULIARITIES OF OTHER PREPARATIONS

Benzylpenicillin potassium is a short-acting natural penicillin similar to benzylpenicillin sodium, but is not administered IV or endolumbally due to the toxic action of potassium on the CNS and heart.

Benzathine penicillin (Bicillin-1) is a long-acting natural penicillin, has a spectrum of action similar to the same of benzylpenicillin sodium, is administered only IM once a week for the treatment of chronic infections (pharigitis, tonsillitis, erysipelas, syphilis, rheumatism) and for prophylaxis of rheumatism relapse.

Bicillin-3 is a long-acting natural penicillin containig benzylpenicilln sodium (or potassium), benzatine benzylpenicillin, and benzylpenicillin procaine in the equal amounts, has a spectrum of action similar to the spectrum of benzylpenicillin sodium, is administered only IM 1–2 times a week to treat chronic infections (pharigitis, tonsillitis, erysipelas, syphilis or rheumatism).

Bicillin-5 is a long-acting natural penicillin, contains ¼ of benzylpenicillin procaine and ¾ of Bicillin-1; has a spectrum of action similar to benzylpenicillin sodium, is administered only IM once a month to treat chronic streptococcal and spirochetal infections.

Oxacillin is a semisynthetic penicillin, is acid resistant and may be taken by mouth, is penicillinase resistant and is effective against *Staphylococcus spp.*; is not as effective against the other organisms that older penicillins are effective against. Oxacillin and other penicillinase-resistant penicillins ***(meticillin, nafcillin)*** are only topically used in the skin infections caused by susceptible organisms. There are numerous strains that are now resistant to these agents – so-called methicillin-resistant staphylococci (MRSA).

Ampicillin is a semisynthetic penicillin, is acid resistant and may be taken by mouth as well as IM and IV, is destroyed by penicillinase of staphylococci; has

a wide spectrum of action: is more effective against Gram (–) organisms than the older drugs of the class (These include *Haemophilus influenzae, Escherichia coli, and Proteus mirabilis)*; is most often used in the treatment of urinary tract infections, respiratory tract infections, and otitis media caused by susceptible organisms

Amoxicillin is a wide spectrum penicillin, is an active metabolite of ampicillin, has a better bioavailability in a comparison to ampicillin.

Carbenicillin, piperacillin are extended spectrum penicillins, are more active against Gram (–) and anaerobic organisms including *Pseudomonas spp., Enterobacter spp.,* and *Proteus spp.*; are used primarily in the treatment of infections caused by susceptible organisms, often associated with bacteremia and burns. Piperacillin shows the greatest activity against *Pseudomonas* and *Klebsiella spp*.

Ampiox is a combined preparation containing ampicillin and oxacillin, that's why it has a wide spectrum and acts on staphylococci.

Amoxiclav is a combined preparation containing ampicillin and clavulanic acid (β-lactamase inhibitor), may be used to treat infections caused by penicillin resistant microbes.

CEPHALOSPORINS

Cephalosporins are derivatives of the 7-aminocepalosporanic acid and contain β-lactam ring (Fig. 31.1).

They are wide spectrum antibiotics with a bactericidal action. Mechanism of action is similar to that of penicillins.

CLASSIFICATION

1. The 1st generation:
   - Cefazolin (Kefzol);
   - Cephaloridine;
   - Cephalexin.
2. The 2nd generation:
   - Cefamandole;
   - Cefuroxime;
   - Cefaclor.
3. The 3rd generation:
   - Cefotaxime;
   - Ceftriaxone;
   - Cefixime;
   - Cefazidime.

– Cefoperazone.

4. The 4th generation:
   – Cefpirome.

Spectrum of action

Cephalosporins of the 1st generation act on Gram (+) cocci including staphylococci resistant to penicillins, Gram (–) cocci, some Gram (–) bacilli. They are not effective against MRSA.

Cephalosporins of the 2nd generation act on Gram (–) bacilli including *Enterobacter, Klebsiella, Haemophilus*, and *Proteus spp*., but they are less active against Gram (+) cocci. Some preparations (cefoxitin, cefmetazole) are effective against *Bacteroides spp.*

Cephalosporins of the 3rd generation act on Gram (+) cocci, Gram (–) cocci as well as on Gram (–) bacilli; they are more resistant to the effects of β-lactamase. Ceftazidime and cefoperazone are also effective against *Pseudomonas*.

Cephalosporins of the 4th generation have a spectrum similar to the 3rd generation, they are also effective against *Pseudomonas aeruginosa* and anaerobic bacteria. They are alternative antibiotics.

Indications

- severe respiratory infections;
- urinary tract infections;
- gynecologic infections;
- osteomyelitis;
- infections of the skin and soft tissues;
- sepsis;
- peritonitis;
- the prophylaxis of infectious complications of surgeries.

Side effects

1. Allergy (there is some cross-sensitivity with the penicillins: 1–20% of patients exhibit sensitivity to both classes of antibiotics).
2. Dyspepsia.
3. Renal disturbances (cephaloridine is the worst offender).
4. Changes in the blood film, the suppression of the bone marrow resulting in granulocytopenia (relatively rare).
5. A decrease in the prothrombin amount in the blood.
6. Dysbacteriasis (for drugs administered orally).

PECULIARITIES OF PREPARATIONS

Cefazolin is from the 1st generation; is administered IM, IV; acts during 8–12 hrs, is excreted unchanged with urine; is used to treat infections of the respiratory pathways, urinary pathways, bones, skin and soft tissues, may be used for the prevention of infection before the surgery; has low nephrotoxicity.

Cephalexin is less active than other preparations of the 1st generation, but it is taken orally.

Cefotaxime is a 3rd generation cephalosporin; is administered IM 2–3 times a day, well penetrates CNS, tissues, and liquids of the body; is used in severe infections of the respiratory and urinary pathways, sepsis, meningitis, osteomyelitis; is the antibiotic of choice for infections caused by non-identified microbes, may be applied for prophylaxis of infection before the surgery.

Ceftriaxone is more active than other preparations of the 3rd generation; is administered IM or IV 1–2 times a day; has indications similar to indications of cefotaxime.

Cefoperazone is a 3rd-generation cephalosporin antibiotic, one of few cephalosporins effective in treating *Pseudomonas* bacterial infections. It is also used as a co-formulation with sulbactam. Cefoperazone exerts its bactericidal effect by inhibiting the bacterial cell wall synthesis, and sulbactam acts as β-lactamase inhibitor, to increase the antibacterial activity of cefoperazone against β-lactamase-producing organisms. The drug is administered IM or IV every 12 hrs. It can cause hypoprothrombinemia and disulfiram-like reaction as side effects.

Cefpirome is highly effective against Gram (+) and Gram (–) aerobic and anaerobic microorganisms: *Escherichia coli, Salmonella spp., Shigella spp., Proteus mirabilis, Proteus vulgaris, Providencia, Morganella morganii, Citrobacter freundii, Klebsiella oxytoca, Serratia spp., Enterobacter spp., Haemophilus influenzae, Neisseria spp., Moraxella catarrhalis, Streptococcus spp., Staphylococcus spp., Peptostreptococcus spp., Clostridium perfringens, Pseudomonas aeruginosa.* As a representative of the 4th generation cephalosporins, it is resistant to the action of known β-lactamases. When administered IV, it remains in the blood in a therapeutic concentration for 12 hrs and penetrates well the tissues and body fluids. The drug is used for infections of the urinary system, skin and soft tissues, pneumonia, lung abscess, pleural empyema, septicemia and infections in patients with impaired immunity. Side effects include nausea, vomiting, diarrhea, transient increase liver transaminases, leukopenia, transient increase in the concentration of urea and creatinine in the blood plasma, phlebitis at the injection site, and allergic reactions.

CARBAPENEMS

Imipenem and Meropenem are carbapenems (Fig. 31.1):

- act in a manner identical to the penicillins and cephalosporins;
- Imipenem is given with the agent cilastatin. Imipenem is rapidly metabolised by renal dehydropeptidases. Cilastatin inhibits this renal metabolism, promoting renal reabsorption and an extended half-life of the drug;
- Meropenem demonstrates a long half-life with higher blood levels and therefore does not require the co-administration of cilastatin;
- have the broadest spectrum of action: Gram (+), Gram (–) microorganisms, anaerobs, *Pseudomonas aerugirosa*. They are extremely resistant to the action of β-lactamase;
- are used in the treatment of urinary tract infections, lower respiratory tract infections, gynecological infections, and soft tissue infections caused by susceptible organisms;
- may cause nausea, vomiting, and seizures in high doses (meropenem is less likely to cause seizures).

MONOBACTAMS

Aztreonam is an antibiotic from the monobactams group:

- has a mechanism of action similar to other β-lactams;
- has a narrow spectrum of action; is highly effective against Gram (–) organisms, especially enterobacteria; is resistant to the action of β-lactamases;
- is well tolerated with minimal side effects: there is no cross sensitivity with the β-lactam antibiotics.

GLYCOPEPTIDES

Vancomycin is an antibiotic from the glycopeptides group:

- binds to the D-alanyl-D-alanine terminus of the glycopeptide polymer inhibiting a loss of the terminal D-alanine, inhibits cross-linking and weakens the cell wall of the microorganism;
- is bactericidal in action;
- has activity against Gram (+) organisms including those that produce penicillinase, some Gram (–) and anaerobic bacteria; is effective against methicillin-resistant staphylococci;
- is used for the parenteral administration in serious infections and orally in the treatment of pseudomembranous colitis; may be applied in patients with

serious allergy to β-lactams; is used prophylactically in dental patients as well as in patients with the prosthetic heart valves;

- may cause vancomycin flush syndrome (after rapid IV infusion) characterised by flushing, hypotension, tachycardia due to histamine release. Other adverse effects include hypersensitivity, chill, fever, rash, and, in high doses, ototoxicity and nephrotoxicity.

β-LACTAMASE INHIBITORS

Clavulanic acid, sulbactam, tazobactam are β-lactamase inhibitors. The spectrum of penicillins may be extended to include β-lactamase producing bacteria by the addition of agents which inhibit the lactamase enzyme and preserve the structural integrity of the β-lactam antibiotic. These will allow the use of penicillins in penicillase producing resistant organisms, but will not be beneficial in organisms with altered PBP characteristics.

ANTIBIOTICS – INHIBITORS OF PROTEIN SYNTHESIS

AMINOGLYCOSIDES

Aminoglycosides are compounds containing amino sugars joined to a hexose nucleus in glycosidic linkage (Fig. 31.4). They are polar compounds of polycationic structure and are used in the form of sulfates.

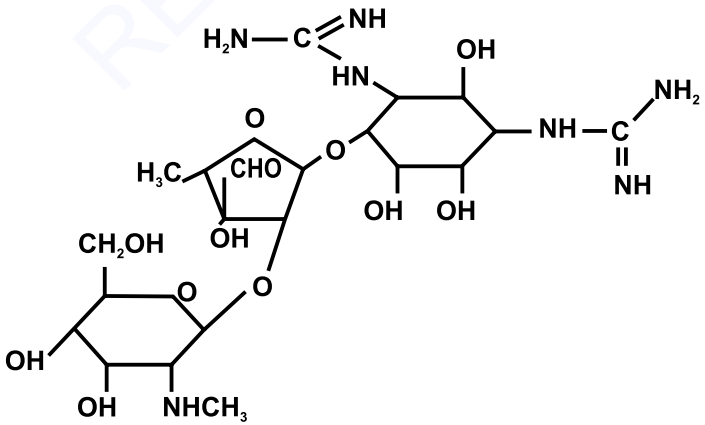

Fig. 31.4. Chemical structure of streptomycin

CLASSIFICATION

1. The 1st generation:
- Streptomycin;
- Neomycin;
- Kanamycin.

2. The 2nd generation:
- Gentamycin.

3. The 3rd generation:
- Amikacin.

Pharmacokinetics

- are not absorbed after the oral administration;
- must be given parenterally for a systemic effect;
- have limited tissue penetration;
- are distributed in all extracellular fluids, but tissue concentrations are low, except in the kidney and ear;
- cross the blood-brain barrier only in meningitis;
- are excreted with urine.

Mechanism of action

- aminoglycosides bind irreversibly to the 30S subunit of bacterial ribosomes (Fig. 31.5);
- they prevent the formation of an initiation complex with the messenger RNA;
- they reduce the rejection rate for tRNAs that are near matches for the codon. This leads to the misreading of the codons or premature termination of protein synthesis;
- aminoglycosides inhibit protein synthesis;
- they increase membrane leakage;
- they have bactericidal type of action;
- they are capable of exerting such a postantibiotic effect that their killing action continues when their plasma levels have declined below measurable levels;
- aminoglycosides have greater efficacy when administered as a single large dose than when given as multiple smaller doses;

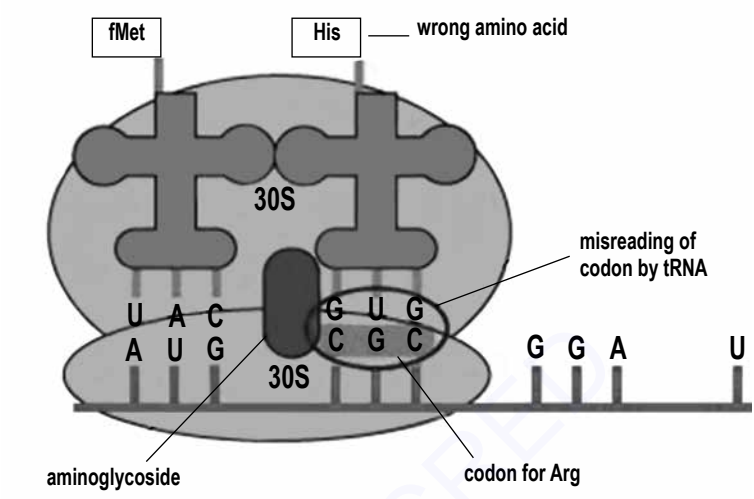

Fig. 31.5. Aminoglycosides' mechanism of action *(http://www.picsearch.com)*

- aminoglycosides transport into the cell can be enhanced by cell wall synthesis inhibitors that may be the basis of antimicrobial synergism.

Spectrum of action

The antibacterial spectrum is broad. It includes only aerobic organisms because anaerobes lack the oxygen requiring transport system. Aminoglycosides act on Gram (–) bacilli: *Proteus, Pseudomonas, Serratia, Escherihia coli, Klebsiela pneumoniae, Francisella tularensis, Yersinia pestis,* some Gram (+) cocci: enterococci, streptococci, some strains of *Staphylococcus.* Kanamycin, amikacin and streptomycin have some activity against *Mycobacterum tuberculosis.*

Resistance is connected with decreased uptake of the drug, an altered receptor for the binding of aminoglycoside to the 30S ribosomal subunit, and the plasmid associated synthesis of enzymes that modify and inactivate the antibiotic.

Indications

- pneumonia;
- chronic urinary tract infections;
- infections due to *Pseudomonas aeruginosa;*
- tularemia;
- tuberculosis.

Side effects

1. Ototoxicity.
2. Nephrotoxicity.
3. Neurotoxic effects including dysfunction of the optic nerve, neuromuscular junction blockade when aminoglycoside is given at high doses or in a combination with antidepolarizing drugs.
4. Allergic reactions.

PECULIARITIES OF PREPARATIONS

Streptomycin is effective against the organisms which cause plague, tularemia and, in a combination with penicillin, against Gram (+) enterococci and streptococci; suppresses tubercle bacilli; is used very seldom in tuberculosis, subacute bacterial endocarditis, tularemia, and plague, severe cases of brucellosis.

Neomycin is effective against many Gram (–) species and several Gram (+) bacteria (e.g., *Staphylococcus aureus*); because of its serious toxic effects, it is used topically to treat wounds. infected burns or skin diseases; can be used orally for the prevention of infection before gastrointestinal surgery or for the treatment of enterocolitis.

Gentamycin is bactericidal against a wide variety of Gram (–) organisms including *Proteus, Pseudomonas, Serratia,* and some strains of *Staphylococcus;* is used IM, IV, and topically in the treatment of many infections caused by: *Pseudomonas aeruginosa, Serratia, Enterobacter, Klebsiella;* methicillin-resistant staphylococci; is the most nephrotoxic among the aminoglycosides.

Amikacin has a spectrum of activity similar to that of gentamycin, but is often reserved for situations in which resistance to gentamycin emerges; is active against *Mycobacterium tuberculosis* and is an alternative preparation in this disease.

Kanamycin has a more limited spectrum of activity than gentamycin. It is ineffective against *Pseudomonas* and most Gram (–) organisms, but is active against *Mycobacterium tuberculosis* and can be used as 2nd-line preparation in this disease.

TETRACYCLINES

Tetracyclines contain 4 heterocyclic rings in their molecules (Fig. 31.6).

CLASSIFICATION

1. Natural:
   – Tetracycline.
2. Semisynthetic:

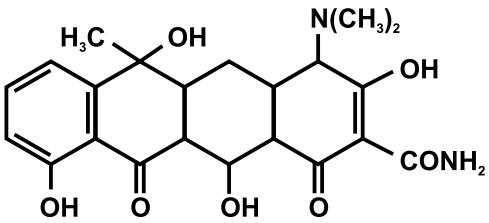

Fig. 31.6. Chemical structure of tetracyclines

– Doxycycline;
– Methacycline.

Pharmacokinetics

- are absorbed from the GI tract, particularly from the stomach and the upper small intestine: oral absorption is variable and may be impaired by food and multivalent cations (calcium, iron, aluminium);
- penetrate CNS, but the levels are insufficient for therapeutic efficacy;
- have a wide tissue distribution;
- cross the placental barrier and concentrate in fetal bones and dentition;
- undergo entero-hepatic cycling;
- concentrate in bones and dental bone, in the liver, and some malignant tumors. The drugs are deposited in the teeth and bones because of their chelating properties and form a tetracycline-calcium orthophosphate complex;
- are eliminated primarily in the urine; doxycycline is excreted mainly in feces.

Mechanism of action

- tetracyclines are transported into the microbial cell by transport proteins unique to the bacterial inner cytoplasmic membrane;
- the drugs bind to 30S ribosomal subunits;
- they block access of the amino acyl-tRNA to the mRNA-ribosome complex at the acceptor site and inhibit protein synthesis (Fig. 31.7);
- they interact with ions of bivalent metals and disturb tissue respiration in microbes; are the antagonists of riboflavin.
- they are bacteriostatic.
- resistance to tetracyclines is due to the inability of microbes to accumulate the drug as well as to the modification of the tetracycline binding site.

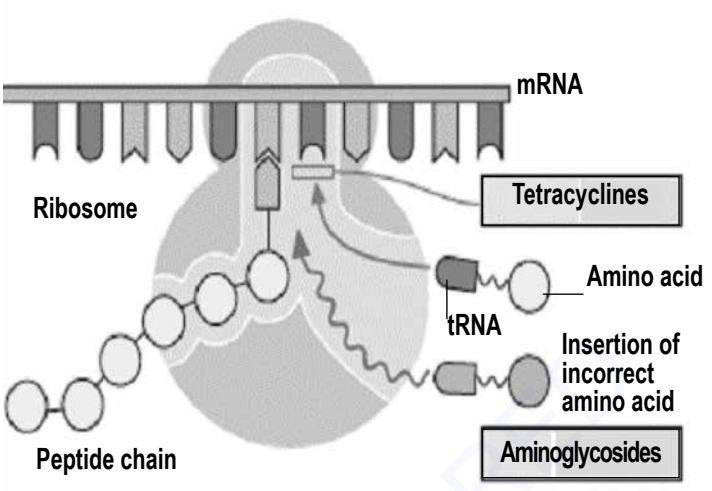

Fig. 31.7. Mechanism of action of tetracyclines in a comparison with the mechanism of action of aminoglycosides *(by H. Lüllmann, 2000)*

Spectrum of action

Tetracyclines are broad-spectrum antibiotics with activity against Gram (+) bacteria (*Corynebactrium acnes*), Gram (–) enteric rods, Gram (–) bacilli *(Haemophylus influenzae, Vibrio cholerae),* rickettsiae, chlamydiae, mycoplasma, spirochetes *(Borrelia burgdorferi, Treponema pallidum),* actinomyces, and some protozoa *(Amoebae)*.

Indications

- rickettsial infections including: Rocky Mountain spotted fever, Brill's disease, murine and scrub typhus;
- chlamydial infections (lymphogranuloma venereum, psittacosis, trachoma)
- mycoplasmal infections;
- bacillary infections (brucellosis, tularemia, cholera, some shigella and salmonella infections);
- venereal infections;
- amebiasis;
- lyme disease.

Side effects

1. Gastrointestinal disturbances.
2. Hepatic dysfunction.
3. Dermatitis, phototoxicity.
4. Teratogenic action ("tetracycline teeth").
5. Yellow-brown discoloration of the teeth and depressed bone growth if tetracyclines are given to children.
6. A pseudotumor of the brain.
7. Dysbacteriasis and superinfection which can result in staphylococcal enterocolitis, candidiasis, and pseudomembranous colitis.
8. Stomatitis, gingivitis.

Contraindications

1. Diseases of the liver and kidney.
2. Pregnancy.
3. Children younger than 8 years old.

PECULIARITIES OF PREPARATIONS

Tetracycline is administered orally 3–4 times daily or applied topically (ointment), has the bioavailability of 66%, binds to plasma proteins (65%), penetrates different tissues and body fluids, crosses the blood-brain barrier and placenta, is not metabolized, is excreted with urine (60%) and feces (20–30%).

Doxycycline is used in the form of hydrochloride; is administered orally and by IV infusion, binds to plasma proteins (90%), is metabolized in the liver, has a half-life of 18–24 hrs thus the preparation may be given once a day; developes high concentration in the eye, prostate, testis, uterus, urinary bladder, bile, liver, bones, teeth, lungs and lymphoid tissue; is excreted with urine (40% of the dose).

CHLORAMPHENICOLS

CHLORAMPHENICOL

Chloramphenicol (Levomycetin) is a nitrobenzene derivative (Fig. 31.8).

Pharmacokinetics

- is administered orally, applied topically (ointment, eye drops);
- is absorbed rapidly from the GI tract;
- undergoes entero-hepatic cycling;

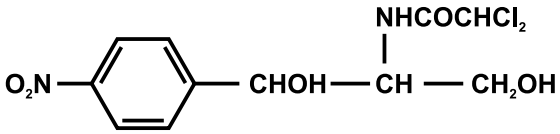

Fig. 31.8. Chemical structure of chloramphenicol

- is widely distributed in body fluids and reaches therapeutic levels in the cerebrospinal fluid; is also present in bile and milk;
- is metabolized in the liver by glucuronyl transferase;
- is excreted with urine in the form of metabolites.

Mechanism of action

- chloramphenicol binds to the 50S ribosomal subunit, blocks peptide synthetase and disturbs elongation of the peptide chain (Fig. 31.9);
- the drug is primarily bacteriostatic although it may be bactericidal to some strains.

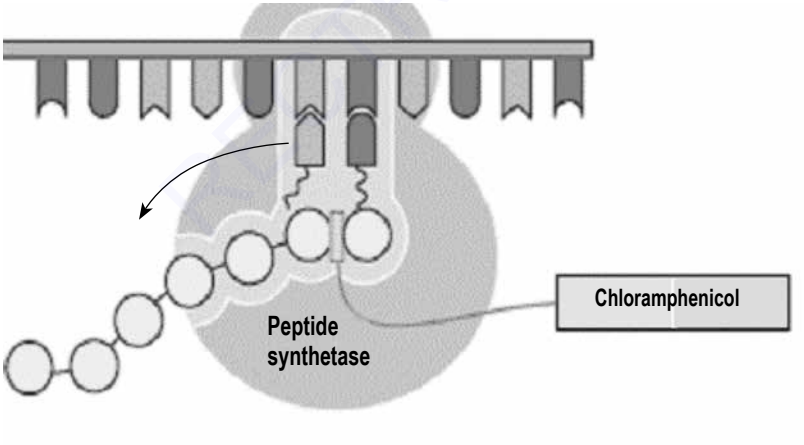

Fig. 31.9. Mechanism of action of chloramphenicol *(by H. Lüllmann, 2000)*

Spectrum of action

Chloramphenicol has a wide spectrum of antimicrobial activity including: many Gram (–) organisms; anaerobic organisms *(Bacteroides spp.)*; *Meningococcus,*

some strains of *Streptococcus* and *Staphylococcus* (at a high antibiotic concentration); spirochetes, *Clostridium, Chlamydia, Mycoplasma;* rickettsiae.

Indications

- typhoid fever and salmonella infections;
- bacterial meningitis;
- anaerobic infections;
- rickettsial diseases;
- brucellosis;
- infections of the skin and soft tissues;
- bacterial conjunctivitis;
- clamidial infections (trachoma).

Side effects

1. Allergic reactions.
2. The inhibition of leukopoesis and erythropoesis.
3. Superinfections including candidiasis and acute staphylococcal enterocolitis.
4. A gastrointestinal upset.
5. The gray-baby syndrome (this condition is seen in neonates, especially premature infants, who have been given relatively large doses of chloramphenicol. Cyanosis, respiratory irregularities, vasomotor collapse, abdominal distention, loose green stools, and an ashen-grey color of the skin characterize this often fatal syndrome. The condition develops because of the immature hepatic conjugating mechanism and the inadequate mechanism for renal excretion in neonates).
6. Endotoxic reactions.

MACROLIDES AND AZALIDES

Macrolides and azalides are the antibiotics that have a large lactone ring structure. These may be 14- or 16-membered rings.

CLASSIFICATION

1. The 1st generation:
   – Erythromycin.
2. The 2nd generation:
   – Azithromycin;

– Clarithromycin;
– Spiramycin.

ERYTHROMYCIN

Erythromycin is the first generation macrolide (Fig. 31.10). It was the first drug in this family.

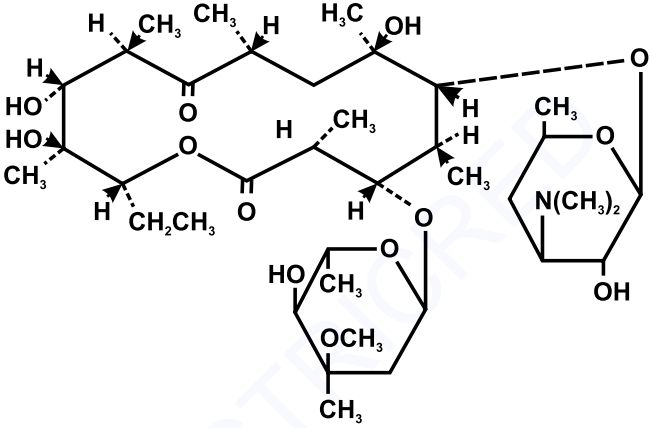

Fig. 31.10. Chemical structure of erythromycin

Pharmacokinetics

- is taken by mouth and applied topically (ointment);
- is destroyed by gastric juice, that's why erythromycin doses are given as either enteric coated or as more stable salts or esters;
- is very rapidly absorbed;
- is diffused into most tissues and phagocytes; due to the high concentration in phagocytes, it is actively transported to the site of infection where large concentrations of erythromycin are released during active phagocytosis;
- is metabolised by demethylation in the liver;
- is excreted with bile (mainly) and with urine (a small portion);
- has a half-life of 1.5 hrs.

Mechanism of action

- erythromycin binds to the 50S ribosomal subunit and inhibits peptidyl transferase activity;

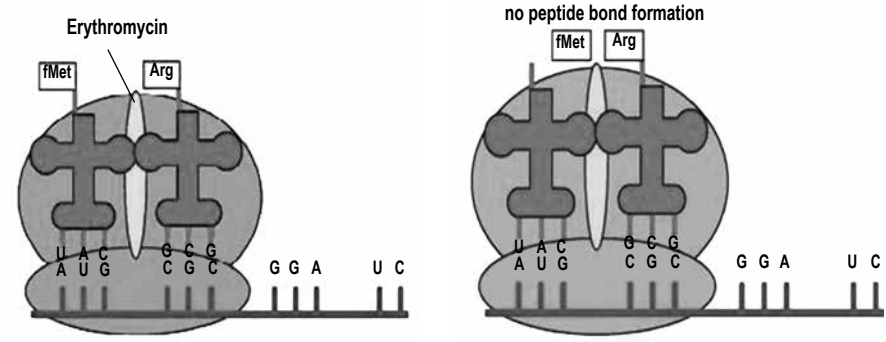

Fig. 31.11. Mechanism of action of erythromycin *(http://www.picksearch.com)*

- it blocks the translocation of peptidyl-tRNA from the acceptor site to the donor site. The incoming charged tRNA cannot access the occupied acceptor site, so the next amino acid cannot be added to the peptide chain (Fig. 31.11);
- it is usually bacteriostatic, but can be bactericidal in certain situations;
- resistance is connected with the inability of microbes to take up the antibiotic, decreased affinity of 50S ribosomal subunit for the antibiotic, and the presence of erythromycin esterase.

Spectrum of action

Erythromycin has activity against many species of *Campylobacter, Chlamydia, Mycoplasma, Legionella,* spirochetes, Gram (+) cocci, and some Gram (–) organisms. Its antimicrobial spectrum is similar to the spectrum of penicillin.

This drug is an alternative antibiotic to penicillin in patients who are allergic to β-lactam antibiotics.

Indications

- non-severe infections of the respiratory system, synusitis, otitis;
- pneumonia due to *Mycoplasma;*
- Legionnaires' disease;
- diphtheria;
- urogenital infection due to *Ureaplasma;*
- chlamydial infections;
- syphilis;
- acne.

Side effects

Erythromycin has a very low incidence of serious side effects:
1. Cholestatic hepatitis, jaundice.
2. Epigastric distress.
3. Ototoxicity (transient deafness).

Contraindications

1. Severe liver diseases.

PECULIARITIES OF OTHER PREPARATIONS

Clarithromycin is taken by mouth; is absorbed in the gut on 55% that does not depend on meals, is widely distributed in the body, except CNS, is metabolized in the liver with the formation of the active metabolite, is excreted with urine, has a half-life of 4 hrs; has an increased activity compared to erythromycin; is active against *Streptococcus agalactiae, Streptococcus pyogenes, Streptococcus viridans, Streptococcus pneumoniae, Haemophilus influezae, Neisseria gonorrhoeae, Listeria monocytogenes, Legionella pneumophila, Mycoplasma pneumoniae, Helicobacter pylori, Campilobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Moraxella catarrhalis, Bordetella pertussis, Propionibacterium acnes, Mycobacterium avium, Mycobacterium leprae, Staphylococcus aureus, Ureaplasma urealyticum, Toxoplasma gondii;* is used to treat bronchitis, pneumonia (including mycoplasmial atypical pneumonia), infections of the nose, ear, and throat, synusitis, infections of the skin and soft tissues, is prescribed for the eradication of *Helicobacter pylori.*

Azithromycin is administered orally with bioavailability of 37% due to first-pass-metabolism; develops maximal concentration in 2.5–3 hrs, displays tissues concentration exceeding that in the blood plasma in 10–100 times; concentrates in phagocytes; has a half-life of 14–20 hrs, is metabolized in the liver; is excreted with urine unchanged (50%) and in the form of metabolites; has an increased activity as compared to erythromycin; has a broad spectrum of action which is similar to the spectrum of clarithromycin; does not act on microbes resistant to erythromycin; has indications like clarithromycin; is well tolerated.

Spiramycin a natural antibiotic, the first representative of 16-member macrolides. It is administered orally and IV. Absorption for oral administration is incomplete; bioavailability is 33–39%, reaches high concentrations in the lungs, bronchi, tonsils, sinuses, and pelvic organs of women. An increased concentration is also found in bile, polymorphonuclear neutrophils and macrophages. Unlike

other macrolides, the metabolism is unrelated to the cytochrome P-450 system. 80% of a dose is excreted with bile. It acts bacteriostatically, but can act bactericidally at high doses: suppresses protein synthesis in the microbial cell due to reversible binding to the ribosome 50S subunit. In contrast to the 14-member macrolides, has a longer antibacterial effect. Spiramycin has immunomodulatory properties characterized by an increase in the neutrophils phagocytic activity, a decrease in the lymphocytes transformation, and an increase in the production of interleukin-6. The drug is characterized by prolonged post-antibiotic effect as well as pro-antibiotic effect. Spiramycin is present in the cells in the active state, as a result of which there is a high clinical effectiveness even in the case of infections caused by microorganisms that are weakly susceptible to it *in vitro* – "spiramycin paradox". Spectrum of action includes: *Streptococcus pyogenes, Streptococcus viridans, Corynebacterium diphtheriae, Staphylococcus aureus, Streptococcus pneumoniae, Enterococcus, Neisseria meningitidis, Bordetella pertussis, Campylobacter, Clostridium, Haemophilus influenzae, Neisseria gonorrhoeae, Mycoplasma pneumoniae, Chlamydia trachomatis, Toxoplasma gondii, Legionella pneumophila, Spirochaetes.* Indications are toxoplasmosis, bacterial infections (second line drug) caused by sensitive microorganisms; prevention of meningococcal meningitis among persons who have been in contact with patients, prevention of acute joint rheumatism, treatment of bacterial carriage of pertussis and diphtheria. Possible side effects are nausea, vomiting, diarrhea, allergic reactions, cholestatic hepatitis, acute colitis, and ulcerative esophagitis.

LINCOSAMIDES

The lincosamides include ***lincomycin*** (Fig. 31.12) and ***clindamycin***.

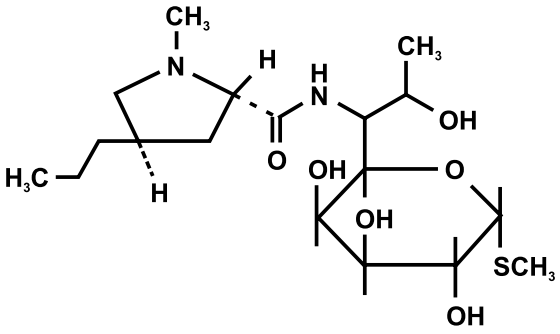

Fig. 31.12. Chemical structure of lincomycin

- are administered orally and parenterally, penetrate most tissues including bone, concentrate in phagocytic cells, pass through the placental barrier, are metabolized in the liver and excreted with urine;
- bind to the 50S ribosomal subunit and block peptide bond formation; have bacteriostatic type of action;
- are very active against staphylococci, streptococci, and obligate anaerobic pathogens;
- are used to treat infections of bones (osteomyelitis), respiratory organs, the urinary tract, anaerobic abdominal infections caused by bacteroides. Clindamycin is also used in ulcer disease;
- may cause side effects, such as pseudomembranous colitis resulting in diarrhea, abdominal pain, fever, and admixtures of the mucus and blood in the stool; allergic reactions.

STEROIDS

Fusidic acid (or Fusidin-sodium) is an antibiotic of steroid structure:

- is a protein synthesis inhibitor, acts by preventing the translocation of peptidyl tRNA;
- influences Gram (+) microbes (*Staphylococcus* and *Streptococcus*);
- is osteotropic;
- is an alternative antibiotic to treat Gram (+) infections;
- is usually administered in a combination with another antibiotic because of easily selected resistant mutants during monotherapy with the fusidic acid.

ANTIBIOTICS WHICH DISTURB FUNCTIONS OF NUCLEIC ACIDS

RIFAMICINS

Rifampin (Rifampicin) belongs to the group of complex macrocyclic antibiotics (Fig. 31.13).

Pharmacokinetics

- is given orally;
- is well absorbed in the GI tract;
- is distributed to most body tissues including CNS;
- undergoes entero-hepatic cycling and is partially metabolized in the liver; is the inducer of microsomal oxidation;
- is eliminated mainly in feces (both free drug and metabolites).

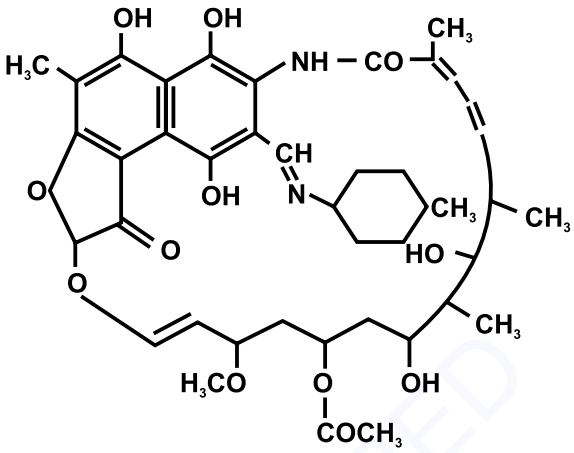

Fig. 31.13. Chemical structure of rifampin

Mechanism of action

It inhibits the RNA synthesis in bacteria and chlamydia by binding to DNA-dependent-RNA polymerase (Fig. 31.14).

Fig. 31.14. Mechanism of action of rifampin

Spectrum of action

Most Gram (+) and many Gram (–) microorganisms are susceptible to rifampin. It is highly effective against *Mycobacterium tuberculosis, Mycobacterium leprae*. Prolonged administration of the drug as the single therapeutic agent promotes the emergency of highly resistant organisms.

Indications

- tuberculosis (in a combination with other agents);
- atypical mycobacterial infections;
- leprosy;
- bacterial infections caused by susceptible microbes: pneumonia, cholecystitis, osteomyelitis, etc (as an alternative antibiotic).

Side effects

1. Red discoloration of urine, sweat, tears, and contact lenses.
2. Proteinuria and impaired antibody response.
3. Changes in the half-life of a number of co-administered drugs metabolized by cytochrome P-450 system.
4. Rash.
5. Gastrointestinal disturbances.
6. Renal damage.
7. Jaundice and severe hepatic dysfunction.

ANTIBIOTICS INFLUENCING STRUCTURE OF CELL MEMBRANES

POLYENES

Nystatin and Amphotericin B are polyene antibiotics. Their chemical structure is like that of unsatureted fatty acids (Fig. 31.15). These antibiotics are antifungals and decribed also in Chapter 30.

Mechanism of action

- the drugs are fungistatic and fungicidal;
- they bind to sterols, especially ergosterol which is present in the membrane of fungi. As a result, the drugs appear to form channels in the membrane which allow small molecules to leak out of the cell. This disturbs the chemical intracellular contents.

PECULIARITIES OF PREPARATIONS

Nystatin is poorly absorbed from the GI tract; is used orally and topically; has a narrow spectrum of action; influences *Candida albicans;* is used to treat *Candida*

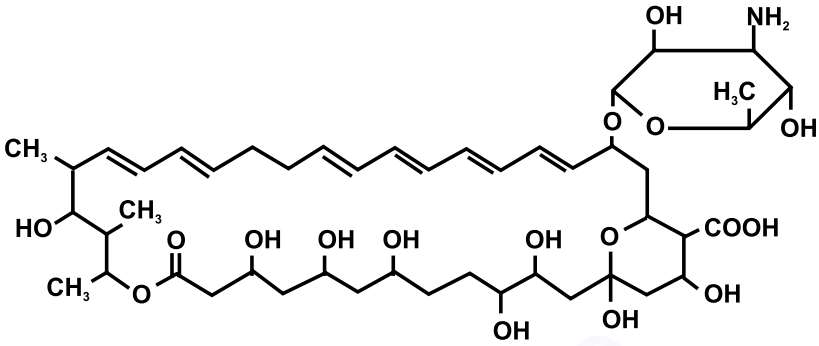

Fig. 31.15. Chemical structure of nystatin

infections of the skin, mucous membranes, and intestinal tract: thrush (oral candidiasis) and vaginitis are treated by topical application, whereas intestinal candidiasis is treated by the oral administration; is well tolerated.

Amphotericin B is administered by IV infusion and applied topically; is a broad-spectrum antifungal agent effective against *Histoplasma capsulatum, Cryptococcus neoformans, Coccidioides immitis, Candida spp.*, *Blastomyces dermatitidis,* some strains of *Aspergillus* and *Sporotrichum;* it is the most effective drug available for systemic fungal infections; it is frequently used for the treatment of life-threatening fungal infections in patient with impaired defence mechanisms; pulmonary, cutaneous, and disseminated forms of blastomycosis, acute pulmonary coccidioidomycosis, pulmonary histoplasmosis, *Cryptococcus neoformans* infections, candidiasis, including disseminated forms; may cause side effects, such as hypersensitivity reactions, anaphylaxis, fever, chill, headache, gastrointestinal disturbances; decreased renal function (in over 80% of patients treated with amphotericin B), anemia, and thrombophlebitis.

POLYPEPTIDES (POLYMYXINS)

Polymyxins M and B are polypeptides used in the form of sulfates.

Mechanism of action

- polymyxins interact with a specific lipopolysaccharide component of the bacterial cell membrane;
- the membrane lipid structure is distorted with an increase in permeability to polar molecules resulting in the marked changes in the cell metabolism.

Spectrum of action

The spectrum of action is narrow and includes Gram (–) bacteria *(Pseudomonas aeruginosa, Salmonella, Shigella, Escherihia coli, Pasteurella, Brucella, Haemophilus influenzae, etc.)*.

PECULIARITIES OF PREPARATIONS

Polymyxin M is not absorbed in the GI tract; is administered orally (for the action in the gut) and topically, is used to treat infected burns, wounds, skin diseases, intestinal infections, for the sterilization of bowels before surgeries; the topical administration of polymyxin M is not accompanied by denominated side effects.

Polymyxin B is administered parenterally; its clinical usage is limited to the therapy of resistant Gram (–) infections. Polymixin B is used in severe infections caused by Gram (–) bacilli: meningitis, sepsis or peritonitis; if it is absorbed into the systemic circulation, adverse effects include neurotoxicity (paresthesias, dizziness, ataxia) and acute renal tubular necrosis (hematuria, proteinuria, nitrogen retention).

TESTS FOR SELF-CONTROL

1. The most long-acting cephalosporin of 3rd generation is:
A. Cefalexin
B. Cefasolin
C. Ceftriaxone
D. Cefaclor
E. Cefpirome.

2. All the concerning the mechanism of action of penicillins is true, except:
A. They inhibit cell wall synthesis
B. They inhibit transpeptidase
C. They have a bactericidal action
D. They cause disturbances of the structure and function of the cell membrane
E. They act on microbes in the growth phase.

3. Erythromycin is:
A. Destroyed by the gastric acid
B. Destroyed by intestinal enzymes
C. Entered the phagocytes

D. Crossing blood-brain barrier
E. Mainly excreted with bile.

4. Tetracycline is stored in the body in:
A. The liver
B. Some malignant tumors
C. Hairs, nails, skin
D. Bones and dentition
E. Fat tissue.

5. A 6-year old boy was admitted to the hospital with pneumonia. The treatment with amoxicillin was not effective. Bacterial analysis revealed mycoplasmial pneumonia. Choose the most suitable drug for the treatment of this child.
A. Tetracycline
B. Azithromycin
C. Bicillin-5
D. Nystatin
E. Oxacillin.

Answers

1 – C; 2 – D; 3 – A, C, E; 4 – A, B, D; 5 – B.

Chapter 32 ANTISPIROCHETAL DRUGS. ANTIMYCOBACTERIAL DRUGS. ANTIVIRAL AGENTS

SPIROCHETAL INFECTIONS AND THEIR TREATMENT

Syphilis is one of the most widely spread spirochetal infections caused by *Treponema palidum.* It is a chronic infection developed in few stages from the primary tissue affect to the systemic disorders in the CNS and other organs.

ANTISPIROCHETAL DRUGS

Drugs for the treatment of syphilis and other spirochetal infections are named ***antispirochetal drugs.***

CLASSIFICATION

A. *Antibiotics:*

1. Basis antibiotics:
   - Benzylpenicillin sodium;
   - Benzathine benzylpenicillin (Bicillin-1);
   - Benzathine benzylpenicillin + benzylpenicillin (Bicillin-5).
2. Alternative antibiotics:
   - Cefaloridine;
   - Erythromycin;
   - Chloramphenicol (Levomycetin).

B. *Bismuth preparations:*

- Bijochinol.

ANTISPIROCHETAL ANTIBIOTICS

Benzylpenicillin sodium is the inhibitor of cell wall synthesis with a short duration of action and a narrow spectrum. It is effective against *Treponema palidum* and used as a basic antibiotic in syphilis.

Bicillins are long-acting natural penicillins which have a narrow spectrum of action and are administered IM once a week (Bicillin-1) or once a month (Bicillin-3) for the treatment of syphilis.

Cefaloridine is the 1st generation cephalosporin. It is the inhibitor of cell wall synthesis with a wide spectrum of action. It is an alternative preparation in syphilis.

Erythromycin is a macrolide antibiotic. It is a protein synthesis inhibitor whose spectrum of action is similar to the spectrum of benzylpenicillin. It is used as an alternative antibiotic in patients hypersensitive to basis antibiotics.

Chloramphenicol is a wide spectrum antibiotic, a protein synthesis inhibitor. It may be used as an alternative antibiotic in syphilis.

BISMUTH PREPARATIONS

BIJOCHINOL

- is a compound between bismuth, iodine and quinine suspended in *Oleum Persicorum;*
- is administered IM once per 3 days, accumulates in the body; is excreted with urine and saliva;
- interacts with SH-groups of enzymes and has a bacteriostatic action on *Treponema palidum;*
- is indicated for all stages of syphilis (together with benzylpenicillin), non-syphilitic encephalitis and myelitis;
- may cause grey spots on gums, stomatitis and renal disturbances;
- is contraindicated in patients with renal failure and diseases of the oral mucosa.

TUBERCULOSIS AND ITS THERAPY

Tuberculosis is a chronic infection caused by *Mycobacterium tuberculosis*. The treatment of tuberculosis is a serious problem due to some peculiarities of mycobacteria, such as:

- a slow growth;
- the ability to be dormant and completely resistant to many drugs;

- the impermeability of the mycobacterial cell wall to many agents;
- the persistence in macrophages;
- the development of resistance to any single drug.

General principles of chemotherapy of tuberculosis

- to begin the therapy with the 1st line drugs;
- to use the 2nd line preparations after the development of drug resistance in microbes;
- to apply 2–3 preparations together to delay or prevent the emergency of resistant strains;
- to carry out a long lasting treatment (6–24 months);
- to continue the regimen after the disappearance of clinical disease to eradicate any persistant organisms;
- to carry out laboratory monitoring of the efficacy of treatment.

ANTIMYCOBACTERIAL DRUGS

Antimycobacterial drugs are preparations to treat tuberculosis. Some of the most active drugs are effective in leprosy.

CLINICAL CLASSIFICATION OF ANTIMYCOBACTERIAL DRUGS

There are 2 groups of antimycobacterial drugs: the 1st line and the 2nd line preparations (Fig. 32.1). The 1st line preparations have high efficacy and low to-

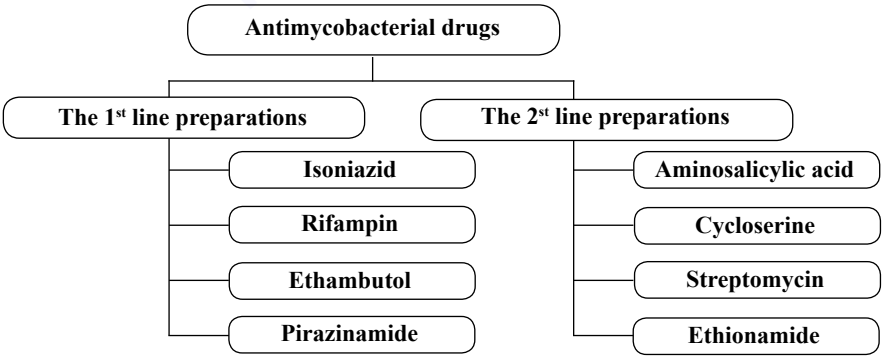

Fig. 32.1. Classification of antimycobacterial drugs according to their activity

xicity. The efficacy of the 2nd line preparations is lower, but they act on resistant strains of mycobacteria.

ISONIAZID (INH)

It is a hydrazide of the isonicotinic acid, a synthetic analogue of pyridoxine (Fig. 32.2). Isoniazid is the most potent antitubercular agent.

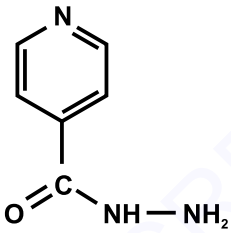

Fig. 32.2. Chemical structure of isoniazid

Pharmacokinetics

- is administered orally, IM, IV; absorption after the oral administration is impaired by food and antacids;
- diffuses into the whole body: infected tissues tend to retain the drug longer
- penetrates CNS;
- is metabolized in the liver by acetylation and hydrolysis; acetylation is genetically regulated: the fast acetylator trait is autosomal dominant (Fig. 32.3);
- is excreted with urine, parthialy with saliva, sputum, and milk.

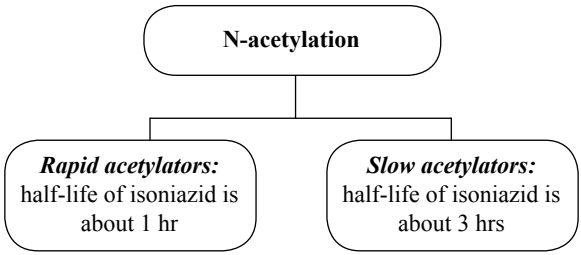

Fig. 32.3. Groups of patients according to speed of isoniazid's acetylation

Mechanism of action

- It disturbs the synthesis of the mycolic acids which are an important constituent of the mycobacterial cell wall.
- It competes with vitamins B_6, B_1, PP.
- For bacilli in the stationary phase, isoniazid is bacteriostatic; for dividing bacilli, it is bactericidal.
- Isoniazid is effective against extracellular as well as intracellular bacteria.
- When it is used alone, resistant organisms rapidly emerge.

Spectrum of action

Mycobacterium tuberculosis

Indications

It is used for all forms of diagnosed tuberculosis.

Side effects

1. Hypersensitivity.
2. Peripheral neuritis (paresthesia).
3. Mental abnormalities, psychotic episodes, euphoria and convulsions.
4. Optic neuritis.
5. Hepatitis.

Neurological side effects are due to the competition to B_6 and pyridoxine deficiency.

PECULIARITIES OF OTHER PREPARATIONS

RIFAMPIN

It is a wide-spectrum antibiotic produced by *Streptomyces*. The drug interacts with DNA-dependent-RNA polymerase, suppresses the initiation step of transcription in procaryotes. It is bactericidal for both intracellular and extracellular mycobacteria. Rifampin is the 1st line preparation in tuberculosis and the most effective antileprosy drug. For detail information – see Chapter 31.

PYRAZINAMIDE

- is a pyrazine analogue of nicotinamide;
- is taken orally and widely disrtributed in the body, penetrates the CNS;

- is transformed into the active form (the pyrazinoic acid);
- has an unknown mechanism of action (probably the inhibition of oxygen dependent mycolic acid synthesis); acts on extra- and intracellular mycobacteria;
- is the 1st line antitubercular preparation; is widely used in the multi-agent short-term therapy of uncomplicated pulmonary tuberculosis;
- may cause the liver dysfunction and urate retention.

ETHAMBUTOL

- is taken orally and widely disrtributed in the body, penetrates the CNS;
- is an ethylenimine derivative, blocks nucleic acids synthesis and inhibits arabinozyl transferases involved in the synthesis of arabinogalactan, a component of the mycobacterial cell wall;
- is a bacteriostatic antitubercular agent;
- is the 1st line antitubercular preparation;
- may cause optic neuritis, a loss of ability to discriminate between red and green.

ALTERNATIVE SECOND LINE DRUGS

Aminosalicylic acid is a competitive inhibitor of PABA in the folate metabolism, is bacteriostatic, is taken in a high dose (10–15 g per day) and causes many side effects (dyspepsia, crystalluria, the enlargement of the thyroid gland), is used rarely.

Ethionamide is a structural analogue of isoniazid, inhibits acetylation**,** may cause side effects, such as hepatotoxicity, gastric irritation, peripheral and optic neuritis.

Cycloserine is an antibiotic-inhibitor of the cell wall synthesis, is toxic; may cause CNS and peripheral neurological disturbances.

Streptomycin is an aminoglycoside antibiotic, the inhibitor of protein synthesis, is used in a drug combination for the treatment of life-threatening tuberculosis disease (meningitis, miliary dissemination, severe organ tuberculosis).

Amikacin is an aminoglycoside antibiotic, is used for the treatment of tuberculosis caused by streptomycin-resistant strains, is applied in the combination drug regimen.

Ciprofloxacine, ofloxacine are fluoroquinolones, block DNA gyrase, are used as the 2nd line preparations in the combination drug regimen.

VIRAL INFECTIONS AND THEIR CHEMOTHERAPY

Viruses are obligate intracellular parasites. A mature virus (virion) can exist outside a host cell, but to reproduce, the virus must enter the host cell and direct

this cell to make new viral particles. Viruses are composed of a nucleic acid (core) enclosed by a protein coat (capsid). Viral cores can contain either DNA or RNA (DNA viruses or RNA viruses). Examples of DNA viruses and the diseases produced by them include herpesviruses (cytomegalovirus, chickenpox, shingles), adenoviruses (colds, conjunctivitis), hepadnaviruses (hepatitis B), etc. Pathogenic RNA viruses are arborviruses (tick-borne encephalitis, yellow fever), arenaviruses (Lassa fever, meningitis), orthomyxoviruses (influenza), paramyxoviruses (measles, mumps); picornaviruses (polio, meningitis, colds), rhabdoviruses (rabies); rubella virus (German measles), coronaviruses (severe atypical respiratory syndrome, COVID-19) and retroviruses (AIDS).

Life cycle of viruses consists of five phases: attachment and penetration, uncoating, synthesis of viral components, assembly of virus particles, and release of the virus. Following the release of their genome in the cell, the DNA viruses transcribe the immediate-early genes. These genes code for regulatory proteins that in turn initiate the transcription of the early genes responsible for viral genome replication. After the viral DNA is replicated, the late genes are transcribed and translated, producing proteins required for the assembly of the new virions. RNA viruses have other strategies for genome replication and protein expression. Certain RNA viruses contain enzymes that synthesize mRNA using their RNA as a template; others use their own RNA as mRNA. The retroviruses use viral reverse transcriptase to produce DNA using viral RNA. The newly synthesized DNA integrates into the host genome and is transcribed into mRNA and genomic RNA for progeny virions. The viral components are assembled to form a mature virus particle. Release of the virus from the host cell may be rapid and produce cell death or slow allows the host cell to survive.

COMMON APPROACHES OF ANTIVIRAL THERAPY

Three main approaches are used to control viral diseases: vaccination, antiviral chemotherapy, and stimulation of host non-specific resistance:

- vaccination is used to prevent many viral infection (measles, rubella, mumps, poliomyelitis,etc), but the usefulness of vaccines is limited when many stereotypes are involved or when the infection has been established. Passive immunization with human immune globulin or antiserum can be used to assist the body's own defense in the last case;
- the chemotherapy of viral infections may involve interference with any of the steps in the viral replication cycle. Viruses have some specific enzymes which can be the targets for antiviral drugs (e.g., reverse transcriptase, HIV-specific protease, DNA polymerase). Because viral replication and host cell

processes are closely linked, the main problem is finding a drug that is selectively toxic to the virus;
- stimulation of host resistance mechanisms is the least used strategy. Interferons as natural antiviral substances, their analogues made by biotechnology, and interferons inductors are proposed for this purpose.

ANTIVIRAL AGENTS

Antiviral drugs are preparations for the treatment of viral infections.

CLASSIFICATION

According to the mechanism of action

1. Inhibitors of attachment to the host cell or penetration into the host cell:
   – Amantadine;
   – Rimantadine.
2. Inhibitors of DNA polymerase:
   – Acyclovir;
   – Gancyclovir;
   – Famcyclovir;
   – Valacyclovir;
   – Vidarabine.
3. Inhibitors of RNA-dependent RNA polymerase:
   – Ribavirin;
   – Remdesivir
4. Reverse transcriptase inhibitors:
   – Zidovudine (Azidothymidine, AZT);
   – Didanosine;
   – Zalcitabine.
5. HIV protease inhibitors:
   – Saquinavir;
   – Ritonavir;
   – Nelfinavir;
   – Amprenavir;
6. Neuroaminidase inhibitors:
   – Zanamivir;
   – Oseltamivir.
7. Interferons and intrferon synthesis inductors:
   – Laferon (IFN-α-2β).

According to the clinical usage

1. For influenza and respiratory virus infections:
   – Amantadine, Rimantadine;
   – Zanamivir and other neuroaminidase inhibitors.
2. For herpes and cytomegalovirus infection:
   – Acyclovir and other inhibitors of DNA polymerase.
3. For viral hepatitis, hemorrhagic fevers, Ebola and coronavivus disease:
   – Ribavirin and other inhibitors of RNA polymerase.
4. For HIV infection:
   – Zidovudine and other reverse transcriptase inhibitors;
   – Sanquinvir and other HIV protease inhibitors.
5. Preparations with a wide antiviral spectrum:
   – Laferon and other interferons.

PREPARATIONS FOR TREATMENT OF INFLUENZA

RIMANTADINE

It is a midantan derivative, structurally related to amantadine.

Pharmacokinetics

- is taken orally;
- does not penetrate CNS;
- is concentrated in the cells of epithelium of the upper respiratory pathways;
- is metabolized in the liver; has elimination half-life averages 25 hrs in young adults and 32 hrs in the elderly;
- is excreted with urine as a parent drug and metabolites.

Mechanism of action

The drug blocks the viral membrane matrix protein M_2 which functions as an ion channel (it is required for the fusion of the viral membrane with the cell membrane) (Fig. 32.4).

It also inhibits the viral assembly and the release of new virions.

Spectrum of action

The virus of influenza A (both three antigenic subtypes of influenza A (H_1N_1, H_2N_2 and H_3N_2) and have negligible activity against influenza B), the virus of encephalitis.

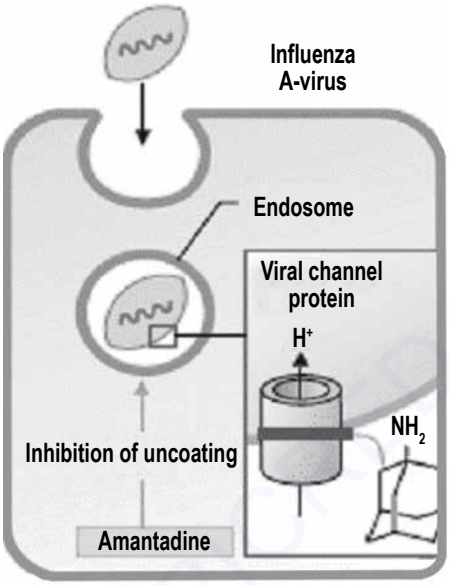

Fig. 32.4. Mechanism of action of midantan derivatives *(by H. Lüllmann, 2000)*

Indications

- the treatment of influenza A;
- the prevention of influenza (when vaccination is contraindicated or early vaccination is not possible, rimantadine can protect 70–90 % of patients from influenza A infection);
- the prophylaxis of epidemic encephalitis.

Side effects

1. Headache.
2. Hallucinations.
3. Ataxia.
4. Disturbances of speesh.
5. Insomnia.
6. Confusion.
7. Seizures.

PECULIARITIES OF OTHER DRUGS

Amantadine is structurally similar to rimantadine, crosses the blood-brain barrier; does not metabolized in the body; has antiparkinsonian action; displays side effects associated with CNS; should be employed cautiously in patients with psychiatric problems, epilepsy, cerebral atherosclerosis, renal failure and pregnancy.

Zanamivir (Relenza) is a potent and highly selective inhibitor of neuraminidase, the surface enzyme of the influenza virus which releases viral particles from the infected cell and speeds up their penetration through the mucosal barrier to other respiratory cells. It is administered by oral inhalation 2 times a day, has low bioavailability, is precipitated in the airways at high concentrations, is excreted unchanged by the kidneys for 24 hrs. Zanamivir acts in the extracellular space, reducing the reproduction of influenza virus, is used for the treatment and prevention of influenza type A and B, can cause bronchospasm, skin rash, allergic reactions as side effects.

Oseltamivir (Tamiflu) is taken orally, has bioavailability over 80% and a half-life about 1–3 hrs (for its active metabolite $T_{1/2}$ = 6–10 hrs), is excreted with urine as the active metabolite. The drug is used to treat and prevent influenza A and influenza B, it is recommended in people who are at high risk of complications within 48 hrs of first symptoms of infection. It may cause such side effects as nausea, vomiting. headache, psychiatric events, seizures, confusion, heart arhythmia, hepatitis and elevated liver enzymes, rash, allergic reactions, aggravation of diabetes, hemorrhagic colitis, and Stevens–Johnson syndrome.

PREPARATIONS FOR TREATMENT OF HERPES AND CYTOMEGALOVIRUS INFECTION

ACYCLOVIR

It is a synthetic purine nucleoside analogue (acycloguanosine) (Fig. 32.5).

Pharmacokinetics

- is administered orally, IV, or topically;
- is widely distributed through the body; the plasma half-life of acyclovir is 3–4 hrs;
- penetrates CNS; significant amounts may be found in amniotic fluid, placenta, and breast milk;
- is partially metabolized and excreted with urine.

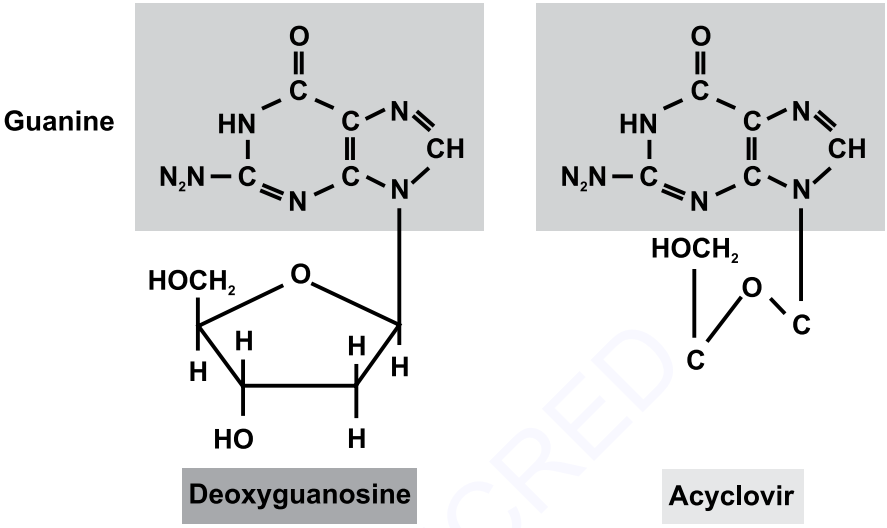

Fig. 32.5. Structural resemblance between acyclovir and guanine-containing nucleotide *(http://www.picsearch.com)*

Mechanism of action

- acyclovir is converted to its active metabolite via three phosphorylation steps. First, viral thymidine kinase converts it to acyclovir monophosphate. Next, host cell enzymes convert the monophosphate to the diphosphate and then to the triphosphate. Because viral thymidine kinase has a much greater affinity for acyclovir triphosphate than does mammalian enzyme, it accumulates only in virus-infected cells;
- the active metabolite of acyclovir acts as a competitive inhibitor for the incorporation of deoxyguanosine triphosphate (dGTP) into the viral DNA (Fig. 32.6);
- acyclovir incorporated into viral DNA acts as a chain terminator. Viral DNA polymerase becomes irreversibly bound to an acyclovir-terminated DNA chain and is unavailable for further replicative activity;
- the effect of acyclovir on host cell DNA synthesis is much smaller than its effect on the viral enzyme;

Spectrum of action

Herpes simplex virus types I and II, *Varicella-zoster virus*, *Epstein-Barr virus*, *Cytomegalovirus*.

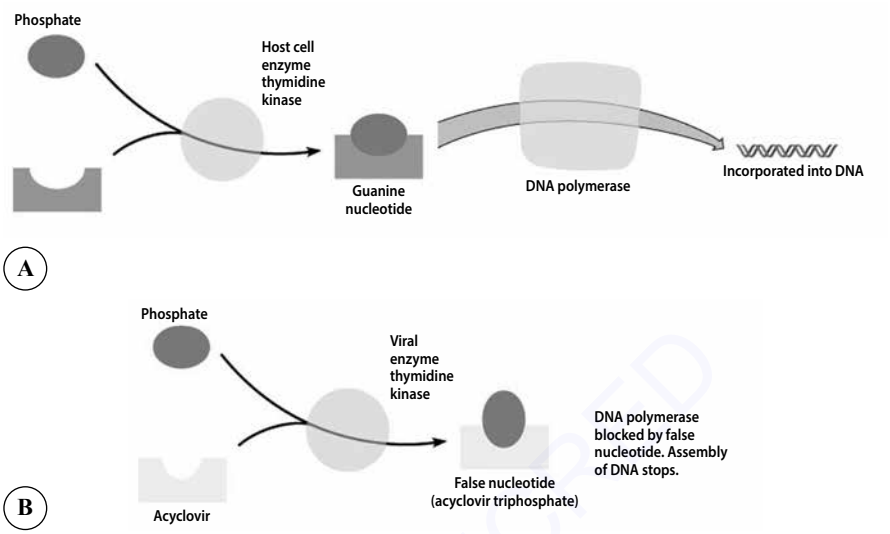

Fig. 32.6. Mechanism of acyclovir's action:
A – synthesis of normal viral DNA guanine nucleotide; B – synthesis of false viral DNA nucleotide with acyclovir *(adapted from http://www.picsearch.com)*

Indications

- primary mucocutaneous herpes infection, including herpes infection in immunocompromised individuals;
- recurrent mucocutaneous herpes infection;
- herpes genitalis;
- herpes simplex encephalitis;
- prophylaxis of herpes infection before and after tissue transplantation (in seropositive patients);
- neonatal herpes;
- lesions due to Varicella zoster virus;
- chickenpox treatment and prophylaxis in highrisk individuals.

Side effects

1. Local discomfort, itch (after the topical application)
2. Nausea, vomiting
3. Headache, encephalopathy (after the IV administration)
4. Nephrotoxicity.

PECULIARITIES OF OTHER PREPARATIONS

Gancyclovir is an acyclic analogue of 2-deoxyguanosine with inhibitory activity toward all herpesviruses, especially cytomegalovirus; is up to 100-fold more concentrated in cytomegalovirus-infected cells than in normal cells; is used for the treatment of cytomegalic retinitis in immune suppressed patients.

Famcyclovir is a diacetyl ester prodrug of the acyclic guanosine analogue 6-deoxypenciclovir; has a mechanism of action similar to that of acyclovir, but does not cause chain termination; is indicated for the treatment of acute herpes zoster; herpes simplex in immunocompetent patients, is approved for the treatment and prophylaxis of recurrent genital herpes and recurrent mucocutaneous herpes in HIV-infected individuals.

Valacyclovir is a prodrug converted to the active drug acyclovir via intestinal and hepatic first-pass metabolism, has greater bioavailability than acyclovir (the bioavailability of acyclovir following oral valacyclovir dosing is 3-5 times that resulting from oral acyclovir administration and is comparable to that of IV acyclovir). The drug is predominantly active against *Herpes simlex virus*, and to a lesser extent *Varicella zoster virus*, is only of limited efficacy against *Epstein – Barr virus* and *Cytomegalovirus* (however, valacyclovir has recently been shown to eliminate the presence of *Epstein – Barr* virus in subjects afflicted with acute mononucleosis), can prevent the establishment of viral latency This preparation is not approved for use in immunocompromised individuals or for the therapy of disseminated herpes zoster.

Vidarabine (ara-A) is an adenine nucleoside analogue containing arabinose in place of ribose. It has activity against herpeviruses, poxviruses, hepadnaviruses, rhabdoviruses, and certain RNA tumor viruses. Cellular enzymes convert this drug to a triphosphate that inhibits DNA polymerase activity and acts as a chain terminator. Vidarabine also nhibits ribonucleoside reductase and other enzymes. The principal use of a drug is the treatment of herpetic keratoconjunctivitis.

PREPARATIONS FOR TREATMENT OF VIRAL HEPATITIS

RIBAVIRIN

Ribavirin is an antiviral medication administered orally. Is a prodrug.

Pharmacokinetics

Ribavirin is administered IV, orally or as an aerosol when has only minimal systemic absorption. Oral absorption is rapid and oral bioavailability is 64%. It is

metabolized in the liver to a triazole carboxylic acid metabolite that is eliminated in the urine along with the parent compound.

Mechanism of action

- It is a guanosine analogue used to stop viral RNA synthesis and viral mRNA capping, thus, it is a nucleoside inhibitor. For the RNA viruses, when ribavirin is incorporated into RNA, as a base analogue of either adenine or guanine, it pairs equally well with either uracil or cytosine, inducing mutations in RNA-dependent replication in RNA viruses. Such hypermutation can be lethal to RNA viruses.
- For DNA viruses, ribavirin 5'-monophosphate inhibits cellular inosine monophosphate dehydrogenase, thereby depleting intracellular pools of GTP, but the mechanism of ribavirin action on DNA viruses stays unclear.

Spectrum of action

Viruses of influenza A and B, parainfluenza, respiratory syncytial virus, hepatitis C virus, HIV-1, and various herpesviruses, arenaviruses, and paramyxoviruses.

Indications

- ribavirin is used primarily to treat hepatitis C and viral hemorrhagic fevers. For hepatitis C ribavirin is used in a combination with pegylated interferon-α;
- it is the only known treatment for a variety of viral hemorrhagic fevers, including Lassa fever, Crimean-Congo hemorrhagic fever, Venezuelan hemorrhagic fever, and Hantavirus infection;
- it can be used in the combined treatment of rabies;
- ribavirin aerosol is indicated in the treatment of high-risk infants and children with severe bronchiolitis or pneumonia due to respiratory syncytial virus.

Side effects

1. Feeling tired, headache, nausea, fever, muscle pains, and an irritable mood.
2. Serious side effects include red blood cell breakdown, liver problems, and allergic reactions.
3. Use during pregnancy results in harm to the embrio and fetus. Ribavirin is mutagenic, teratogenic, and embryotoxic. Effective birth control is recommended for both males and females for 7 months after use.

REMDESIVIR

- is an adenosine nucleoside analogue;
- is a prodrug for IV administration;
- is a direct-acting antiviral agent that works as a chain terminator. The active metabolite of remdesivir interferes with the action of viral RNA-dependent RNA polymerase and evades proofreading by viral exoribonuclease, causing a decrease in viral RNA production. In some viruses such as the respiratory syncytial virus it causes the RNA-dependent RNA polymerases to pause, but its predominant effect (as in Ebola) is to induce an irreversible chain termination;
- has activity against multiple filoviruses, pneumoviruses, paramyxoviruses, and coronaviruses including viruses of severe acute respiratory syndrome and Middle East respiratory syndrome;
- can be used as a specific treatment for coronavirus disease COVID-19 (may shorten the time it takes to recover from the infection) and Ebola fever, but evidence base is not sufficient;
- side effects may include gastrointestinal distress, elevated transaminase levels in the blood, and infusion related reactions with nausea, low blood pressure, and sweating. Respiratory failure and organ impairment are also reported.

PREPARATIONS FOR TREATMENT OF HIV INFECTION

HIV INFECTION AND APPROCHES TO ITS CONTROL

Human immunodeficiency virus (HIV) is a RNA retrovirus that causes acquired immunodeficiency syndrome (AIDS), a condition accompanied by opportunistic infections and malignancies. The virus exists in two major forms: HIV-1, the most prevalent worldwide, and HIV-2, the most common in western Africa.

The replicative cycle of HIV presents many opportunities for the targeting of antiviral agents. The drugs in clinical use are classified as nucleoside reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, nucleotide reverse transcriptase inhibitors, and protease inhibitors.

Single agents are seldom used to treat HIV infection Multidrug therapy is used to counteract the rapid mutation rate of HIV and to minimize drug toxicity. Highly active antiretroviral therapy (HAART) uses combinations of reverse transcriptase inhibitors and protease inhibitors. In this system, drugs working by different mechanisms produce a sequential blockade of steps required for viral reproduction. But

even with multidrug regimens, viruses in 85% of infected people develop resistance to one or more of the antiretroviral agents.

ZIDOVUDINE (AZT)

It is a nucleoside (thymidine) analogue (Fig. 32.7).

Pharmacokinetics

- is taken orally;
- has bioavailability of 60%;
- is widely distributed through the body;
- penetrates CNS;
- is metabolized in the liver;
- is excreted with urine in the form of metabolites;
- has a half-life of 1–3 hrs.

Mechanism of action

AZT is a nucleoside reverse transcriptase inhibitor (NRTI). Its mechanism of action includes:

- the phosphorilation of AZT by host cell kinases;
- the formation of nucleotide analogue AZT-triphosphate;
- AZT-triphosphate incorporation into the growth chain of the viral DNA by the reverse transcriptase;
- the immature chain termination and inhibition of viral replication (Fig. 32.7).

Spectrum of action

HIV-1, HIV-2.

Indications

- the treatment of HIV/AIDS in a combination regimen with other antiretroviral drugs;
- the prophylaxis of HIV infection through accidental needle sticks;
- the prevention of vertical HIV transmission from the mother to the neonate.

Side effects

1. Anemia, neutropenia.
2. Gastrointestinal distress.
3. Headache, agitation, insomnia.
4. Myalgia.
5. Hepatitis and cholestasis.

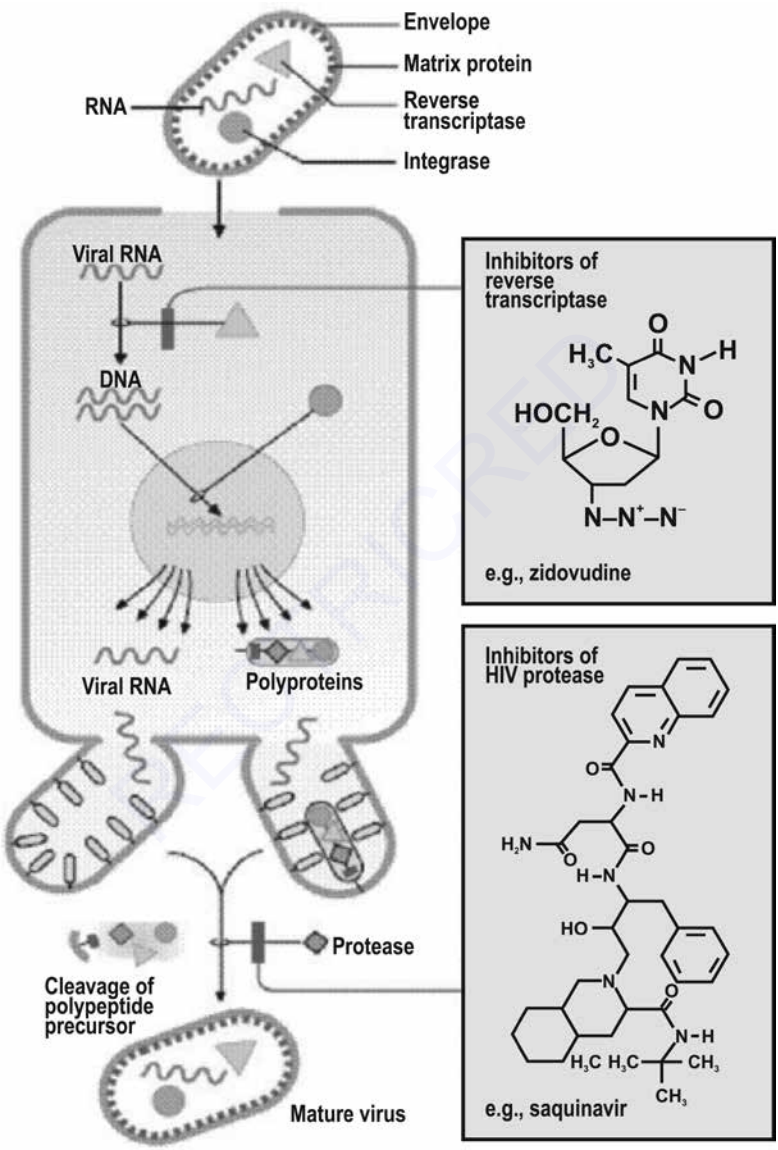

Fig. 32.7. Chemical structure and mechanism of action of NRTI and HIV protease inhibitors *(by H. Lüllmann, 2000)*

PECULIARITIES OF OTHER NRTI

Didanosine is a nucleoside analogue of adenosine. It differs from other nucleoside analogues, because it does not have any of the regular bases, instead it has hypoxanthine attached to the sugar ring. Like other anti-HIV nucleoside analogues, this drug acts as a chain terminator by incorporation and inhibits viral reverse transcriptase by competing with natural dATP. It is used by mouth as a part of HAART, especially for AZT-resistant HIV-infection. The most common side effects are diarrhea, nausea, vomiting, abdominal pain, fever, headache, and rash. Peripheral neuropathy, pancreatitis, retinal changes, optic neuritis and alterations of liver functions are also observed.

Zalcitabine is an analogue of pyrimidine (a derivative of the naturally existing deoxycytidine). It is phosphorylated into its active triphosphate form, which works as a substrate for HIV reverse transcriptase, and also by incorporation into the viral DNA, hence terminating the chain elongation due to the missing hydroxyl group. The drug appears less potent than some other NRTIs and is associated with serious side effects (peripheral neuropathy, oral ulcers, oesophageal ulcers and pancreatitis). For these reasons it is now rarely used to treat HIV infection.

HIV PROTEASE INHIBITORS

Saquinavir, ritonavir, indinavir, nelfinavir, amporenavir belong to this group. Protease inhibitors act in the stage of late protein synthesis (Fig. 32.7). At this stage, HIV-specific protease cleaves biochemically inert polypeptides to produce the final structural and functional proteins of virus. They are used in a combination with AZT, reduce opportunist infections and prolonge the lives of patients.

There are attempts to use of lopinavir/ritonavir or other HIV protease inhibitors for the treatment of coronavirus infection COVID-19. They are based on the idea that replication of the virus depends on the cleavage of polyproteins into an RNA-dependent RNA polymerase and a helicase. The enzymes responsible for this cleavage are two proteases, which can be inhibited by lopinavir/ritonavir. Although lopinavir/ritonavir has *in vitro* activity against severe acute respiratory syndrome coronavirus, the data of clinical trials are controversial.

AGENTS OF WIDE ANTIVIRAL SPECTRUM OF ACTION

INTERFERONS

They are glycoproteins produced by leukocytes (INF-α), fibroblasts (INF-β) and immune cells (INF-γ).

Mechanism of action

- interferons interact with receptors on the host cell membrane and induce the formation of protein kinase that leads to phosphorilation and blockage of peptide chain initiation;
- they also induce phosphodiesterase activation that leads to the degradation of terminal nucleotides of tRNA.

Spectrum of action

Interferons have wide antiviral spectrum of action. They also have anticancer, antitoxic, and immune stimulating properties.

Indications

- INF-α is used to treat viral hepatitis B and C, Kaposi's sarcoma, papillomatosis, hairy cell leukemia, melanoma, and breast cancer;
- INF-β is applied for the treatment of multiple sclerosis;
- INF-γ is used for chronic granulomatous disease.

Side effects

1. Flulike symptoms, including fever, chills, weakness, fatigue, myalgia, and arthralgia.
2. CNS complaints, such as headache, dizziness, impaired memory and concentration, agitation, insomnia, anxiety, and depressio.
3. Bone marrow suppression.
4. Gastrointestinal symptomsm, such as nausea, vomiting, diarrhea, and anorexia.
5. Alopecia.
6. A decrease in fertility and miscarriage (at high doses).
7. Disturbances of the thyroid function.
8. Rarely: renal toxicity, autoimmune disease, pulmonary dysfunction, and cardiovascular effects.

TESTS FOR SELF-CONTROL

1. Bijochinol:
A. Is a synthetic antitubercular drug
B. Is a basic antibiotic for the treatment of syphilis
C. Is a bismuth preparation for the treatment of syphilis

D. Is administered orally
E. Is used only in syphilis.

2. Antiviral agents that inhibit viral nucleic acid synthesis do not include:
A. Rimantadine
B. Acyclovir
C. Gancyclovir
D. Famcyclovir
E. Vidarabine.

3. Isoniazid:
A. Is highly effective against tuberculosis
B. Inhibits the synthesis of mycolic acids
C. Is the 2nd line preparation for the treatment of tuberculosis
D. Does not act on intracellular mycobacteria
E. Is less neurotoxic if given together with pyridoxine.

4. Zidovudine has such properties as:
A. Inhibits HIV reverse transcriptase
B. Is taken orally
C. Can be used for the treatment of herpes and cytomegalovirus infection
D. Significantly reduces mortality and morbility from AIDS
E. Is used in a combination with HIV protease inhibitors.

5. A patient came to a doctor with complaints of urine and lacrimal liquid painted red. It is known from the patient's anamnesis, that he was treated for pulmonary tuberculosis. What antitubercular drug became the cause of such complications?
A. Isoniazid
B. Rifampin
C. Ethionamide
D. Streptomycin sulfate
E. Ethambutol.

Answers

1 – C; 2 – A; 3 – A, B, E; 4 – A, B, D, E; 5 – B.

Chapter 33 ANTIPROTOZOAL DRUGS

MALARIA AND CONTROL STRATEGY FOR IT

Malaria is an acute infectious disease caused by the parasites called plasmodia. There are 4 species of plasmodia*: Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae, Plasmodium ovale. Plasmodium falciparum* is the most dangerous species causing acute disease characterized by high fever, orthostatic hypotension, and massive hemolysis. This infection can cause capillary obstruction and death.

The life cycle of parasite consists of sexual and asexual stages (Fig. 33.1). The 1st stage takes place in female anopheles mosquito. At this stage, parasite exists as gametocyte. The 2nd one develops in the human body. Here it may reside in the liver (pre-erythrocytic schizogoni) and in erythrocytes (erythrocytic shizogoni).

The control of this dreaded menace would therefore involve three living beings: man (the host), plasmodia (the agent), and anopheles mosquito (the vector) (Table 33.1) The control of malaria is a complex chain of measures that often complement one another.

The control strategy for malaria, concerning the human, includes an early diagnosis and treatment:

1. ***Presumptive treatment.*** Tests for malarial parasite should be done in all cases of fever, and presumptive treatment with the first full dose of chloroquine should be administered. Chloroquine is highly effective as schizonticidal drug against all species of malaria and is also gametocytocidal against all, except *Plasmodium falciparum.* Thus, by administering chloroquine to all cases of fever, it is possible to sterilize the gametocytes and thus prevent the spread to mosquitoes.

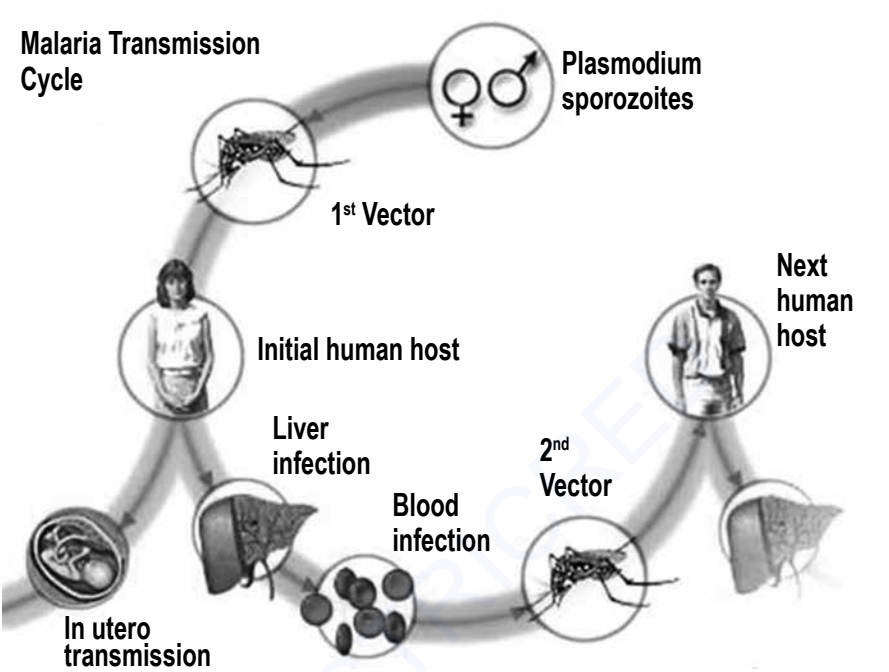

Fig. 33.1. Transmission cycle of malaria *(http://www.picsearch.com)*

Table 33.1. **Control strategy for malaria**

Human (host)	***Parasite (agent)***	***Mosquito (vector)***
Treat the affected Protect the unaffected	Kill the asexual forms Prevent the progression of disease Kill the sexual forms Prevent the spread to mosquitoes Ensure full treatment	Prevent breeding Prevent entry Prevent bites
Problem: Compliance	Problem: Drug resistance	Problems: Resistance to insecticides; compliance

2. ***Radical treatment.*** All confirmed cases of fever should be administered with primaquine. A single dose of primaquine must be administered in *Plasmodium falciparum* malaria to sterilize the gametocytes. A 14 days course of primaquine should be administered in *Plasmodium vivax* infection to destroy the pre-erythrocytic shizontes in the liver and thus to prevent relapse.
3. ***Ensure compliance.*** A complete treatment should be ensured. If the patient vomits the drugs within an hour of ingestion, the same should be repeated. Many patients fail to complete the treatment due to either negligence, the lack of proper education or sometimes due to adverse effects.
4. ***Personal protection.*** A human should be encouraged to protect himself (or herself) against malaria. Personal protection measures include protection against mosquito bites and chemoprophylaxis against malaria.
5. ***Chemoprophylaxis.*** Travelers to endemic areas and high risk individuals living in endemic areas (pregnant, elderly or patients with organ failure) should start on chemoprophylaxis against malaria. This involves taking antimalarial drugs every week (some drugs must be taken every day) so as to suppress malaria.

CLASSIFICATION

According to the chemical structure

1. 4-Aminoquinolines:
   – Chloroquine.
2. Quinoline-methanols:
   – Quinine;
   – Mefloquine.
3. 8-Aminoquinolines:
   – Primaquine.
4. Sulfonamides and sulfone:
   – Sulfadoxine;
   – Sulfamethopyrazine;
   – Dapsone (pyrimethamine + sulfonamide).
5. Diaminopyridines:
   – Pyrimethamine (Chloridine).
6. Biguanides:
   – Chloroguanide (Proguanil).
7. Hydroxynapthoquinone:
   – Atavaquone.
8. Other preparations:

– Halofantrine;
– Artemisinin;
– Fansidar.

According to the antimalarial action

1. Hemato-shizonticidal agents:
   – Quinoline-methanols;
   – 4-Aminoquinolines;
   – Sulfonamides and sulfone;
   – Hydroxynapthoquinone;
   – Diaminopyridines.
2. Tissue-shizonticidal agents:
   – 8-Aminoquinolines.
3. Gameticidic agents:
   – 4-Aminoquinolines;
   – 8-Aminoquinolines;
   – Diaminopyridines.

CHLOROQUINE

Choroquine is the most potent antimalarial agent, 4-aminoquinoline derivative (Fig. 33.2).

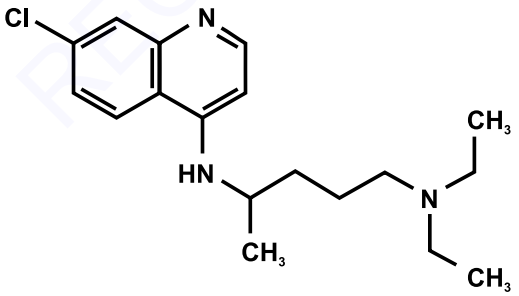

Fig. 33.2. Chemical structure of chloroquine

Pharmacokinetics

- is administered orally and IM;
- is rapidly and completely absorbed after the oral administration; concentrates in the erythrocytes, liver, spleen; has a very large volume of distribution;
- penetrates CNS and placenta;

- is metabolized in the liver: some metabolic products retain antimalarial activity;
- is excreted with urine.

Mechanism of action

- the food vacuole is a lysosome-like organelle in which the breakdown of hemoglobin and the detoxification of heme occur. Chloroquine concentrates up to several 1000-fold in the food vacuole of the parasite;
- this accumulation may involve ion trapping following protonation, specific transport, and/or binding to a receptor;
- the major action of chloroquine is to inhibit the formation of hemozoin from the heme released by the digestion of hemoglobin (Fig. 33.3);
- the free heme then lyses membranes and leads to the parasite death;
- chloroquine resistance is due to a decreased accumulation of chloroquine in the food vacuole.

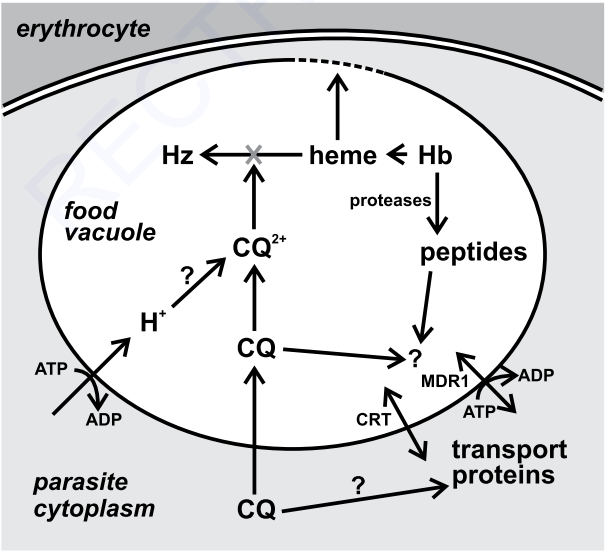

Fig. 33.3. Mechanism of action of chloroquine: CQ – chloroquine, Hb – hemoglobin, Hz – hemozoin *(http://www.picsearch.com)*

Spectrum of action

Erythrocytic shizontes of *Plasmodium falciparum, Plasmodium vivax* (less effective), gametocytes of *Plasmodium falciparum*, *Entamoeba histolytica*.

The drug also has an anti-inflammatory, weak cytostatic action, suppresses immunity and excerts antiarrhythmic effect in the human body.

Indications

- an acute attack of malaria;
- malarial coma;
- the prevention of the spread of malaria;
- individual chemoprophylaxis;
- extraintestinal amebiasis;
- rheumatoid arthritis;
- discoid lupus erythematosus.

Side effects

1. A gastrointestinal upset.
2. Headache.
3. Skin rash, itch.
4. Visual disturbances.
5. Depigmentation of nails beds, hair, and mucous membranes.
6. A quinidine-like effect in the heart.

Contraindications

Hepatic dysfunction, severe gastrointestinal diseases, neurological and blood disorders, psoriasis, porphyria.

PECULIARITIES OF OTHER PREPARATIONS

Quinine is an alkaloid of the bark of a cinconha tree; is administered orally, is widely distributed in the body, penetrates CNS, crosses placental barrier; is a ***blood shizonticide***; realizes its action by complexes with double-stranded DNA to prevent strand separation resulting in the block of DNA replication and transcription of RNA; is used to treat an attack of *Plasmodium falciparum* malaria resistant to chloroquine; in humans, inhibits CNS, has M-cholinoblocking action on the smooth muscles, stimulates uterus contractions, suppresses the conduction system of the heart (a quinidine-like effect) and the contractility of the myocardium; may cause cinchonism, a syndrome including gastrointestinal distress, headache, ver-

tigo, blurred vision, tinnitus, AV block, heart incompetence; also causes hemolytic anemia (blackwater fever); is fetotoxic and contraindicated in pregnancy.

Mefloquine is structurally relative to quinine; is administered orally, is well absorbed in the GI tract, concentrates in the liver and lungs, has a long half-life (17 days), is excreted with feces; is a ***blood shizonticide*** of the unknown mechanism of action (Fig. 33.4); is an effective single agent for suppressing and curing multi-drug resistant forms of *Plasmodium falciparum*; is less toxic than quinine, but may cause nausea, vomiting, dizziness, disorientation, depression, ECG disturbances a heart arrest if is given together with antiarrhythmics.

Primaquine is an 8-aminoquinoline derivative; is administered orally, is well absorbed in the gut, rapidly oxidized, and excreted with urine; has a mechanism of action connected with oxidative damage of the parasite cell; is ***tissue shizonticide*** (Fig. 33.4); acts on pre-erythrocytic forms of *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale* as well as on gametocytic forms of all four plasmodia;

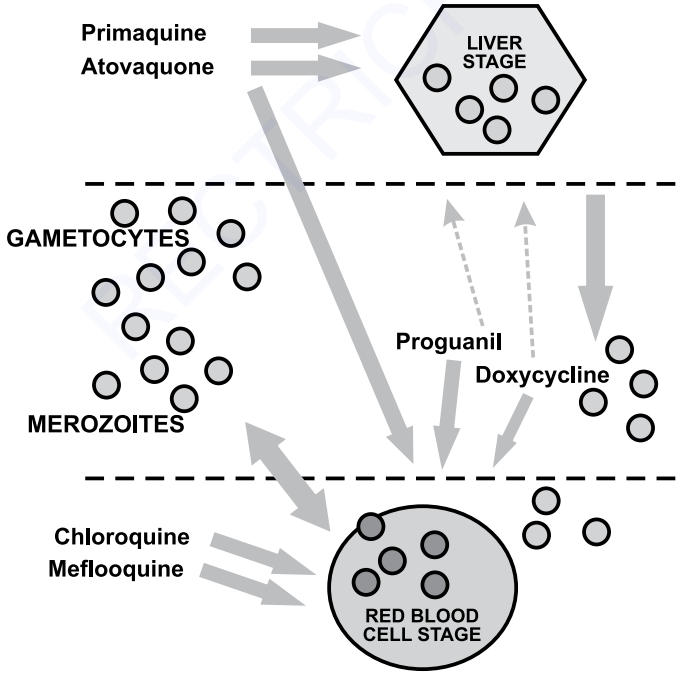

Fig. 33.4. Stages in the plasmodium life-cycle when antimalarial drugs act *(http://www.picsearch.com)*

is used to eradicate liver stages of *Plasmodium vivax* and *Plasmodium ovale* (in conjugation with blood shizonticides); is also used for the interruption of malaria transmission; is well tolerated, but may cause gastrointestinal disturbances, methemoglobinemia, headache, itch, hemolysis in patients deficit in glucose-6-phospate dehydrogenase.

Sulfonamides and sulfone are ***blood shizonticides*** active mainly against *Plasmodium falciparum*. The malaria parasite synthesizes folates de novo, whereas the human host must obtain preformed folates and cannot synthesize folate. The inability of the parasite to utilize exogenous folates makes folate biosynthesis a good drug target. One of these enzymes, dihydropteroate synthase (DHPS), is inhibited by sulfa-based drugs. ***Sulfadoxine and dapsone*** are two common antimalarials that target DHPS. The sulfa drugs are structural anlalogues of PABA and are converted into non-metabolizable adducts by DHPS. This leads to depletion of the folate pool and thereby reduces the amount of thymidylate available for the DNA synthesis.

Pyrimethamine and ***proguanil*** are the two most common dihydrofolate reductase (DHFR) inhibitors used as antimalarials. Inhibiting DHFR prevents the formation of thymidylate and leads to the arrest in the DNA synthesis and the subsequent parasite death. ***Pyrimethamine*** alone is a ***blood shizontocide and strong sporonticide*** in the mosquito's gut, is effective against *Plasmodium falciparum* in a combination with sulfonamide, is used against *Plasmodium malariae* and *Toxoplasma gondii*. It may cause deficit of the folic acid and megaloblastic anemia, has teratogenic action. ***Proguanil*** has similar targets of action (Fig. 33.4).

Fansidar is a combined antimalarial drug that contains sulfadoxine and pyrimethamine. It violates the metabolism of the folic acid in plasmodium, also is effective against *Toxoplasma gondii* and *Pneumocystis carinii*. The drug is used for the treatment of malaria, especially caused by *Plasmodium falciparum* resistant to other preparations, prevention of malaria in the regions endemic to *Plasmodium falciparum*, toxoplasmosis and prophylaxis of pneumocystic pneumonia. It can cause such side effects as nausea, vomiting, stomatitis, hepatitis, hematologic changes (leukopenia, thrombocytopenia, megaloblastic anemia, agranulocytosis, or purpura), lethargy, headache, fever, polyneuritis, pulmonary infiltrates, cough, dyspnea, skin reactions, Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome).

Artemisinin and its semisynthetic derivatives are a group of drugs used against *Plasmodium falciparum* malaria. It was isolated from the plant *Artemisia annua* and has a sesquiterpene lactone containing peroxide bridge. The mechanism of action appears to involve the heme-mediated decomposition of the endoperoxide bridge to produce carbon-centred free radicals. The involvement of heme

explains why the drug is selectively toxic to malaria parasites. The World Health Organisation has recommended artemisinin combination therapies be the first-line therapy for *Plasmodium falciparum* malaria worldwide. Combinations are effective because the artemisinin component kills the majority of parasites at the start of the treatment, while the more slowly eliminated partner drug clears the remaining parasites. Artemisinin is not used for malaria prophylaxis because of the short half-life. The drug is potent anthelmintic active against many trematodes including different species of *Schistosoma, Clonorchis sinensis, Fasciola hepatica,* and *Opisthorchis viverrini*. Artemisinin is well tolerated and displays the side effects which are similar to the symptoms of malaria: nausea, vomiting, anorexia, and dizziness

DRUGS FOR TREATMENT OF AMEBIASIS

AMEBIASIS

Amebiasis is a disease caused by one-celled parasite called *Entamoeba histolytica*. It is more common in people who live in tropical areas with poor sanitary conditions. In European countries and the USA amebiasis is most often found in travellers to and immigrants from these areas as well as in people who live in the institutions with poor sanitary conditions.

Only about 10% to 20% of people who are infected with *Entamoeba histolytica* become sick from the infection. The symptoms often are quite mild and can include loose stools, stomach pain, and stomach cramping. Amebic dysentery is a severe form of amebiasis associated with stomach pain, bloody stools, and fever. Rarely, *Entamoeba histolytica* invades the liver and forms an abscess. Even less commonly, it spreads to other parts of the body, such as the lungs or brain.

Life cycle of *Entamoeba histolytica* includes ingestion of cysts, formation of trophozoites, penetration of intestinal wall, multiplication of trophozoites within the colon wall and excretion of cysts with feces. If amoebas enter the blood and travel to another organs, they cause systemic invasion.

CLASSIFICATION

1. Mixed amebicides (for all localizations):
   – Metronidazole;
2. Tissue amebicides:
   – Metronidazole;
   – Tinidazole;

- Emetine hydrochloride;
- Chloroquine.

3. Luminal amebicides:
   - Iodoquinol;
   - Tetracyclines;
   - Diloxanide furoate;
   - Quiniodochlor.

METRONIDAZOLE

It is a nitroimidazole derivative (Fig. 33.5).

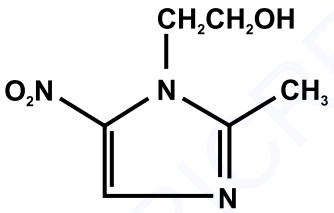

Fig. 33.5. Chemical structure of metronidazole

Pharmacokinetics

- is administered orally, IV, rectally, vaginally, applied topically as gel or ointment;
- is well absorbed in the gut;
- binds to plasma proteins (about 10% of a drug);
- has the volume of distribution of 70–95% of body mass;
- penetrates CNS and placenta; develops therapeutic levels in vaghinal and semenal fluids, saliva, breast milk and cerebro-spinal fluid;
- concentrates in the liver;
- is metabolized in the liver (30–60%), has entero-hepatic circulation, is excreted with bile to the intestine and is absorbed again, produces a high concentration in the bile;
- is the inhibitor of liver enzymes;
- is excreted with urine, bile, and feces;
- has a half-life of 8–10 hrs, completely leaves the body during 2–3 days.

Mechanism of action

- the drug is activated by a reduction of the nitro group to an anion radical (Fig. 33.6);

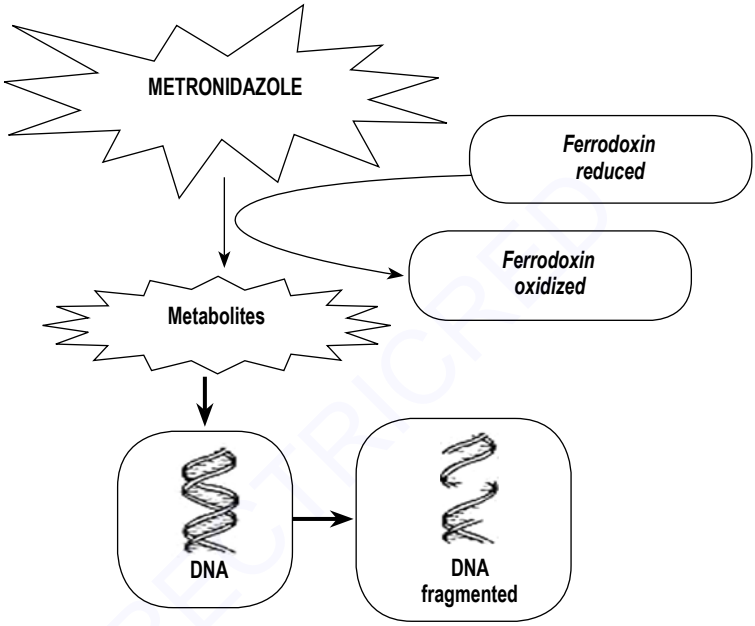

Fig. 33.6. Mechanism of action of metronidazole

- in the case of metronidazole, reduced ferredoxin appears to be the primary electron donor responsible for its reduction;
- the anion radical is highly reactive and forms adjunctions with proteins and DNA leading to a loss of the function. In particular, the reactions with DNA result in the strand breakage and inhibition of replication and will lead to the cell death;
- there is a good correlation between the presence of the pyruvate-ferredoxin oxidoreductase (PFOR) and sensitivity to metronidazole. All three of the protozoa (*Giaridia, Entamoeba,* and *Trichomonas*) affected by metronidazole lack mitochondria and have PFOR similar to that found in many anaerobic bacteria. Aerobic microbes use other electron transport systems and are not sensitive to metronidazole.

Spectrum of action

Protozoa *(Giardia lamblia, Entamoeba histolytica, Trichomonas vaginalis, Leishmania)*, anaerobic cocci, anaerobic Gram (+) and Gram (–) bacilli (*Bacteroides spp., Eubacterium spp., Fusobacterium spp., Clostridium spp., Helicobacter pylori,* etc).

Indications

- amebiasis;
- trichomoniasis;
- giardiasis;
- cutaneous leishmaniasis;
- sepsis, peritonitis, meningitis, brain abscess caused by susceptible microbes (IV);
- respiratory infections, infections of the intestine and urinary pathways caused by susceptible microbes;
- pseudomembranous colitis;
- prophylaxis of anaerobic infection before the abdominal surgery;
- peptic ulcer associated with *Helicobacter pylori;*
- infections of the skin (perioral dermatitis) and soft tissues (topically);
- paradontitis, ulcerative stomatitis (topically).

Side effects

1. A loss of appetite
2. An unpleasant taste in the mouth
3. Nausea, vomiting
4. Diarrhea
5. Headache, reversible polyneuropathy
6. Skin rash, itch
7. Leukopenia
8. Red-brown discoloration of urine
9. Changes in pharmacokinetics of some other drugs (e.g., ethyl alcohol, lithium salts).

Contraindications

1. Hemopoiesis disturbances
2. Organic lesions of the CNS
3. Pregnancy
4. Lactation
5. Should not be used together with alcohol drinks due to disulfiram-like reaction.

PECULIARITIES OF OTHER PREPARATIONS

Tinidazole is a nitroimidazole derivative similar to metronidazole; is only taken orally; is not used in leishmaniasis.

Chloroquine is an antimalarial preparation with amebicidic properties. It is a systemic amebicide; is used in a conjugation with metronidazole and diloxanide to treat and prevent amebic liver abscesses.

Emetine is an alkaloid from *Ipecacuanna*; is administered IM, SC, concentrates in the liver, is metabolized slowly, can accumulate, has a half-life of 5 days; inhibits protein synthesis at the stage of elongaion; is an alternative drug in the treatment of tissue amebiasais; is toxic and causes nausea, vomiting, cardiotoxicity, weakness and dizziness.

Diloxanide furoate is a luminal amebicide; is used to treat intestinal amebiasis; is well tolerated, but may cause flatulence, dry mouth, itch or urticaria; is contraindicated to pregnant women and children younger than 2 years of age.

DRUGS FOR TREATMENT OF TRICHOMONIASIS

Trichomoniasis is the most common curable sexually transmitted disease in young women. As estimated, 7.4 million new cases occur each year in women and men. Trichomoniasis is caused by the single-celled protozoan parasite, *Trichomonas vaginalis*. The vagina is the most common site of infection in women, and the urethra is a typical site of infection in men.

Trichomoniasis can usually be cured with ***nitroimidazole derivatives (metronidazole, tinidazole, or ornidazole) and nitrofuran derivatives (furozolidone)***. These drugs are described in Chapter 30 and as amebicides in presented Chapter.

DRUGS FOR TREATMENT OF GIARDIASIS

Giardiasis is an intestinal illness caused by infection with the parasite *Giardia lamblia* which lives in contaminated water. Although the illness most frequently occurs in developing countries, giardiasis is also one of the most common causes of waterborne illness in the United States. *Giardia lamblia* parasites are found in the feces of infected people. Two-thirds of persons infected with the organism do not have any symptoms. When symptoms occur, they typically start one to three weeks after exposure and include a sudden onset of watery diarrhea, abdominal cramping, bloating, nausea and gas.

Although most people will recover from giardiasis without treatment, medications, such as ***metronidazole, quinacrine hydrochloride (mepacrine) or furazolidone (furoxone),*** are used to treat giardiasis.

PECULIARITIES OF PREPARATIONS

Quinacrine is an acridine derivative that is effective in the treatment of giardiasis, malaria, leishmaniasis, and tapeworm invasion; is taken orally, concentrates in the liver, skin and brain tissue, accumulates; in parasites, binds to membrane phospholipids, blocks phospholipase A_2, disturbs functions of DNA; may cause dizziness, headache, vomiting, liver lesions, yellow pigmentation of the skin and psychosis as side effects.

Metronidazole and furazolidone are described in detail as amebicides and chemotherapeutics of different chemical structure.

DRUGS FOR TREATMENT OF TOXOPLASMOSIS

Toxoplasmosis is caused by a microscopic parasite *Toxoplasma gondii* that can live inside the cells of humans and animals, especially cats and farm animals. Toxoplasmosis passes from animals to humans, sometimes without causing any symptoms. Occasionally there may be a few weeks of mild flu-like illness such as muscle aches and tender lymph nodes. In those with a weak immune system, seizures and poor coordination may occur. If infected during pregnancy, a condition known as congenital toxoplasmosis may affect the child.

Toxoplasmosis is treated with ***pyrimethamine*** which is described as an antimalarial agent and its combinations with sulfonamides ***(sulfadiazine)***.

DRUGS FOR TREATMENT OF LEISHMANIASIS

LEISHMANIASIS

Leishmaniasis is a parasitic disease that is found in the tropics, subtropics, and southern Europe. It is caused by infection with *Leishmania* parasites which are spread by the bite of infected sand flies. There are several different forms of leishmaniasis in people. The most common forms are cutaneous leishmaniasis which causes skin sores, and visceral leishmaniasis which affects some of the internal organs of the body (e.g., the spleen, liver, and bone marrow).

CLASSIFICATION

1. The drugs for the treatment of cutaneous leishmaniasis:
   - Quinacrine;
   - Metronidazole;

– Monomycine;
– Amphotericin B.

2. The drugs for the treatment of visceral leishmaniasis:
– Sodium stibogluconate;
– Pentamidine.

SODIUM STIBOGLUCONATE

- is a compound of pentavalent antimony
- is administered IV; has minimal metabolism; is excreted with urine
- is not active *in vitro*
- has an unclear mechanism of action: probably it is connected with the inhibition of glycolysis and blockade of SH-groups in the parasite
- is used in visceral leishmaniasis as a preparation of choice
- may cause asthenia, headache, anemia and hepatitis.

Some other preparations for the treatment of leishmaniasis ***(quinacrine, metronidazole, amphotericin B)*** are presented in other parts of this Chapter and in Chapter 30.

TESTS FOR SELF-CONTROL

1. The blood shizonticides are all the drugs, except:
A. Chloroquine
B. Primaquine
C. Quinine
D. Pyrimethamine
E. Mefloquine.

2. The mechanism of the action of chloroquine is connected with:
A. The conversion of nitro-group into the toxic anion radical
B. A blockade of SH-groups
C. The prevention of hemoglobin digestion
D. The disturbances in DNA reduplication
E. A folate antagonism.

3. The indications for the use of metronidazole are:
A. All forms of malaria
B. All forms of amebiasis

C. Giardiasis
D. Trichomoniasis
E. Visceral leishmaniasis.

4. The correct statements concerning antiprotozoals are:
A. Quinine is used for the radical cure of malaria
B. Chloroquine is used for malaria and amebiasis
C. Metronidazole may cause disulfiram-like adverse reaction
D. Sodium stibogluconate is an antimony compound for leishmaniasis
E. Sodium stibogluconate is a folate antagonist for toxoplasmosis.

5. A patient with an acute attack of malaria was presctibed with erythrocytic shizonticidal fast acting drug. In addition to antimalaial effect, this drug has anti-inflammatory properties and is used in the treatment of rheumatoid arthritis and lupus erythematosus. This preparation is:
A. Pyrimethamine
B. Chloroquine
C. Quinine
D. Metronidazole
E. Emetine.

Answers

1 – B; 2 – C; 3 – B, C, D; 4 – B, C, D; 5 – B.

Chapter 34 ANTIHELMINTHIC DRUGS

HELMINTHIASIS AND ITS CONTROL

Helminthic infection (helminthiasis) is caused by pathogenic worms and may be localized in the alimentary tract or in other tissues. There are several main species of parasitic worms causing human helminthic infections. They are ***tapeworms (cestodes)***: *Taenia saginata, Taenia solium, Hymenolepis nana, and Echinococcus species;* ***roundworms (nematodes)****: Ascaris lumbricoides, Enterobius vermicularis, Ancilostoma duodenale, Necator americanus, Trichinella spiralis;* ***trematodes****: Schistosoma mansoni, Schistosoma haematobium*. Helminthiases are divided into groups by their etiology (Fig. 34.1).

Intestinal helminthiasis is an infestation with one or more intestinal parasitic worms. It is more often than tissue helminthiasis. Infected people excrete helminth eggs in their feces which then contaminate the soil in areas with inadequate sanitation. Other people can then be infected by ingesting eggs or larvae in contaminated food, or through the penetration of the skin by infective larvae in the soil (hookworms).

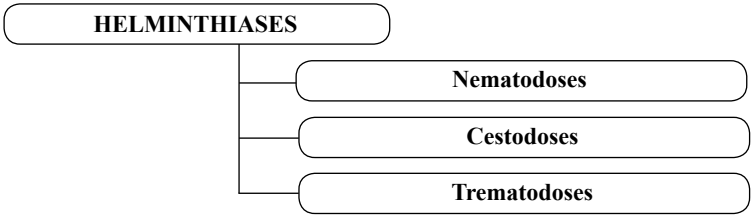

Fig. 34.1. Main classes of helminthiases

Infestation can cause morbidity, and sometimes death, by compromising nutritional status, affecting cognitive processes, inducing tissue reactions, such as granuloma, and provoking intestinal obstruction or rectal prolapse.

Control of helminthiasis is based:

- on drug treatment;
- improved sanitation;
- health education.

ANTIHELMINTHICS

Antihelminthics are drugs that expel parasitic worms (helminths) from the body by either stunning or killing them. They may also be called vermifuges (stunning) or vermicides (killing).

CLASSIFICATION

A. *Drugs for treatment of nematodoses:*

1. For intestinal nematodoses:
   – Pyrantel pamoate;
   – Piperazine adipinate;
   – Levamisole.
2. For extraintestinal nematodoses:
   – Diethylcarbamazine;
   – Ivermectin.

B. *Drugs for treatment of cestodoses:*

1. For intestinal cestodoses:
   – Niclosamide (Phenasal).
2. For extraintestinal cestodoses:
   – Albendazole.

C. *Drugs for treatment of trematodoses:*

1. For intestinal trematodoses:
   – Perchloroethylene.
2. For extraintestinal trematodoses:
   – Praziquantel;
   – Chloxyl.

D. *Drugs of wide spectrum of action:*

   – Praziquantel;
   – Albendazole;
   – Mebendazole.

MEBENDAZOLE

Mebendazole is a benzoimidazole derivative (Fig. 34.2).

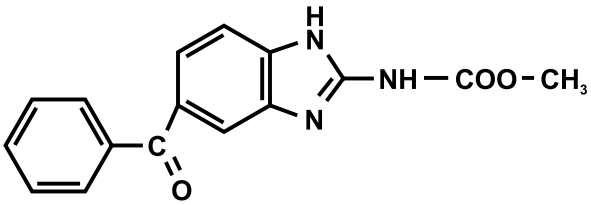

Fig. 34.2. Chemical structure of mebendazole

Pharmacokinetics

- is taken orally;
- is poorly absorbed in the gut (10%); absorption is increased in the presence of fatty meal;
- is rapidly metabolized;
- is excreted with urine and bile within 24–48 hrs.

Mechanism of action

- it inhibits the polymerization of helminth tubulin that leads to inhibiting the synthesis of microtubules in parasitic worms, and destroying extant cytoplasmic microtubules in their intestinal cells;
- thus, the drug interferes with microtubule-dependent functions, such as glucose uptake;
- the effect takes time to develop and the worms may not be expelled for several days;
- the cure rates are 60–100% with most parasites.

Spectrum of action

Pinworm *(Enterobius vermicularis)*, roundworm *(Ascaris lumbricoides)*, guinea worm *(Dracunculus medinensis)*, *Trichinella spiralis*, hookworm *(Ancilostoma duodenale, Necator americanus)*, whipworm *(Trichuris trichiura)*.

Indications

- infection caused by pinworm;
- infection caused by roundworm;
- infection caused by guinea worm;

- trichiniasis;
- infection caused by hookworm;
- infection caused by whipworm.

Is given as a single dose for threadworm, and twice daily for 3 days for hookworm and roundworm infestations.

Side effects

Gastrointestinal disturbances, elevated liver enzymes, low white blood cell count, low platelet count, and hair loss.

Contraindications

Should not be given to pregnant women and children under 2 years old.

PECULIARITIES OF OTHER PREPARATIONS

ALBENDAZOLE

- is a broad-spectrum antihelminthic agent of the benzimidazole type;
- it is taken orally. Oral absorption of albendazole is small and depends on gastric pH and increases with a fatty meal. To target intestinal parasites, albendazole is taken on an empty stomach. For systemic parasites, it acts as a prodrug, while albendazole sulfoxide (active metabolite) reaches systemic circulation and acts as the real antihelminthic. The metabolites mostly excreted in the bile;
- causes degenerative alterations in the intestinal cells of the worm by binding to β-tubulin, thus inhibiting its polymerization or assembly into microtubules. The drug leads to impaired uptake of glucose by parasites, and depletes their glycogen stores. It prevents the formation of spindle fibers needed for cell division, which in turn blocks egg production and development. Cell motility, cell shape, and intracellular transport are also disrupted. At higher concentrations, it inhibits ATP production by the Krebs cycle due to which the parasite is immobilized and eventually dies;
- is an effective treatment for fasciolosis, cestodosis (adult beef tapeworms *(Taenia saginata)*, pork tapeworms *(Taenia solium)*; cysticercosis caused by the larval form of the pork tapeworm; echinococcosis of the liver, lungs, and peritoneum (caused by the dog tapeworm, *Echinococcus granulosus*) or of the alveoli (caused by *Echinococcus multilocularis*); ascariasis; baylisascariasis caused by the raccoon roundworm; enterobiasis (pinworm infection); filariasis; lymphatic filariasis (elephantiasis) caused by *Wuchereria bancrofti or Brugia malayi*; gnathostomiasis; hookworm infections, including cu-

taneous larva migrans caused by hookworms in the *Ancylostoma* genus; intestinal capillariasis, strongyloidiasis, toxocariasis (visceral larva migrans), trichinosis, trichostrongyliasis, trichuriasis (whipworm infection), giardiasis; microsporidiosis; granulomatous amoebic encephalitis;
- side effects are headache and abnormal liver function with elevation of liver enzymes; abdominal pain, nausea or vomiting, bone marrow suppression which usually improves on stopping the medication, dizziness or vertigo, increased intracranial pressure, meningeal signs, hair loss, and fever.

PIPERAZINE

- is taken orally, has poor absorption in the gut, is partly metabolized and excreted with urine;
- acts as GABA on GABA-gated chloride channels in nematode muscles, causes paralysis of worms which are expelled alive by normal intestinal peristaltic movements;
- is effective against *Ascaris lumbricoides* and *Enterobius vermicularis;*
- is used in a single dose to treat roundworm and in the form of 7-days course to treat threadworm;
- may cause gastrointestinal disturbances, urticaria, spasm of the bronchi, rarely dizziness, paresthesias, vertigo or incoordination;
- is contraindicated in pregnancy, renal and hepatic diseases.

LEVAMISOLE

- is taken by mouth, is quickly absorbed and widely distributed in the body, crosses the blood-brain barrier, is metabolized in the liver and excreted with urine, has a half-life of 4 hrs;
- has a nicotine-like action, blocks neuromuscular transmission in nematodes, thus causes paralysis of worms and their expelling;
- is effective against *Ascaris lumbricoides* and less active against other nematodes;
- is used to treat roundworm (a single-dose therapy);
- stimulates immunity in the humans, especially T-dependent processes and phagocytosis, that's why is used in the complex treatment of collagenoses, chronic non-specific diseases of the lungs;
- if a single-dose therapy is used, side effects are few and soon subside; when the drug is used as an immune stimulant, it may cause fever, an influenza-like syndrome and leukopenia.

PYRANTEL

- is taken orally, is poorly absorbed and acts in the gut;
- is a depolarizing neuromuscular blocking agent causing the paralysis of nematode musculature and their expelling from the intestine;
- is effective against *Ascaris lumbricoides, Enterobius vermicularis, Ancilostoma duodenale, Necator americanus;*
- is used to treat infections caused by roundworms, pinworms, and hookworms;
- may cause nausea, vomiting and diarrhea.

IVERMECTIN

- is safe and highly effective antihelminthic of a broad spectrum of action;
- is a semisynthetic agent obtained from actinomycete organism;
- is given orally; has a half-life of 11 hrs;
- acts probably by the opening glutamate-gated chloride channels and increasing the Cl^- influx, by the stimulation of N-cholinoreceptors and motor paralysis of worms, or by binding to GABA-receptors;
- is effective against *Strongiloides stercolaris, Wuchereria bancrofti, Onchocerca volvulus*, roundworms, whipworms;
- is the first choice of the drug for filarial infection, onchocerciasis (river blindness), infestation by *Wuchereria bancrofti* caused elephantiasis;
- is well tolerated, but may cause skin rash, fever, headache, pain in muscles and joints.

NICLOSAMIDE

- is taken orally;
- causes paralysis of muscles of tapeworms and damages their covering tunic, thus provides the damage of tapeworms by intestinal enzymes, their separation from the intestinal wall and expelling of damaged parasites;
- is effective against *Taenia saginata, Taenia solium, Hymenolepis nana;*
- is used to treat infestations by tapeworms: for *Taenia solium* the drug is given in a single dose after a light meal followed by a purgative 2 hrs later for the evacuation of ova and prevention of cysticercosis;
- may cause nausea and vomiting.

PRAZIQUANTEL

- is a highly effective broad-spectrum antihelminthic;
- is administered orally, is well absorbed, is quickly metabolized and excreted with urine, has a half-life of 1–1.5 hrs;
- binds to protein kinase C, increases the Ca^{++} influx into the muscular cells of parasites, thus produces a rapid and prolonged contracture of musculature, paralysis, and death of the worm; also disrupts the teguments of the parasite and make it more susceptible to the host's normal immune responses;
- is effective against blood flukes (*Schistosoma mansoni, Schistosoma haematobium, Schistosoma japonicum), Dracunculus medinensis, Echinococcus granulosus,* larva of *Taenia solium;*
- is used to treat schistosomiasis, cysticercosis, hydated disease; is commonly used in national disease control programmes;
- has minimal side effects, may be used in pregnant and lactating women.

DIETHYLCARBAMAZINE

- is a piperazine derivative;
- is administered orally, is widely distributed in the body, is partly metabolized and excreted with urine, stays in the organism during 48 hrs;
- is active in filarial infections, rapidly removes microfilariae from the blood circulation and has a limited effect on the adult worms in the lymphatics;
- is used to treat filarial infections, whipoworm, wisceral larva migrans;
- may cause gastrointestinal disturbances, arthralgias, headache, weakness, toxic and allergic reactions due to dying filariae.

ANTIHELMINTHICS FROM MEDICINAL PLANTS

There are many medicinal plants with antihelminthic properties which are used in traditional and folk medicine in the different countries. Examples of naturally occurring anthelmintics include: tobacco (*Nicotiana tabacum*), black walnut (*Juglans nigra*), wormwood (*Arthemisia absynthium, Arthemisia cina*), clove (*Syzygium aromaticum*), tansy tea (*Tanacetum vulgare*), hagenia (*Hagenia abyssinica*), garlic (*Allium sativum*), pine-apple (*Ananas comosus*), kalonji (*Nigella sativa*) seeds, male fern (*Dryopteris filix-mas*), plumeria (*Plumeria acutifolia or Plumeria rubra*), pumpkin (*Cucurbita pepa*) seeds (Fig. 34.3).

Many natural anthelminthics are poisonous and, in improper dosages, dangerous for humans as well as for parasites.

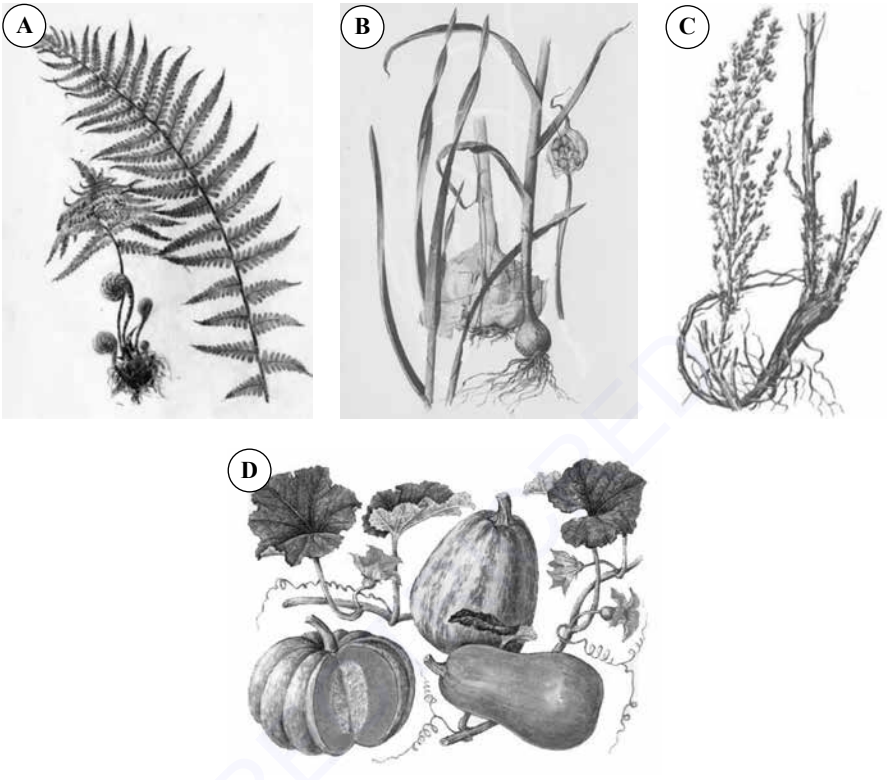

Fig. 34.3. Some medicinal plants used as antihelminthics: A – *Dryopteris filix-mas*; B – *Allium sativum*; C – *Arthemisia cina*; D – *Cucurbita pepa*

TESTS FOR SELF-CONTROL

1. All the listed drugs are antihelminthics, except:
A. Mebendazole
B. Metronidazole
C. Niclosamide
D. Pyrantel pamoate
E. Piperazine adipinate.

2. The antihelminthic affecting microtubular function in nematodes is:
A. Praziquantel

B. Niclosamide
C. Piperazine adipinate
D. Mebendazole
E. Ivermectin.

3. The correct statements concerning the mechanisms of action of antihelminthics are:
A. Mebendazole disturbs parasite's microtubules and glucose uptake
B. Niclosamide causes paralysis of microfilariae
C. Pyrantel is a depolarizing neuromuscular blocking agent for nematodes
D. Ivermectin interferes with receptors of parasite's chloride channels
E. Praziquantel stimulates GABA receptors in parasitic worms.

4. True indications to the use of antihelminthics are:
A. Roundworm disease is treated by pyrantel pamoate or mebendazole
B. Pinworm disease is treated by niclosamide
C. Filariasis is treated by diethylcarbamazine
D. Tapeworm disease is treated by niclosamide
E. Whipworm disease is not treated with mebendazole.

5. A patient with roundworm disease was prescribed with antihelminthic preparation for a single-dose therapy. This drug also stimulates T-dependent immune reactions, increases the activity of phagocytes, and is used to regulate the immune balance in collagenosis. What antihelminthic was prescribed?
A. Mebendazole
B. Pyrantel pamoate
C. Niclosamide
D. Piperazine
E. Levamisole.

Answers

1 – B; 2 – D; 3 – A, C, D; 4 – A, C, D; 5 – E.

Chapter 35 PHARMACOTHERAPY OF ACUTE POISONINGS. RADIOPROTECTORS

POISONINGS

Poisoning is a result of the action of a toxic agent or a toxic dose of the drug on the organism.

Poisonings may be acute and chronic. They are divided into household, environmental, industrial and pharmacological.

Poisoning with pharmacological agents results from:

- an absolute overdose (administration of a toxic dose of the drug);
- a relative overdose (caused by a therapeutic dose under the conditions of drug accumulation, hepatic and renal insufficiency, etc.).

Main syndromes accompanied acute poisonings

Acute poisonings may be accompanied by:

- CNS disturbances: coma, unconsciousness, seizures;
- cardiovascular disturbances: heart failure, collapse, arrhythmia;
- respiration disorders: spasm of the bronchi, pulmonary edema, respiratory arrest, asphyxia;
- Gastrointestinal disorders: vomiting, nausea, diarrhea, constipation, a loss of appetite;
- liver lesions: hepatic necrosis, hepatic insufficiency;
- renal insufficiency;
- lesions of the skin and mucous membranes: necrosis, irritation, exfoliation, rash.

Principles of poisonings treatment

There are four basic principles of poisoning treatment:

- ***the termination of poison exposure;***

- ***the fastening of the elimination of a toxic agent from the body;***
- ***antidote administration;***
- ***general supportive and symptomatic therapy.***

According to this principles, the treatment of poisoning includes:

- detoxification therapy (non-specific);
- symptomatic therapy (non-specific);
- antidote therapy (specific).

DETOXIFICATION THERAPY

The main purposes of detoxification therapy are to reduce poison absorption and to enhance the removal of poison.

For the reduction of poison absorption the following is used:

1. The irrigation of the skin and mucous membranes with cold water or isotonic solution of sodium chloride, in some cases with special antidotes (e.g., weak solution of ammonia for the neutralizing of formaldehyde; oil for the washing out of phenol; 2% solution of sodium chloride for the neutralizing of silver nitrate).
2. Lavage of the stomach with potassium permanganate solution (in poisoning with alkaloids), cold water (in poisoning with acids or alkalis), etc.
3. Emesis induced with apomorphine (parenterally), solution of ammonia (dissolved in water, per os), or mechanically.
4. The use of adsorbents (activated charcoal, enterosgel).
5. The use of astringents (tannin, milk, egg-white).
6. The use of osmotic purgatives (magnesium sulfate) which form high osmotic pressure in the lumen of the intestine and bowel and in such a way inhibit absorption of the toxic agent.

For the enhancement of poison removal the following is used:

1. Forced diuresis with furosemide or mannitol.
2. The altering of urinary pH (alkalinization for acidic substances and acidification for alkaline drugs).
3. Peritoneal dialysis, hemodialysis or hemosorption.
4. The use of osmotic purgatives (magnesium sulfate, sodium sulfate).
5. The administration of drugs stimulating enzymes activity in the liver for the fastening of poison metabolism (e.g., phenobarbital; glucose, and vitamins in poisoning with ethanol).
6. Analeptics for the stimulation of respiration and an increase of the excretion of poison through the lungs (carbogen, etimizol).

SYMTOMATIC THERAPY

It is a therapy aimed at the supporting of damaged functions of the organism and resuscitation. General supporting and symptomatic therapy are needed in most cases of poisonings. It is achieved according to the main syndromes of intoxication and is the same in different poisonings.

A seizures attack is treated by:

– anxiolytics: diazepam (IV, IM);
– neuroleptics: chlorpromazine (IV, IM);
– IV general anesthetics: sodium hydroxybutyrate (IV, IM);
– magnesium salts: magnesium sulfate (IV, IM).

Respiratory arrest needs:

– N-cholinergic agonists: lobeline hydrochloride (IV).

The inhibition of respiration should be treated with:

– analeptics: niketamide (IV, SC), camphor (SC), sulfocamphocaine (IV, IM, SC), bemegride (IV), etimizol (IV), carbogen (carbon dioxide + oxygen, by inhalation).

Pulmonary edema needs emergency help, such as:

– diuretics: furosemide (IV), mannitol (IV infusion), Urea pura (IV infusion);
– drugs caused the redistribution of blood: ganglia blockers (hygronium, IV infusion; pentamine, IV, or IM); peripheral vasodilators (nitroglycerine, IV; sodium nitroprusside, IV infusion);
– cardiac glycosides: strophanthin (IV), corglycon (IV);
– glucocorticoids: prednisolone (IM, IV);
– narcotic analgesics: morphine hydrochloride;
– surfactants: exosurf, curosurf;
– oxygen with antifoam agents (vapor of ethanol).

Collapse is overcome by the administration of:

– α- and α,β–adrenergic agonists: phenylepiphrine (IM, SC, or IV), noradrenaline hydrotartrate (IV infusion), adrenaline hydrochloride (SC);
– analeptics: niketamide (SC, IV), camphor (SC), sulfocamphocaine (IV, IM, SC).

Acute heart failure is treated by:

– cardiac glycosides from *Strophanthus* group: stophanthin (IV), corglycon (IV);
– non-glycoside inotropic agents: dobutamine (IV infusion).

ANTIDOTE THERAPY

Antidotes are drugs specifically interacting with some poisons. They act either by the preventing of absorption or by inactivating or antagonizing the action of the poisons. Specific antidotes are not available for all poisons (e.g., acute poisoning with phenol).

GENERAL MECHANISMS OF ANTIDOTE ACTION

Antidotes exert an antitoxic effect by a variety of mechanisms:

- binding to receptors (e.g., atropine, naloxone);
- acting on enzymes (e.g., cholinesterase reactivators);
- displacement from tissue binding sites (e.g., ethanol under the conditions of poisoning with methanol);
- exchanging with poison, binding to poison (e.g., chelating agents);
- the replenishment of depleted essential substances (e.g., sulfur containing agents).

CLASSIFICATION OF ANTIDOTES

1. Sulfur containing compounds:
   – Dimercaprol (Unithiol);
   – Sodium thiosulfate;
   – Acetylcysteine.
2. Chelating agents:
   – Sodium edeteate (Trilon B, EDTA–Natrium);
   – Tetacin-calcium (Calcium-EDTA);
   – Deferoxamine (Desferal);
   – Penicillamine.
3. Cholinesterase reactivators:
   – Pralidoxim (PAM);
   – Alloxim;
   – Dipiroxim;
   – Izonitrozine.
4. Antagonists of opioids:
   – Naloxone.
5. M-cholinoblockers:
   – Atropine sulfate.
6. Anticholinesterases:

– Neostigmine (Proserine).

7. Preparations of other groups:
   – Cromosmon (Methylene blue);
   – Ethanol;
   – Potassium permanganate;
   – Activated charcoal.

SULFUR-CONTAINING AGENTS

DIMERCAPROL (UNITHIOL)

- is a mercaptide by its chemical structure;
- contains two SH-groups and forms two bonds with metal ions;
- is an analogue of the drug British anti-lewisite (BAL);
- is administered IM, orally (in chronic poisonings);
- has a complex mechanism of action: 1) it forms bonds between SH-groups and metal ions with the formation of inactive complexes which are excreted with urine; 2) it prevents metals binding to tissue proteins; 3) it restores the activity of SH-groups of enzymes as a donator of SH- groups (Fig. 35.1);
- is indicated in poisonings with arsenic compounds, mercury, lead, in cardiac glycosides poisoning, streptomycin poisoning, hepatocerebral dystrophy and the treatment of alcoholism;
- may cause nausea, tachycardia, dizziness, paleness.

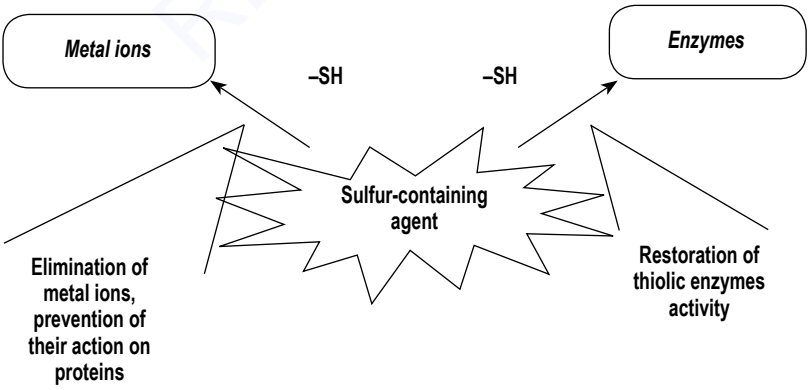

Fig. 35.1. Mechanism of action of sulfur-containing drugs

SODIUM THIOSULFATE

- is administered orally or IV;
- contains sulfur and forms non-toxic compounds with ions of metals, the cyanic acid, bromides and iodides; converts cyanomethemoglobin to thiocyanate which is excreted;
- has antitoxic, anti-inflammatory, and anti-allergic properties;
- is used in poisonings with heavy metals, cyanides, iodine and bromine salts as well as for allergic diseases, arthritis and neurolgia.

ACETYLCYSTEINE

- is known as mucolytic for the treatment of diseases of the lungs and bronchi;
- is administered IM and orally (for intoxication);
- contains one SH-group;
- is used in poisonings with metals and acetominophen (paracetamol). In the last case, it is used for the replacement of depleted essential substance (as glutathion substitute).

CHELATING AGENTS

Chelators are organic compounds which can form stable covalent-coordinate bonds with cationic metal ions excreted from the body (Fig. 35.2).

SODIUM EDETEATE

- is administered by IV infusion;
- forms complex compounds with different metal ions, especially with calcium;
- is used in poisonings with metal salts, cardiac glycosides as well as in pathological calcification;
- can cause hypocalcemia and tethany in a quick administration.

TETACIN-CALCIUM

- is administered IV and orally (in chronic intoxication);
- is used for the treatment of poisonings with compounds of thorium, lead, cobalt, mercury, uranium or yttrium;

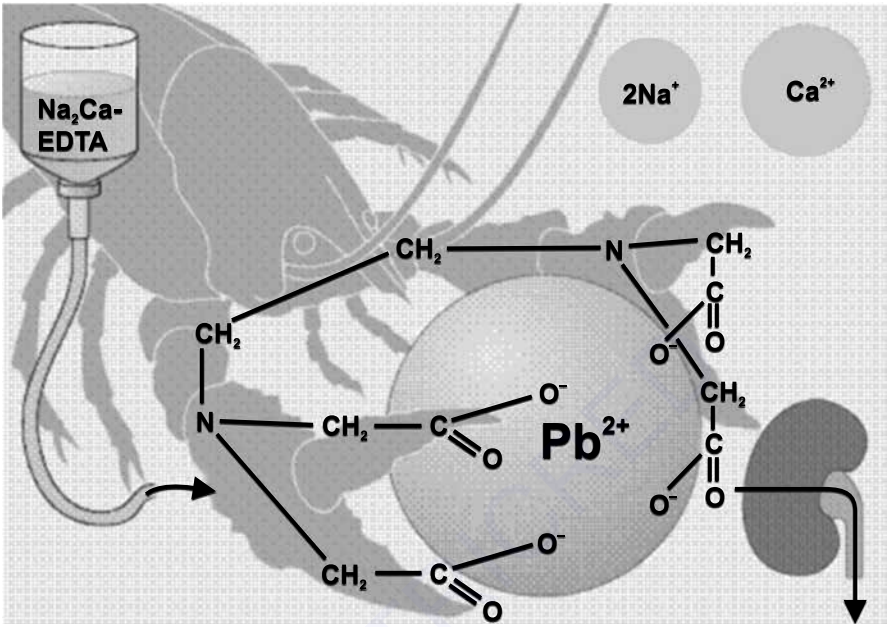

Fig. 35.2. Mechanism of action of chelators (e.g., EDTA-Sodium or Calcium-EDTA) *(by H. Lüllmann, 2000)*

- may cause gastrointestinal disturbances, toxic nephrosis, a decrease in the contents of hemoglobin, ferrous, and vitamin B_{12};
- is contraindicated for patients with diseases of the liver and kidney.

PENICILLAMINE

- is a synthetic preparation similar to the fragment of penicillin's molecule;
- is taken orally;
- forms complex compounds with metal ions (copper, lead, mercury, iron or calcium);
- is used in acute and chronic poisonings with heavy metals as well as in hepapocerebral dystrophy (Wilson's disease) and some collagen diseases (rheumatoid arthritis, scleroderma);
- may cause leukopenia, thrombocytopenia, hematuria, proteinuria, myalgia, arthralgia, itch, utricaria and gastrointestinal disturbances.

DEFEROXAMINE

- is administered IM, IV, orally, or used for lavage of the stomach;
- binds to free ions of iron and to iron from ferrous-containing proteins (ferritin and hemosiderin); does not interact with iron from hemoglobin and enzymes; does not influence the content of other ions;
- is used for the treatment of acute poisoning with ferrous compounds, hemochomatosis, hemosiderosis;
- may cause skin rash and collapse (after a quick IV injection).

CHOLINESTERASE REACTIVATORS

Cholinesterase reactivators (alloxim, dipiroxim, izonitrozine, obidoxime) are drugs for the restoration of acetylcholine esterase activity in acute poisonings with organophosphate compounds (Fig. 35.3).

Mechanism of action

- they interact with phosphor and split off phosphor from the etheric site of cholinesterase, cause the reactivation of enzyme;
- they interact with poison and neutralize it;
- they are the most effective if are used for the prophylaxis of poisoning or at the beginning of poisoning;
- cholinesterase reactivators are administered together with atropine.

ANTAGONISTS OF OPIOID RECEPTORS

Naloxone is an antidote of narcotic analgesics. It displaces drugs from opioid receptors (Fig. 35.4).

M-CHOLINOBLOCKERS

Atropine is an antidote to M-cholinergic agonists. It is also used in poisonings with anticholinesterases and morphine.

ANTICHOLINESTERASES

Neostigmine, physostigmine, galanthamine are antidotes to M-cholinoblockers and antidepolarizing myorelaxants.

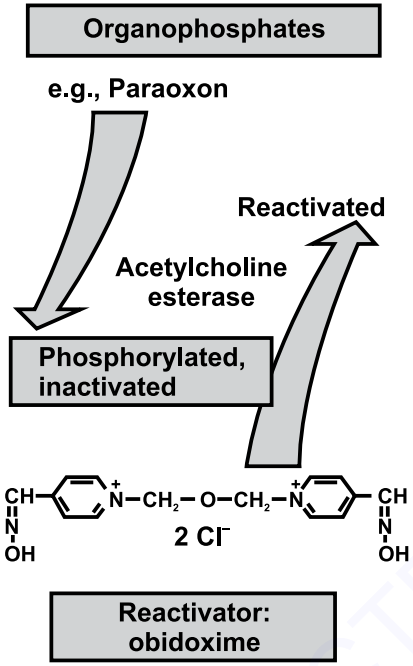

Fig. 35.3. Reactivation of acetylcholine esterase with obidoxime
(by H. Lüllmann, 2000)

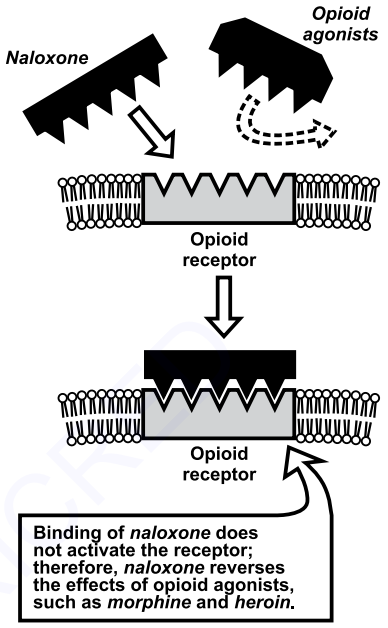

Fig. 35.4. Competition between morphine and naloxone
(by R. Finkel et al., 2000)

METHYLENE BLUE

- is an antiseptic with the properties of a donator and acceptor of hydrogen;
- is administered IV in the form of sterile solution ***(Chromosmon);***
- is used for the treatment of acute poisonings with cyanides, carbon oxide, hydrogen sulfide. Under the conditions of cyanide poisoning Methylene blue converts hemoglobin into methhemoglobin which interacts with cyanides and transforms them into non-toxic compounds.

ETHANOL

- is an antidote to methyl alcohol;

- replaces methanol in metabolic systems and in such a way prevents methylaldehyde forming.

POTASSIUM PERMANGANATE

- is an antiseptic from oxidazers group;
- is an antidote in poisonings with morphine, some alkaloids, and phosphor;
- is used for lavage of the stomach as 0.1–0.5% solution;
- is not effective in poisonings with atropine, cocaine, and barbiturates.

ACTIVATED CHARCOAL

- is an adsorbent containing pores which absorb low weight molecules of toxic agents;
- is taken orally in the form of aqueous suspension or tablets (in light intoxication or in chronic toxicity);
- is an universal antidote.

SOME INTOXICATIONS AND THEIR TREATMENT

Acute poisoning with organophosphates (irreversible anticholinesterases)

Signs:

hypersalivation, nausea, vomiting, spasm of the bronchi, then edema of the lungs, convulsions, unconsciousness.

Emergency help:

1. Reactivators of cholinesterase (dipiroxim, alloxim, izonitrozine), IM;
2. Atropine, IM.

Acute poisoning with ethanol

Signs:

specific odor; excitement, then sleeping and coma; hyperemia of the face, then paleness; a decrease in BP; suppression of respiration; hyporeflexia; hypothermia; involuntary urination and defecation.

Emergency help:

1. Lavage of the stomach with solution of potassium permanganate.
2. Analeptics (bemegride).
3. Glucose, insulin, and vitamins preparations (IV).
4. Nootropics (piracetam, IV).

Acute poisoning with morphine

Signs:

sleep or unconsciousness, normal or increased reflexes, a normal muscles tone, miosis, bradycardia, Cheyne – Stokes breath, the retention of urination, spasm of the intestine and bowel.

Emergency help:

1. Lavage of the stomach with 0.5% solution of potassium permanganate.
2. Naloxone, IV (an antagonist of narcotic analgesics).
3. Atropine (for a decrease in the vagal action of morphine).

Acute poisoning with cardiac glycosides

Signs:

bradycardia, then tachycardia and arrhythmia (premature ventricular beats, fibrtillation); changes in ECG; an increase in signs of CHF; anorexia, vomiting, nausea; headache, fatigue, hallucination; vision disturbances (xantopsia, micro- and macropsia).

Emergency help:

1. The abolishing of cardiac glycoside.
2. Drugs containing potassium (potassium chloride, panangin).
3. SH-group donator (dimercaprol, or unithiol).
4. Antiarrhythmic agents (phenytoin, lidocaine, propranolol, atropine for AV block).
5. Digoxin antibodies (digibind).
6. Glucose, vitamins preparations, oxygen inhalation.

Acute poisoning with hypnotics (barbiturates)

Signs*:*

sleeping, unconsciousness, hypotonia, the lowering of reflexes, the suppression of respiration, a decrease in BP.

Emergency help:

1. Lavage of the stomach.
2. The alkalinization of urine and forced diuresis.
3. Hemodialysis.
4. Salt purgatives (magnesium sulfate).

Acute poisoning with acids and alkalis

Signs*:*

necrosis of the skin and mucous membranes (coagulation necrosis caused by acid or coliquation necrosis caused by alkali); metabolic acidosis (if an acid is a toxic agent); severe pain.

Emergency help:

1. The neutralizing of the acid by solution of sodium bicarbonate and the neutralizing of the alkali by weak solution of the acid (acetic acid, citric acid) on the surface of skin.
2. Gastric lavage with cold water.
3. The administration of covering drugs, astringents, and local anesthetics into the stomach.
4. In poisoning with acids – sodium bicarbonate (IV) for the correction of metabolic acidosis.
5. Narcotic analgesics for a decrease in pain.

Acute poisoning with salts of heavy metals (e.g., mercury)

Signs:

severe pains in the abdomen, vomiting and diarrhoea with admixtures of blood, metal aftertaste, hypersalivation, bleeding gums, 2–3 days after – acute renal failure, hypochomic anemia, irritability.

Emergency help:

1. Gastric lavage.
2. The administration of activated charcoal and astringents in the stomach.
3. Dimercaprol (unithiol), tetacin-calcium, or sodium thiosulfate.
4. Atropine for a decrease in a spasm of the GI tract.
5. Morphine.
6. Hemodialysis.

RADIOPROTECTIVE AGENTS

Radioprotectors are compounds that are designed to reduce the damage in normal tissues caused by radiation. These compounds are often antioxidants and must be present before or at the time of radiation for effectiveness. Other agents, termed ***mitigators***, may be used to minimize toxicity even after radiation has been delivered.

Effective radioprotectors include compounds containing sulfhydryl (thiol) groups (-SH), such as cysteine, mercaptoamines and indolylalkylamines. Radioprotectors diminish the consequences of irradiation, that fatal and non-fatal effects, including genetic effects. They also reduce the intracellular or interstitial oxygen pressure and increase the amount of endogenous thiols.

The effectiveness of radioprotectors is expressed by a dose reduction factor, which is equal to the ratio of radiation doses producing identical effects in the presence or absence of radioprotectors. The dose reduction factor depends on the

physical properties of radiation, conditions of irradiation, and properties of the body.

CLASSIFICATION

1. Thiols and other SH-containing compounds:
   – Cysteine;
   – Cystamine;
   – 2-mercaptoethylguanidine;
   – Thiourea;
   – Thiouracil;
   – Dithiocarbamate.
2. Indolalkylamines:
   – Tryptamin;
   – Serotonin;
   – Mexamine.
3. Arylalkylamines:
   – Epinephrine;
   – Norepinephrine;
   – Dopamine.
4. Other agents:
   – Ethyl alcohol;
   – Analgesics (morphine, salicylates);
   – Cholinergic drugs (metacholine);
   – Hormonal preparations (corticosteroids, thyroid hormones);
   – Derivatives of nucleic acids (ATP);
   – Imidazole;
   – Adenosine 3',5'-cyclic monophosphate (cAMP);
   – Antibiotics;
   – Lipids (olive oil);
   – Adsorbents (enterosgel);
   – Vitamins-antioxidants (ascorbic acid, α-tocopherol acetate);
   – Chelating agents.

CYSTAMINE

- is well known radioprotective preparation;
- belongs to the group of aminothiols, is used as dihydrochloride;

- is taken orally; quickly and completely absorbed; penetrates well various organs and tissues; is excreted with urine. The effect develops within 10–30 min and lasts about 5 hrs;
- radioprotective effect is based on the ability to bind free radicals, ionized and excited molecules formed in tissues upon irradiation as well as on the ability to interact with certain enzymes and to impart them the resistance to ionizing radiation;
- is used to prevent harmful effects of irradiation including the prevention of the complications in radiotherapy;
- side effects are burning sensation in the esophagus, nausea, gastralgia, a decrease in BP, allergic reactions and increased action of antihypertensive drugs.

TESTS FOR SELF-CONTROL

1. All the statements regarding the treatment of acute poisoning are correct, except:
A. Activated charcoal binds to many toxins
B. Gastric lavage decreases the absorption of poison
C. Potassium permanganate is used for lavage of the stomach
D. Apomorphine is an ideal emetic in poisonings with acids and alkalis
E. Specific antidotes are not available for all poisons.

2. Deferoxamine is:
A. A sulfur-containing compound
B. An acetylcholine esterase reactivator
C. A chelating agent used in poisoning with ferrous compounds
D. An antidote in mercury poisoning
E. A drug for the treatment of hepatocerebral dystrophy.

3. The treatment of mercury poisoning includes:
A. Deferoxamine
B. Unithiol
C. Penicillinamine
D. Atropine
E. Hemodialysis.

4. Forced diuresis is:
A. Specific antidote therapy
B. Realized by the hydratation and further administration of furosemide

C. Non-specific detoxification therapy
D. Used to hasten the elimination of poison from blood through the kidney
E. Realized by the dehydratation and use of potassium-sparing diuretics.

5. A patient with symptoms of the organophosphate poisoning was admited to the emergency department. Which combination of drugs must be used as first aid?
A. Naloxone and atropine
B. Unithiol and potassium chloride
C. Neostigmine and chlorpromazine
D. Unithiol and EDTA
E. Alloxim and atropine.

Answers

1 – D; 2 – C; 3 – B, C, D, E; 4 – B, C, D; 5 – E.

Chapter 36 GENERAL PRESCRIPTION

STRUCTURE OF PRESCRIPTION AND MAIN RULES OF PRESCRIBING

The prescription of medicinal preparations is a practical skill in Pharmacology.

A prescription is a written doctor's appeal to a pharmacist about the making, delivery and marks of medicinal form. A prescription is a juridical document for which a doctor bears justifiable responsibility.

The component parts of the prescription (in Latin):

- *Inscriptio;*
- *Prepositio;*
- *Designatio materiarum:*
  - *adjuvans;*
  - *corrigens;*
  - *constituens.*
- *Subscriptio;*
- *Signatura;*
- *Nomen medici.*

A prescription is written according to the current decree with an ink or ball-point pen clearly without corrections.The names of medicinal substances in ***Designatio materiarum*** are written with a capital letter in a column in Latin and in Genitive Case. The word "gram" is not written, it is replaced with a point (comma in Ukraine).

Basis is the main substance which removes a cause or a leading symptom of illness;

Adjuvans is an auxiliary substance which strengthens or adds the action of the main substance or lessen side effects.

Corrigens improves the taste, color, or smell of medicine. They use sugar, syrup, essential oils as *corrigens*.

Constituens is a forming inert substance that gives medicine consistence and mass.

Signature is filled in the native language of a patient. In this part of prescription a dose for one administration is shown (a tablespoon, one powder, etc), the time of taking (for the night, after meal), the number of daily takings (3 times a day, in an hour, etc), the way of taking (by mouth, for injections, etc). It is impossible to use unclear expressions: "inside", "taking is known".

Abbreviation in a prescription is possible according to a generally used one and it must not attribute to the substances which have similar names. Marking the amount of substances which are taking in equal dose, a doctor must use the word *"ana"* and hand mark the dose only once at the last ingredient.

At the beginning of the urgent prescription it is necessary to make a note *"Cito!", "Citissime" or "Statim!"* The recurring making of medicine according to a prescription is made with the help of *"Repetatur!"*

Prescribing poison or drastic substance in a dose which exceeds the maximum one, a doctor must write out a dose of this substance in words and put an exclamation mark.

Units of mass measuring of medicinal substances which are supplied to patients are: gram – 1.0; decigram – 0.1; centigram – 0.01; milligram – 0.001. A prescription is written out as a special form.

MEDICINMAL FORMS AND THEIR CLASSIFICATION

Medicinal form is a shape of medicine in which it is supplied to a patient.

Medicinal forms are divided into dosed and non-dosed forms. Forms for internal use and injections are prescribed with the indication of a dose and are called dosed medicinal forms. Forms for external use are prescribed with the total amount of the drug and are dosed by patient. Dosed medicinal forms are divided into non-liquid (solid), liquid, soft, and sterile forms (Fig. 36.1). Non-dosed medicinal forms may also be non-liquid (solid), liquid, and soft.

NON-LIQUID DOSED MEDICINAL FORMS

Non-liquid dosed medicinal forms are represented by powders, capsules, dragee, and tablets (Fig. 36.2). The positive qualities are: stability, a convenient taking, the exactness of dosage, protection from the action of destroying enzymes for some forms. For dragee, it is an opportunity of incompatible medicinal substances'

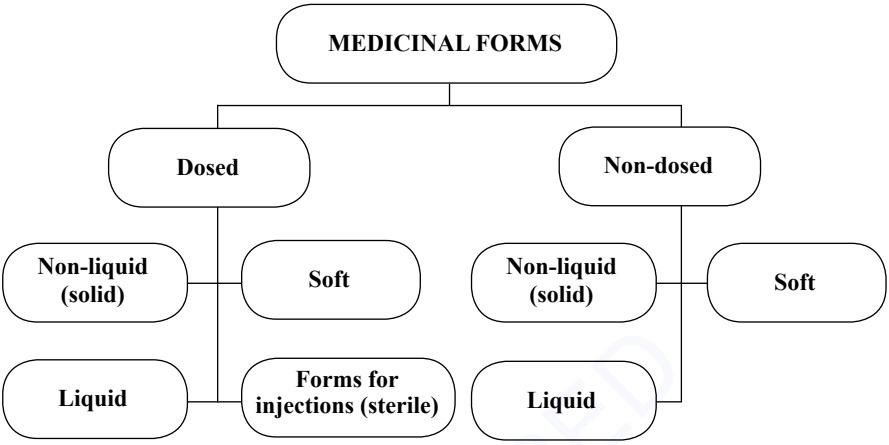

Fig. 36.1. Classification of medicinal forms

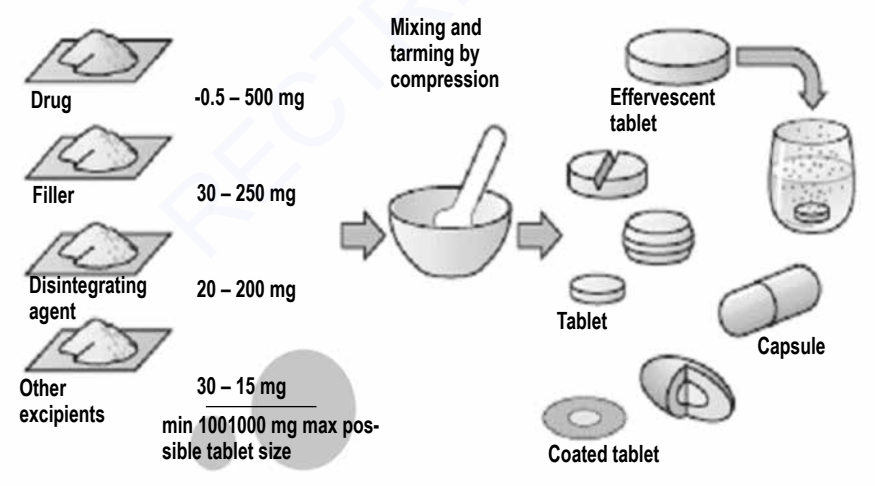

Fig. 36.2. Non-liquid (solid) dosed medicinal forms (by H. Lüllmann, 2000)

combinations. The defects are: a slow action, the impossibility to prescribe to little children, to patients in faint state, etc.

Dosed powders are non-liquid medicinal forms with the exact dosage of the medicine for one taking. The mass of powders is minimum – 0.1 g, maximum – 1.0 g, average – 0.3–0.5 g.

The classification is: 1) simple powders which contain only one substance; 2) complex powders which have two and more ingredients.

To prescribe a simple powder with the mass of more than 0.1 are written the name of drug, the dose, then the sentence "*Da tales doses numero 10*", and "*Signa*" after which there are instructions about drug taking.

Powders which have a less mass than a minimal one need the addition of filling (sugar, glucose) and are written in a full form with the list of all the ingredients and indication "*Misce ut fiat pulvis*" in the subscription.

Capsules are the covers for packing powders or some liquid medicines in them for taking inside. The rules of the prescribing capsules differ from the rules of prescribing of simple powders with the mass exceeding 0.1 only that in *Subscriptio* after showing the amount of supplying doses the name of capsule form is written: *"in capsules" (in caps.)*.

Tablets and dragee are industrial medicinal forms of industrial manufacture. The positive qualities of them are: the exactness of dosage, portability, the convenience of preservation and delivery. Tablets and dragee mask unpleasant taste, protect the teeth and mucous membrane of the oral cavity from the destruction. In dragee it is possible to combine substances which are incompatible for different reasons (e.g., vitamins of B complex). Their negative quality is slow action; sometimes they don't dissolve.

The rules of tablets prescribing are the same as the ways of prescribing capsules, but in *Subscriptio* it is written *"in tabulettis" (in tab.)*.

The rules of dragee prescribing are similar to tablets prescribing, but the word "*Dragee*" is written before the drug's name. In this case, there is no name of medicinal form in *Subscriptio*.

Combined tablets and dragee with a commercial name (trade mark) are prescribed in another way: *Tabulettarum (or Dragee)*, the drug's name, the amount of doses *(numero 10)*, then *"Da", "Signa"* and instructions how to use this medicinal form. In such prescriptions, drug's name is given in the Nominative Case and in inverted commas.

Beside above mentioned non-liquid dosed medicinal forms there are other ones prescribed more rarely. ***Cachets*** are shells for powders, which are obtained by pressing a mixture of wheat flour, starch and water between heated metal plates. ***Glossettes*** are small tablets intended for sublingual use. ***Lorenge*** is a solid mass of

a flat shape that is obtained by mixing medicinal substances with sugar and mucus used to treat patients with pathology of the oral mucosa or inside in diseases of the digestive canal. ***Caramel*** is a solid dosed medicinal form made similar to sweets by mixing medicinal substances with sugar, molasses, flavoring substances, and dyes. ***Microdragees*** have a diameter of 30–50 μm and are characterized by different release times of the active substances depending on the ratio of the drug and the coating substance. ***Spansules*** are capsules for oral administration, which contain a microdragee of medicinal substances with different duration of action. ***Granules*** is non-liquid dosed medicinal form with homogeneous particles (0.2 –3 mm) of round, cylindrical or irregular shape for oral administration manufactured in industrial way.

The main abbreviations used for prescribing of non-liquid dosed medicinal forms are: *Rp. (Recipe), D. t. d. N. 10 (Da tales doses numero decem); M. f. pulv. (Misce ut fiat pulvis); in caps. (in capsulis); in tab. (in tabulettis); drag. (dragee); S. (Signa)*.

Examples of prescribing of non-liquid dosed medicinal forms:

Powders

1. Simple powders with a weight more than 0.1
Rp.: Amidopyrini 0.25
D. t. d. N. 10.
S. Take 1 powder 3 times a day.

#

2. Powders with a weight less than 0.1 (Sugar should be added in a dose of 0.2–0.3)
Rp.: Pyridoxini hydrochloridi 0.005
Acidi nicotinici 0.05
Riboflavini 0.01
Sacchari 0.2
M. f. pulv.
D. t. d. N. 10.
S. Take 1 powder twice a day.

#

Capsules

1. Capsules containing a powder
Rp.: Rifampicini 0.15
D. t. d. N. 10 in caps.
S. Take 1 capsule 3 times daily.

#

2. Capsules containing oil solution
Rp.: Sol. Tocopheroli acetatis oleosae 20% – 0.5 ml
D. t. d. N. 10 in caps.
S. Take 1 capsule 2 times daily.

Tablets

1. Simple and combined tablets
Rp.: Reserpini 0.0001
D. t. d. N.10 in tab.
S. Take 1 tablet twice a day.

#

2. Tablets with a commercial name
Rp.: Tab. “Biseptolum” N. 10
D. S. Take 2 tablets twice daily.

#

Dragee

1. Simple dragee
Rp.: Drag. Diazolini 0.05
D. t. d. N. 10.
S. Take 1 dragee 2 times a day.

#

2. Dragee with a commercial name
Rp.: Drag. “Undevitum” N. 10
D. S. Take 1 dragee once a day.

MEDICINAL FORMS FOR INJECTIONS

Injections may be intravenous (IV), intramuscular (IM), subcutaneous (SC), etc. The positive qualities of injections are: the exactness of dosage, the quickness of acting, the convenience of use for patients (in the state of unconsciousness). The negative qualities are: pain, the necessity of sterility, the possibility of vessel damage, transmission of infection, etc.

For injections, drugs are often given as solutions and, less frequently, in crystalline suspension for IM and SC injection. Injectable solution must be free of infectious agents (sterile), pyrogens (apyrogenic) and suspended matter (homogenic). It should have the same osmotic pressure and pH as body fluids in order to avoid tissue damage at the site of injection.

Solutions for injections are preserved in an airtight glass or plastic sealed containers (ampoules and flacons) (Fig. 36.3, 36.4).

From ampoules and flacons the solution is aspirated via a needle into a syringe (Fig. 36.3). If injectable solutions are instable, ampoules or flacons contain dry substances dissolved aseptically before use. The cartridge ampoule is fitted into a special injector that enables its contents to be emptied via a needle (Fig. 36.3).

An infusion refers to solution being administered over an extended period of time (Fig. 36.5). The solution for infusion must meet the same standards as the solution for injection.

Medicinal forms for injections are of industrial manufacture (ampoules, flacons) and of chemist's making (flacons).

Medicinal forms for injections of industrial manufacture (officinal) are prescribed in a short form of prescription by the method of a single dose. If a dose

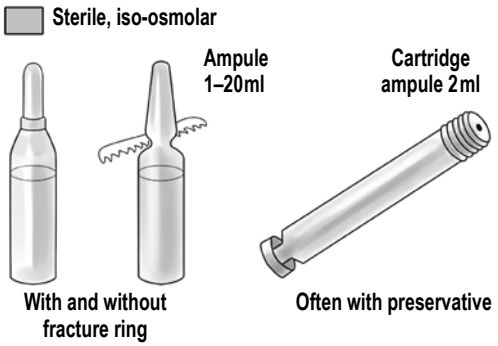

Fig. 36.3. Ampoules with sterile medicinal forms *(by H. Lüllmann, 2000)*

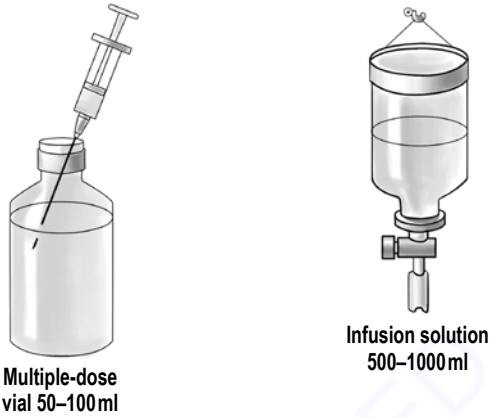

Fig. 36.4. Flacons containing sterile solutions *(adapted from H. Lüllmann, 2000)*

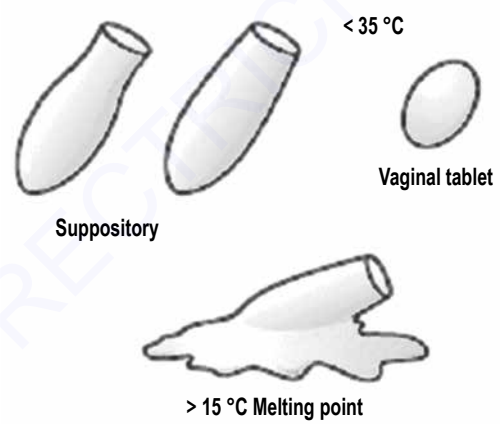

Fig. 36.5. Suppositories as soft dosed medicinal form *(by H. Lüllmann, 2000)*

for one occasion has its packing (an ampoule), in *Subscriptio* after the amount of doses *"in ampullis" (in ampull.)* is written.

The rules of prescribing of the officinal sterile forms in flacons are similar, but the name of medicinal form is not indicated.

Medicinal forms for injections of chemist's making (magistral) can be prescribed in a short as well as in a full form of prescription. In subscription, except usual marks, a note about medicine's sterility must be done: *"Sterilisetur!" (Steril.!)*.

Main abbreviations: *Sol. (solutio), in ampull. (in ampullis), Steril.! (Sterilisetur), IM (intramuscularly), SC (subcutaneously), IV (intravenously).*

Examples of prescribing of the sterile medicinal forms (ampoules and flacons):

Ampoules

Rp.: Sol. Promedoli 1% – 1 ml
D. t. d. N.10 in ampull.
S. Administer 1 ml IM, for pain.
#

Rp.: Sol. Retabolili oleosae 5% – 1 ml
D. t. d. N. 5 in ampull.
S. Administer 1 ml IM, once a month.
#

Rp.: Cordiamini 2 ml
D. t. d. N.10 in ampull.
S. Administer 2 ml SC.
#

Rp.: Cocarboxilasi 0.05
D. t. d. N. 10 in ampull.
S. Dissolve in 2 ml of solvent, administer IM twice a day.

Flacons

Rp.: Heparini 5 ml (5000 IU)
D. t. d. N.10.
S. IV.
#

Rp.: Kefzoli 0.5
D. t. d. N. 10.
S. Dissolve, administer IM every 8 hrs.
#

Rp.: Sol. Glucosi 5% – 200 ml
Steril.!
D. S. By IV infusion.

SOFT DOSED MEDICINAL FORMS

The application of a drug via the rectal or vaginal route is achieved by means of ***suppositories and vaginal tablets*** (Fig. 36.5). On rectal application, absorption into the systemic circulation may be intended. With vaginal suppositories or vaginal tablets, the effect is generally confined to the site of application. Suppositories contain cacao oil *(Oleum Cacao)* or some other *Constituens*, which are solid at usual temperature, but become liquid at body temperature. The weight of rectal suppositories is 1.0–4.0 (the average – 3.0). The weight of vaginal suppositories is from 1.5 to 6.0 (the average weight – 4.0).

Suppositories may be prescribed in a full form as well as in a short form. They may be written out by the method of a single dose as well as by the method of a total dose. As a rule, a full form and the method of a single dose are used. A short form is suitable for suppositories of industrial manufacture (officinal) and for combined suppositories with commercial name.

To prescribe ***rectal suppositories*** in a full form, the name of *Basis* and *Adjuvans*, their doses, then – *"Olei Cacao 3.0"* are written. In subscription it should be indicated: *"Misce ut fiat suppositorium rectale. Da tales doses numero 10."*

Prescribing of ***vaginal suppositories*** is similar and differs in a dose of *Ol. Cacao* (4.0) and the indication *"suppositorium vaginale"*.

To prescribe suppositories in a short form, *"Suppositoriorum"*, the name of the drug, the dose and the amount of suppositories (N. 10), are written then *"Da. Signa"* and instructions how to use this medication. The suppositories with a commercial name are prescribed without the dose. The drug's name (a trade mark) is given in the Nominative Case with inverted commas.

Main abbreviations: *supp. rect. (suppositorium rectale), supp. vagin. (suppositorium vaginale), M. f. supp. rect. (Misce ut fiat suppositorium rectale), M. f. supp. vagin. (Misce ut fiat suppositorium vaginale).*

Examples of suppositories prescribing:

Rectal suppositories

1. A full form, the method of a single dose
Rp.: Digitoxini 0.00015
Ol. Cacao 3.0
M. f. supp. rect.
D. t. d. N. 10.
S. Administer rectally once a day.

2. A full form, the method of a total dose
Rp.: Digitoxini 0.0015
Ol. Cacao 30.0
M. f. supp. rect. N. 10.
D. S. Administer rectally once a day.
#

3. A short form
Rp.: Supp. cum Digitoxino 0.00015
N.10.
D. S. Administer rectally once a day.
#

Vaginal suppositories

1. A full form, the method of a single dose
Rp.: Metronidazoli 0.5
Ol. Cacao 4.0
M. f. supp. vagin.
D. t. d. N. 10.
S. Administer vaginally twice a day.

2. A full form, the method of a total dose
Rp.: Metronidazoli 5.0
Ol. Cacao 40.0
M. f. supp. vagin. N. 10.
D. S. Administer vaginally twice a day.
#

3. A short form
Rp.: Supp. cum Metronidazolo 0.5
N. 10.
D. S. Administer vaginally twice a day.
#

4. Suppositories with a commercial name
Rp.: Supp. "Anaesthezolum" N 10.
D. S. Administer vaginally twice a day.

LIQUID DOSED MEDICINAL FORMS

The advantages of ***liquid dosed medicinal forms*** are: 1) they are absorbed and act quicker; 2) they are convenient for children; 3) they are suitable for prescribing hygroscopic substances. The disadvantages are: less portability, unsteadiness and the difficulty of dosage.

All liquid dosed medicinal forms for taking inside are prescribed by the method of a total dose. This is a method when after the name of a substance its total

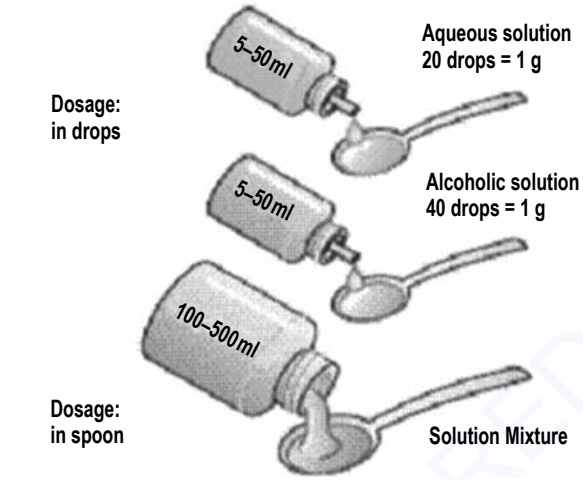

Fig. 36.6. Dosage of liquid medicinal forms for taking inside
(adapted from H. Lüllmann, 2000)

dose and the whole volume of medicine are noticed. The dose of the medicine for one administration (a tablespoon, 10 drops, etc) is noticed in signature (Fig. 36.6).

All liquid medicinal forms which are prescribed for taking inside and are measured by spoons are only prepared with distilled water.

Solution is a liquid dosed medicinal form that consists of a solvent and a dissolved substance. The concentration of solutions prescribed in a short form can be expressed in mass-volume correlation, in percent, but by strong diluting it is expressed in the ratio (1:500, 1:1000, etc).

The generally used volume units of dosage are: a tablespoon – 15 ml, a dessertspoon – 10 ml, a teaspoon – 5 ml. Solutions can be prescribed in a short or full form. They are prescribed for 3–4 days of the treatment in the volume of 100–200 ml (average – 180 ml for 12 administrations). If the solution for internal use is written out in a short form, after *"Recipe"* it is indicated *"Solutionis"*, the name of the dissolved substance in the Genetive Case and with the capital letter, the concentration of solution, its volume, *"Da. Signa",* and instructions about usage.

Solutions of drastic and poisonous substances are dosed in drops. They are named ***drops for internal use***. These medicinal forms are prescribed for 10–30 administrations (average 20 takings). Drops are made on the account that 1 ml of water solution has 20 drops. Drops for taking inside are prescribed to a patient in a little amount (5–10 ml). The total dose of acting substance and the total amount

of solution are also calculated proceeding from doses for one administration multiplied by the amount of takings.

Infusions and decoctions are aqueous extractions from medicinal plants. They are galenic preparations containing ballast substances. Infusions and decoctions are only prescribed in a short form of prescription. Prescribing infusions and decoctions, after *"Recipe"* the name of medicinal form is written, then the name of a plant part, the name of a plant itself, its total dose and the volume of fluid. A total dose is calculated proceeding from a dose for one administration. As infusions and decoctions are unstable forms and even in a refrigerator they are kept not more than 3–4 days, they are usually prescribed for 12 doses. The amount of medicinal raw materials and acting substances in infusion, decoctions, and mixtures are prescribed in grams.

Mixtures, containing medicinal and correction substances in water, infusions or decoctions, are written in a full form of prescription.

Tinctures, liquid extracts, and neogalenic preparations are alcohol-containing extractions from medicinal plants. They are taken by mouth and are dosed in drops. How many drops of such a medicinal form the patient must take inside for one administration, so many milliliters of tincture or extract should be prescribed. Tinctures, liquid extracts, and neogalenic preparations are prescribed in a short form.

Sometimes we prescribe other dosed liquid forms such as ***suspensions*** and ***emulsions***. They are liquid dispersion systems containing insoluble particles of solid substance or liquid. ***Magmas*** are suspensions with a large particle size of white, water insoluble substances, e.g., magnesium sulfate, bismuth, etc. ***Potion*** is a liquid dosed medicinal form, which includes pharmacologically active substances, water and syrup. In fact, these are sweetened mixtures. ***Lemonade*** is sweet or acidified liquid for internal use. ***Elixir*** is transparent, aromatic, pleasant taste liquid, water-alcohol solution of one or more medicinal substances. ***Linctuse*** is liquid of dense consistency for use in small sips. ***Draughts*** is liquid medicinal product for a single use. ***Balsam*** is aromatic liquid of vegetable origin containing organic nitrogen-free compounds: alcohols, essential oils, terpenes, resins, aldehydes, ketones, esters, and synthetic substances for antiseptic, deodorizing, topical, expectorant, and diuretic effect. ***Enema or lavage*** is a solution for administration into the rectum, which is cleansing, nutritious, therapeutic, or containing contrast agents before the investigation of the rectum.

Liquid medicinal forms for adminisration through upper airways are inhalations and aerosols. ***Inhalation*** is dosed medicinal form used as highly dispersed liquid or vapor administered through the upper respiratory passways. ***Aerosol*** is a spray, modern medicinal form of industrial manufacture for inhalation (dosed

aerosol) or external use (non-dosed aerosol). As a rule, all above mentioned forms are prescribed in a short form.

Main abbreviations: *Sol. (solutio), inf. (infusio), dec. (decoctio), tinct. (tinctura), extr. (extractum)*.

Examples of prescribing of liquid dosed medicinal forms:

Solution
Rp.: Sol. Natrii bromidi 3% – 180 ml
D. S. Take 1 tablespoon 2 times a day.
#

Drops for internal use
Rp.: Sol. Atropini sulfatis 0.1% – 10 ml
D. S. Take 5 drops 2 times a day.
#

Infusion or decoction
Rp. Dec. cort. Quercus 10.0 – 200 ml
D. S. Take 1 tablespoon 2 times a day.
#

Tincture
Rp.: Tinct. Valerianae 30 ml
D. S.Take 30 drops 3 times daily.
#

Liquid extract
Rp: Extr. Viburni fluidi 40 ml
D. S. Take 40 drops twice a day.
#

Neogalenic preparation
Rp: Adonisidi 20 ml
D. S. Take 20 drops twice a day.
#

Mixture
Rp.: Inf. herb. Thermopsidis 0.6 – 180 ml
Natrii hydrocarbonatis 3.0
M. D. S. Take 1 tablespoon 2 times a day.

NON-DOSED MEDICINAL FORMS

Non-dosed medicinal forms are forms for external use. They are prescribed without the dose. The total amount of the drug is indicated and the patient takes so much medication, as it's necessary. Non-dosed medicinal forms are divided into 3 groups: ***non-liquid*** (powders for external use, aspersions), ***liquid*** (solutions, eye drops, drops for the ear or nose, infusions, decoctions, tinctures, liquid extracts and mixtures for external use), ***soft*** (ointments, liniments, pastes, plasters, applications and poultices).

The powder for external use is a very fine powder *(Pulvis subtilissimus)* containing only medicinal substances. ***Aspersion*** *(Aspersio)* is a very fine powder containing medicinal substance (or substances) and inert substances. As inert substances, they use *Talcum, Zinci oxydum, Amylum*. Powders for external use and aspersions are prescribed in a short form as well as in a full form. Their amount may be from 5.0 to 100.0. If aspersion is prescribed in a short form, after *"Rp."* it is indicated *"Aspersionis"*, the name of the drug, the percent concentration and the total amount of such a medicinal form.

Solutions *(Solutio)* for external use may be aqueous, oil, or alcohol. The amount of solution depends on the purpose of its application.

Aqueous solutions for processing of dental root channels, drops for eyes, nasal drops, ear drops are prescribed in the amount of 10–20 ml, solutions for processing wounds – 50–500 ml, solutions for gargling – 200 ml, solutions for the lavage of the stomach and for disinfection – 500–1000 ml. As a rule, these solutions are prescribed in a short form, and their concentration is expressed in percent.

Oil solutions are prescribed in the total amount of 10.0–100.0. We can use "grams" as well as "ml" to prescribe such medicinal forms. As a rule, they are prescribed in a short form with the term *"oleosa"* after the name of the drug.

The volume of ***alcohol solution*** should be less than 100 ml. More often, they are prescribed in a short form with the word *"spirituosa"* after the medication's name.

Eye drops are the kind of solutions for external use, but they must be sterile. That is why eye drops are prescribed with the indication *"Sterilisetur!"* or abbreviation *"Steril.!"* (Fig. 36.7).

Infusions and decoctions for external use are always made in the correlation of 1:10, so they are prescribed without the indication of the weight of dry medici-

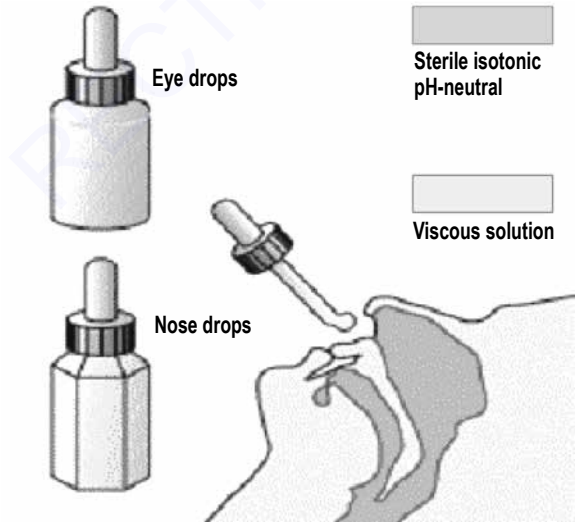

Fig. 36.7. Eye drops and nasal drops as liquid non-dosed medicinal forms *(by H. Lüllmann, 2000)*

nal plant. Only the total amount of such liquid form is indicated according to the purpose of its application.

Tinctures and liquid extracts as non-dosed medicinal forms are prescribed in the total amount less than 100 ml because of alcohol contents.

Mixtures also may be prescribed for external use. In this case we use a full form of prescribing in which list all the ingredients of the drug and point *"Misce"*.

Ointment *(Unguentum*) is a soft non-dosed medicinal form. It is characterized by plasticity and always contains medicinal substances and ointment basis (Fig. 36.8). Ointment basis is represented by different lipids *(Vaselinum, Lanolinum, Adeps suilis depuratus, etc)*. Ointments may be prescribed in a short and a full form. As a rule, it is used a short form: after *"Rp."* it is written *"Unguenti"* or the abbreviation *"Ung."*, then the name of the drug, the percent concentration, and the total amount of ointment (from 10.0 to 100.0). Combined ointments with a commercial name and some simple officinal ointments are prescribed without their concentrations.

There are liquid ointments (liniments) and dense ointments (pastes). ***Liniments*** *(Linimentum)* are made on liquid oils *(e.g., Oleum Vaselini, Oleum Persicorum, Oleum Helianthi)*. They are prescribed similar to ointments.

Pastes *(Pasta)* contain a lot of dry substances (more than 25%) (Fig. 36.8). To form paste such inert substances as *Talcum, Zinci oxydum,* etc. are added to medicinal substances and ointment basis.

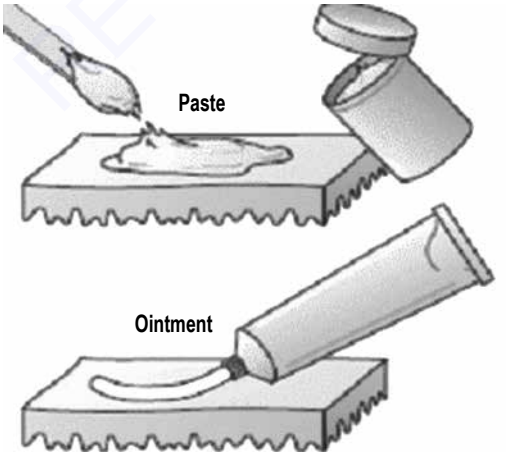

Fig. 36.8. Soft non-dosed medicinal forms *(adapted from H. Lüllmann, 2000)*

Some combined ointments, liniments, and pastes may be prescribed in a full form. In this case, all the ingredients of the medicinal form are listed with the following indication "*Misce ut fiat unguentum (pasta, linimentum)"*.

Plaster is a soft medicinal form, made as plastic mass, which is capable of softening at body temperature and adhering tightly to the skin. There are solid plasters and liquid ones (skin glues that can form elastic film on the skin).

Application is an officinal non-dosed form of ointment-like or liquid consistency. It is intended for application to the skin for treatment of injuries or for the destruction of parasites.

Poultice is a semi-solid form for application to the skin. It causes superficial hyperemia, improves blood circulation in areas of application.

Main abbreviations used to prescribe non-dosed medicinal forms are: *Asp. (Aspersio), subtil. (subtilissimus), Sol. (Solutio), Ung. (Unguentum), Lin. (Linimentum), M. f. ung. (Misce ut fiat unguentum), M. f. pasta (Misce ut fiat pasta), M. f. lin. (Misce ut fiat linimentum)*.

Examples of prescribing of non-dosed medicinal forms:

A powder for external use

Rp.: Sulfadimezini subtil. 5.0
D. S. Apply on the wound.

#

Aspersion

Rp.: Asp. Anaesthesini 5% – 50.0
D. S. Apply on the wound.

#

Solution for external use

Rp.: Sol. Kalii permanganatis 0.1% – 200 ml
D. S. For gargling.

#

Rp.: Sol. Kalii permanganatis 0.5% – 1000 ml
D. S. For lavage of the stomach.

#

Rp.: Sol. Anaesthesini oleosae 5% – 50 ml
D. S. Oil mucous membrane of the oral cavity

#

Rp.: Sol. Viridis nitentis spirituosae 1% – 10 ml
D. S. For the processing of small cuts of the skin.

#

Infusion and decoction for external use

Rp.: Dec. cort. Quercus 200 ml
D. S. For gargling.

#

Tincture and liquid extract

Rp.: Tinct. Calendulae 50 ml
D. S. Dissolve 50 drops in 100 ml of water, use for gargling.

#

Eye drops

Rp.: Sol. Atropini sulfatis 1% – 10 ml
Steril.!
D. S. Eye drops.

#

Ointment

Rp.: Ung. Prednisoloni 1% – 10.0
D. S. Apply on the skin.

#

Rp.: Ung. "Synalar" 10.0
D. S. Apply on the skin.

#

Liniment

Rp.: Lin. Synthomycini 10% – 50.0
D. S. Apply on the wound.

#

#

Paste

Rp.: Pastae Zinci 10.0

D. S. Apply on the injured skin.

Of course, nowadays there are many modern medicinal forms (e.g., aerosols, dissolved tablets, spansules, micronized forms, etc), but the forms described above stay the most spread.

TASKS FOR SELF-CONTROL

Prescribe the following medicinal forms:

1. Powders of *Thyreoidinum* 0.02. Take 1 powder 3 times a day.
2. Tablets of *Pentoxylum* 0.2. Take 1 tablet 3 times daily.
3. Tablets "*Ascorutinum*". Take 1 tablet twice a day.
4. Capsules of *Celecoxibum* 0.1. Take 1 capsule 3 times daily.
5. Dragee of *Aminazinum* 0.025. Take 1 dragee 2 times a day.
6. 5% solution of *Natrii salicylas* for internal use. Take 1 tablespoon 3 times a day.
7. 4% solution of *Dibazolum* as drops for internal use. Take 10 drops 2 times a day.
8. Tincture of *Arnica*. Take 30 drops 3 times daily.
9. Ampoules each containing 1 ml of 50% solution of. *Analginum*. Administer IM.
10. Flacons each containing 5 ml of *Insulinum* (1 ml – 40 IU). Administer SC.
11. 200 ml of sterile 5% solution of *Glucosum* for IV infusion.
12. 10 suppositories "*Betiolum*". Use 1 suppository rectally 2 times a day.
13. 3% aspersion of *Octathionum*. For applying on the skin.
14. 5% ointment of *Iodoformium*. For treatment of the wound.
15. 0.5% solution of *Atropini sulfas* as eye drops. Apply 2 drops into each eye.
16. 2% paste of *Acidum salicylicum*. For applying on the skin.

SELECTED REFERENCES

1. Basic and Clinical Pharmacology / Ed. B. G. Katzung, S. B. Masters, A. J. Trevor – 12th ed. – New-York : McGraw-Hill Education Lange, 2010. – 1345 p.
2. DiPiro J. T. Pharmacotherapy: A Pathophysiologic Approach / DiPiro J. T, Talbert R. L., Yee G. C., Matzke G. R., Wells B. G., Posey L. M. – 10th ed. – McGraw-Hill Education, 2016. – 2512 p.
3. Goodman and Gilman's the Pharmacological Basis of Therapeutics – 13th ed. – McGraw-Hill Education, 2017. – 1440 p.
4. Laurence D. R. Clinical Pharmacology / Laurence D. R., Bennet P. N., Brown M. G. – 8th ed. – London : Churchill-Livingstone Elsevier, 1998. – 710 p.
5. Lippincott's Illustrated Reviews: Pharmacology / Ed.: R. Finkel, M. A. Clark, L. X. Cubeddu. – 4th ed. – Lippincott Williams Wilkins, 2008. – 560 p.
6. Lippincott's Illustrated Reviews: Pharmacology – 5th ed. – Lippincott Williams Wilkins, 2011. – 608 p.
7. Lippincott Illustrated Reviews: Pharmacology / Ed. K. Whalen – 6th ed. – Lippincott Wlliams Wilkins, 2014. – 680 p.
8. Lullman H. Color Atlas of Pharmacology / Lullman H., Albrcht Z., Klaus M, Detlef B. – Stuttgart – New-York : Thieme, 2000. – 386 p.
9. Musil J. Biochemistry in a Schematic Perspective / Musil J., Novakova O., Kurz K. – Prague, 1980. – 216 p.
10. Olson J. Clinical Pharmacology Made Ridiculously Simple / Olson J. – McGrow-Hill International Edition, 2000. – 164 p.
11. Rang H. P. Rang's and Dale's Pharmacology / Rang H. P., Dale M. M., Ritter J. M., Moore P. K. – 6th ed. – London : Churchill-Livingstone Elsevier, 2007. – 830 p.
12. Stefanov O. Pharmacology with General Prescription: a text-book for English-speaking students / Stefanov O., Kucher V. – 2nd ed. – K., 2007.– 318 p.
13. Stringer J. L. Basic Concepts in Pharmacology: What You Need to Know for Each Drug Class / Stringer J. L. – 5th ed. – McGraw Hill Education, 2016. – 256 p.

Навчальне видання

Бобирьов Віктор Миколайович
Важнича Олена Митрофанівна
Дев'яткіна Тетяна Олексіївна
Дев'яткіна Наталія Миколаївна

ФАРМАКОЛОГІЯ

Підручник (англ. мовою)

Редактор: *О. В. Марчук*
Коректор: *Ю. В. Анвар*
Технічний редактор *Ж. С. Швець*
Комп'ютерна верстка: *Г. А. Пешков*

Підписано до друку 25.10.18. Формат 60×84/16.
Гарнітура Таймс. Папір офсетний. Друк офсетний.
Ум. друк. арк. 32,19. Зам. № 1006.

ПП "Нова Книга"
21029, м. Вінниця, вул. М. Ващука, 20
Свідоцтво про внесення суб'єкта видавничої справи
до Державного реєстру видавців, виготівників
і розповсюджувачів видавничої продукції
ДК № 2646 від 11.10.2006 р.
Тел. (0432) 56-01-87. Факс 56-01-88
E-mail: info@novaknyha.com.ua
www.novaknyha.com.ua