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"Ukrainian Medical Stomatological Academy"

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PHARMACOLOGY

Textbook for students of medical higher educational institutions

4th edition, updated

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

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Підручник для студентів вищих медичних навчальних закладів III-IV рівня акредитації складено згідно з програмою з фармакології та адресовано студентам англомовною формою навчання. В підручнику викладено основні розділи фармакології, наведено характеристику лікарських засобів з урахуванням сучасних поглядів на їх механізми дії та застосування.

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The textbook for students of higher medical establishments of the 4th level of accreditation 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.

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CONTENTS

ABBREVIATIONS

ACE – angiotensin-converting enzyme
Ach – acetylcholine
ACTH – adrenocorticotropin
ADH – antidiuretic hormone
AIDS –aquired immune deficiency
syndrome AP – action potential
ATP – adenosin triphosphate
AV – atrio-ventricular
AZT – azidothymidine
BAL – British antilewisite
BP – blood pressure
cAMP – cyclic adenosyl monophosphate
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
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
IM – intramuscular (-ly)
INH – isoniazid
IV – intravenous (-ly)
LDL – low-density lipoproteins
LH – luteinizing hormone
MAO – monoaminooxydase
mRNA – matrix RNA
MRSA – meticillin-resistant staphylococci
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 – nuclear receptors connected with unsaturated fatty acids
REM-sleep – rapid eye movement sleep
RNA –ribonucleic acid
SA – sino-atrial
SANS – sympathetic autonomic nervous
system SC – subcutaneous (-ly)
spp – speciales (Latin)
SSRI – selective serotonin re-uptake inhibitor
STH – somatotropic hormone
T_3 – triiodthyronine
T_4 – thyroxine
TRH – thyrotropin-releasing hormone
t-PA – tissue plasminogen activators
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 medical institutions of the 4th level of accreditation 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 under the conditions of implementation of the educational system of Bolonga. It has been written according to Pharmacology syllabus for higher educatonal medical institu-tions approved by the Ministry of Health of Ukraine.

The textbook consists of 36 chapters. Chapters 1, 2 are devoted to general phar-macology. 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 the drugs for treatment of osteoporosis, obesity, and erectile dysfunction were included into the 2nd edition of the textbook.

To prepare represented book we have used international names of preparations, but sometimes Latin names also have been indicated (they are from the capital letter and with typical endings –um, -as, -a).

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 the science about drugs. It studies their properties and use. The main task of pharmacology is to create new more effective medicinal drugs for 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 a clinic by the special committee of the country.

Medicinal substance is a chemical substance or biological 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 pharmacokinet-ics 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 division 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 the section of Pharmacology that studies how the body acts on the drug. It studies:

Routes of administration
Absorption
Distribution
Biotransformation
Elimination
Excretion.

ROUTS OF DRUGS ADMINISTRATION

Routs of drugs administration are divided into enteral routs (through the gut), parenteral routs (not through the gut), and topical application for local action (table 1.1).

Table1.1. **Routs of drugs administration**

Enteral routs	Parenteral routs	Topical application
1. Sublingual (under the tongue) 2. Oral (by mouth, per os) 3. Rectal (in 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 IV administration the drug has rapid onset and short duration of action. After oral administration it has slow onset of action, lower concentration, and more durative effect (fig. 1.2).

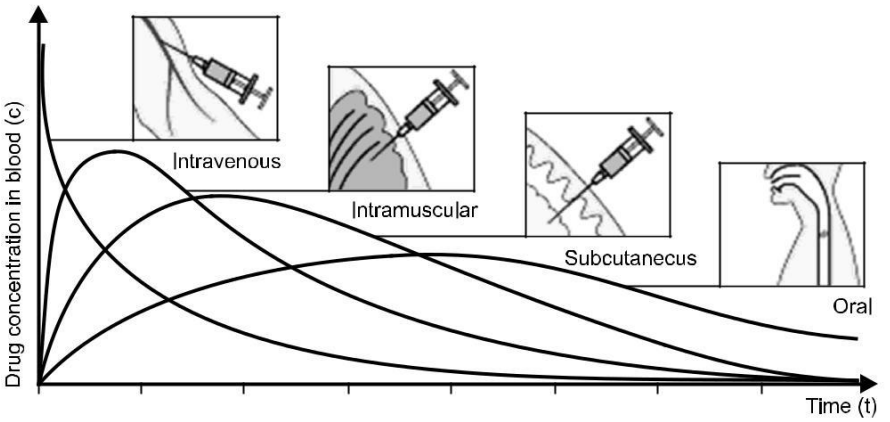


Fig. 1.2. The comparison of drug concentration in blood in different routs of administration *(by H. Lüllmann, 2000)*.

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

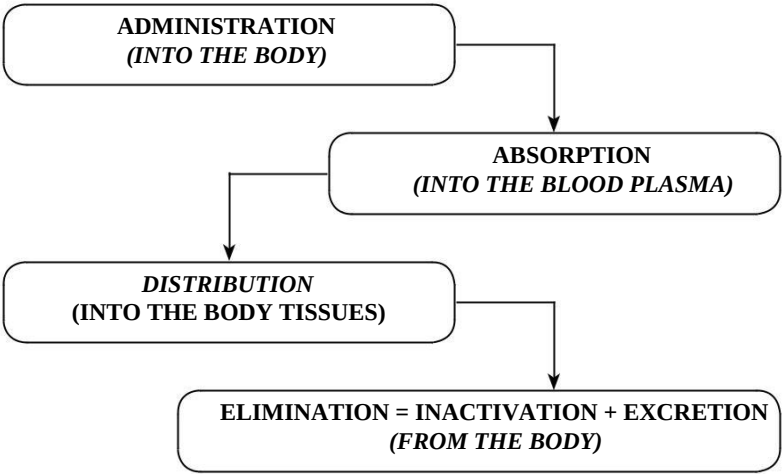


Fig.1.3. Schematic representation of drug absorption, distribution, and elimination.

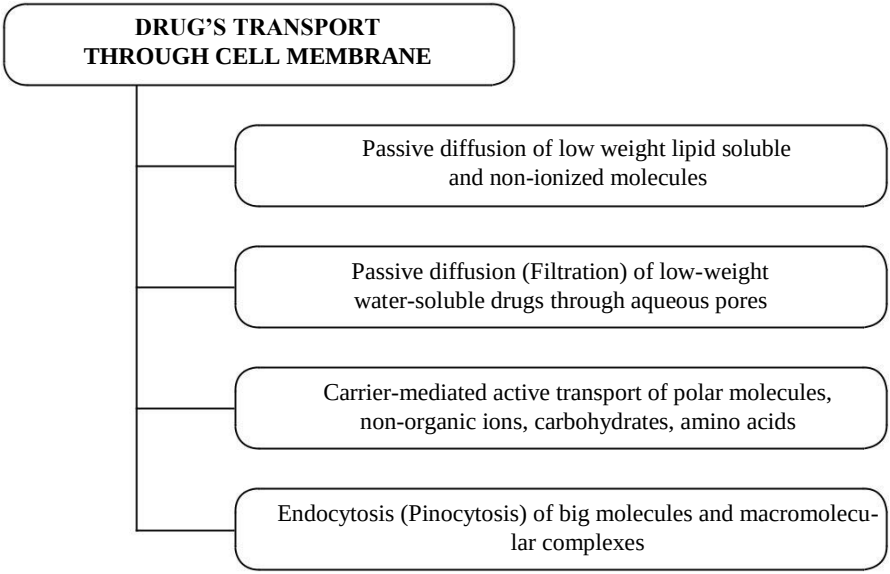


Fig. 1.4. Schematic representation of a drug crossing through the cell membrane.

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 admin-istered 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.***

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.

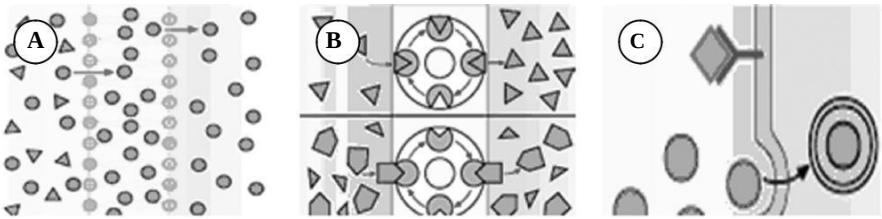


Fig. 1.5. Passive diffusion (A), active transport (B), and endocytosis (C).

Factors influencing absorption are:

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

Bioavailability is the 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.

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

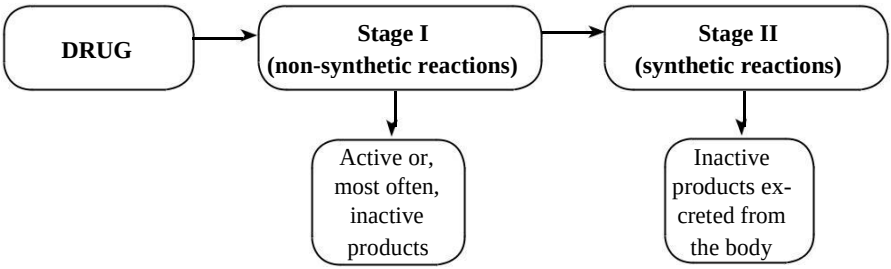


Fig. 1.6. Stages of drugs biotransformation.

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 the process by which drug leaves the body.

Drugs are excreted:

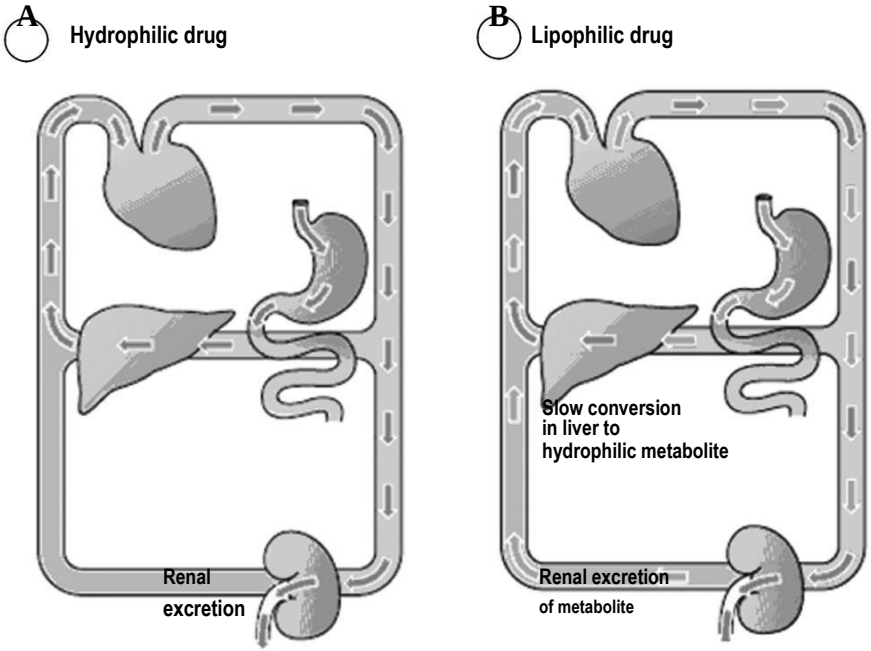


Fig. 1.7. Renal excretion of hydrophilic (A) and lipophilic drugs (B) *(by H. Lüllmann, 2000)*.

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.

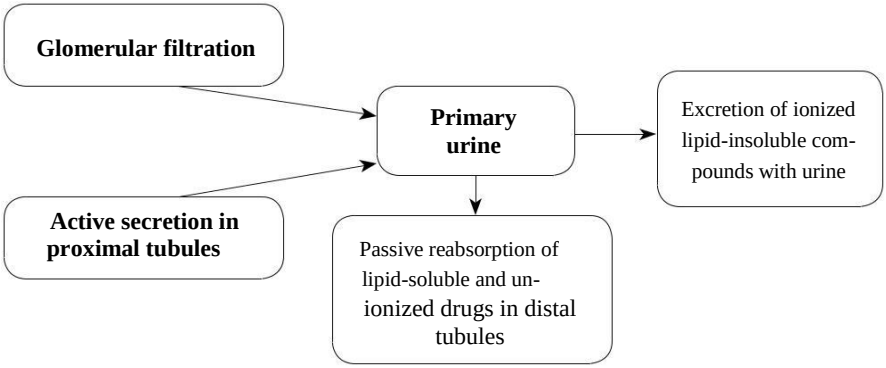


Fig. 1.8. Drugs elimination in the kidney.

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 the systemically available fraction of a drug. Bioavailability is a subcategory of absorption and is the fraction of an administered dose of unchanged

drug that reaches the systemic circulation. When a medication is administered intravenously, its bioavailability is 100%. When the medication is administered 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 ad-ministration. Relative bioavailability measures the bioavailability of a formulation of a 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 elimina-tion. Steady state is reached when a time of 4 to 5 times the half-life for a drug after regular dosing is started.

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

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

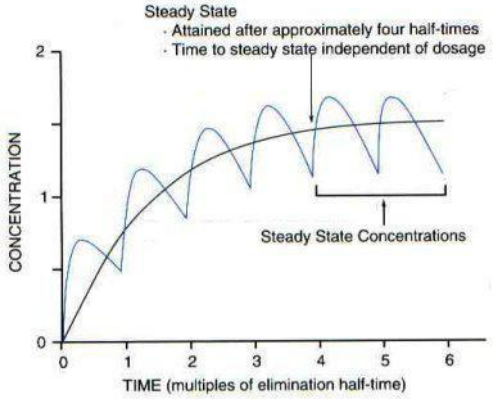


Fig. 1.9. Steady state concentration.

TESTS FOR SELF-CONTROL

№1. Absorption is:

Drug's penetration from the site of administration into the blood
Drug's penetration from the blood into tissues
Chemical transformation of the drug
Drugs interaction
Binding to plasma proteins

№2. In the blood plasma drugs are transported:

In connection with albumens
In connection with lipoproteins
In connection with blood cells
In water fraction
All the listed.

№3. The energy-independent mechanisms of drugs crossing through the cell membrane are:

Active transport
Endocytosis
Passive diffusion
"Biological pumps"
Filtration through pores.

№4. Drugs administered by injections:

Have a slow onset of action
Must be sterile
Are suitable for emergence help
Need the special equipment
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?

The dose should be decreased due to the inhibition of metabolism of the drug
The dose should be increased due to the stimulation of metabolism of the drug
The dose should be without any changes
The dose should be abolished due to its accumulation
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 the section of Pharmacology which studies how the drug acts on the body.

It describes:

Effects
The mechanism of action
Drugs interactions
Doses
Dose-effect dependence
Factors influencing a drug action.

TYPES OF DRUGS DOSES

The ***dose*** is the amount of drug 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 elimi-nation 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, 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 P450-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. anti-cancer drugs).

RECEPTOR THEORY

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

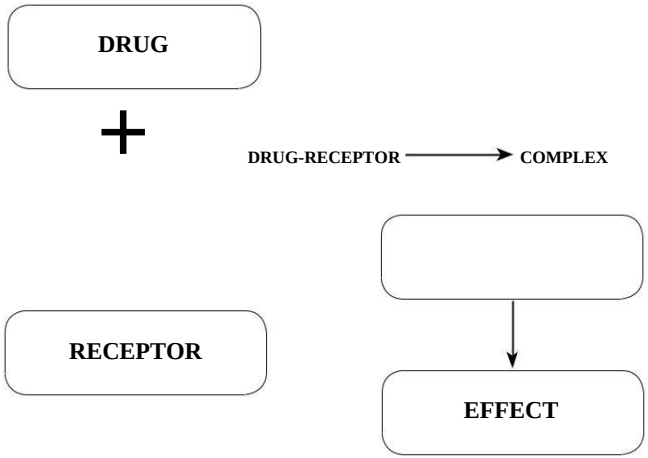


Fig. 2.1. Schematic representation of drug-receptor relationship.

Receptors are located:

– in membrane
– in cytoplasma
– in nuclei.

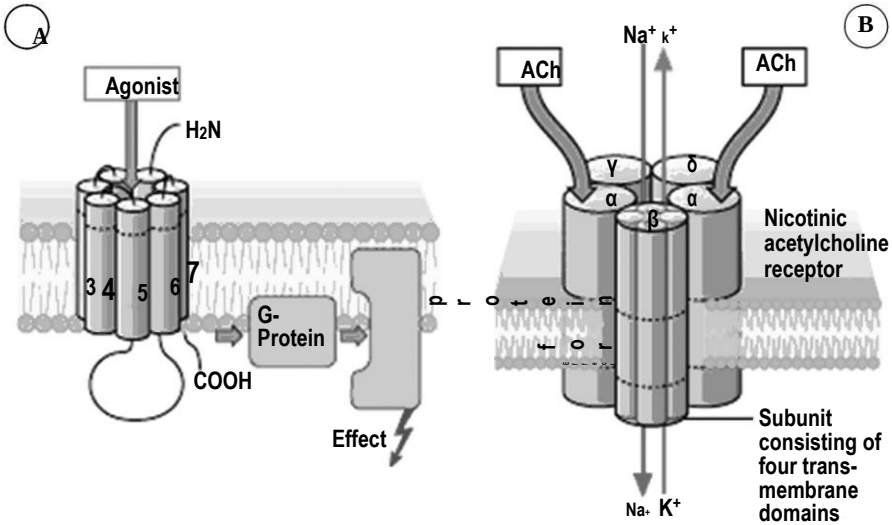


Fig. 2.2. Connection of receptors with G-proteins (A) and ion channels (B) *(by H. Lüllmann, 2000).*

Receptors functions are achieved by:

– ion channels (fig. 2.2)
– cyclic nucleotides (c AMP)
– G- proteins (fig. 2.2)
– Ca^{++} and protein-kinases.

Drugs interaction with receptors (fig. 2.3)***:***

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

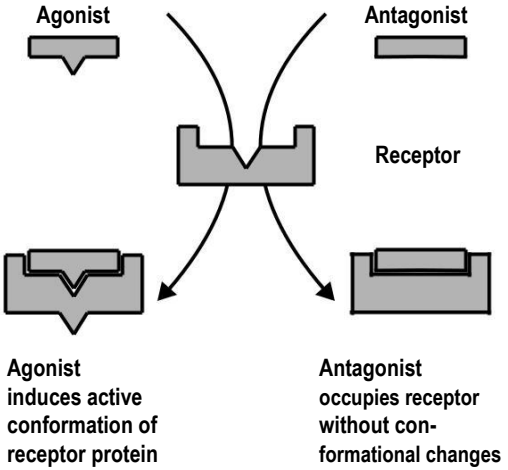


Fig. 2.3. Interaction of an agonist and an antagonist with the pharmacological receptor *(adapted from H. Lüllmann, 2000)*

DRUGS INTERACTION

Drugs interaction is the action of one drug on another one (table 2.1). *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 drugs) 2. Chemical (chemical reactions between the drugs).	1. Pharmacokinetic (interaction during absorption, distribution, biotransformation, and excretion) 2. Pharmacodynamic (intraction in 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).

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).

SIDE-EFFECTS

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

Ā □ Ā □ Ā □ irect toxic effects (e.g. ototoxicity, neurotoxicity, and nefrotoxicity of streptomycin)

Ā □ Ā □ Ā □ llergic reactions as immune reactions of hypersensitivity (e.g. anaphylaxis caused by penicillin) (fig. 2.4)

Ā □ Ā □ Ā □ diosyncrasy as an 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)

Ā □ Ā □ Ā □ mbryotoxic, fetotoxic and teratotogenous 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

Ā □ Ā □ Ā □ cancerogenous and mutagenous action as the ability to provoke the development of malignant tumors (e.g. secondary malignancy caused by leukopoiesis inhibitors).

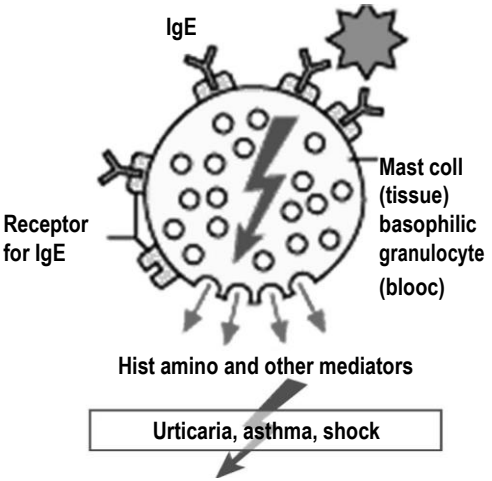


Fig. 2.4. Allergic reaction *(by H. Lüllmann, 2000).*

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

Age of the fetus (weeks)	**1-2**	**2,5-12**	**12-38**
Development stage	Nidation	Embryo: organ development	The fetus: growth and maturation
	Fetal death	Malformation	Functional disturbances

EFFECTS OF REPEATED DOSES OF DRUGS

Accumulation (material and functional) is the accumulation of the drug or its effects (e.g, material accumulation of digitoxin, functional accumulation of antide-pressants).

Tolerance (habituation) is a decrease of drug's action after its repeated admin-istration (e.g, tolerance to hypnotics, alcohol, nitroglycerine, 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 the patent wants to take the drug for altering general state and mood. It is characterized by abstinence. ***Abstinence*** is a phenomena of deprivation. Ethyl alcohol and narcotic analgesics may cause physical dependence.

Psychological dependence – if the patient wants to take the drug for alter-ing 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:

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

№2. The notions connected with a combined action of medications are:

Synergism and antagonism
Material accumulation
Drug dependence
Tolerance and tachyphylaxis
Elimination and excretion.

№3. Types of drugs' action are represented by:

A local and resorptive action
A reversible and irreversible action
A direct and indirect action
Pharmaceutical drugs interaction
A combined action of drugs.

№4. The true information concerning the receptor mechanism of action is:

The drug stimulating the receptor is its agonist
The drug inhibiting the receptor is its antagonist
The drug stimulating one subtype of receptor and inhibiting another one is an agonist-antagonist
The drug bound to the receptor with low affinity is a partial agonist
The drug without affinity to the receptor is its strong agonist.

№5. The 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 direct toxic action
Idiosyncrasy
An allergic reaction
A cancerogenous action
A teratogenous 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, astrin-gents, adsorbents, and protectives (coverings).

DRUGS FOR LOCAL ANESTHESIA

Local anesthesia

Local anesthesia is reversibly 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: lypophilic 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).

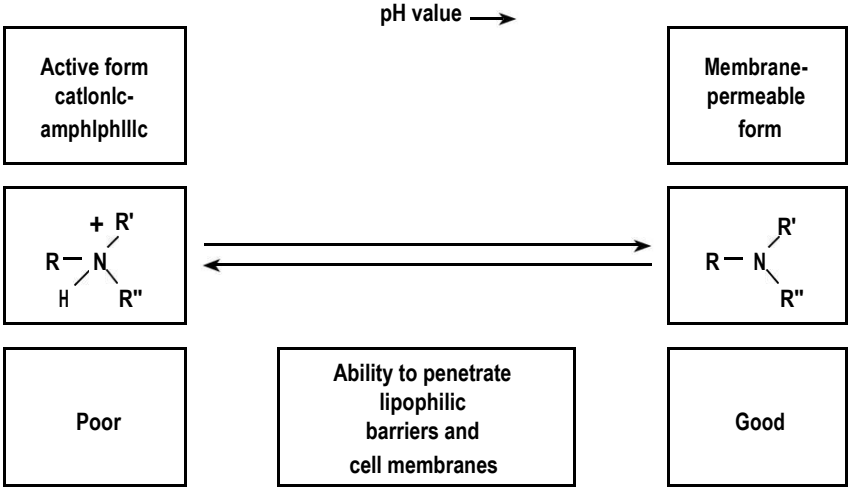


Fig. 3.1. The influence of pH on properties of local anesthetics.

Classification

Esters of para-aminobenzoic acid
- Procaine (Novocainum)
- Benzocaine (Anaesthesinum)
- Tetracaine (Dicainum)

Substituted amides of acetalinidin
- Lidocaine
- 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 the amides**

Esters	***Amides***
Have short action	Have long action
Are metabolized by esterases of blood	Are metabolized in the liver
Are not active at acid pH (in the site of purulent inflammation)	Are active at acid 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 (fig. 3.2).

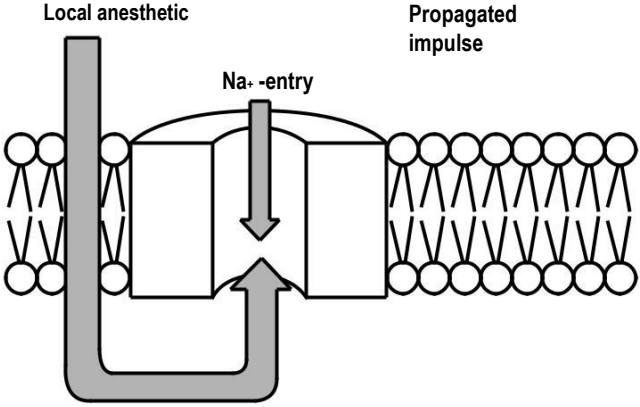


Fig. 3.2. Mechanism of action of local anesthetics *(by H. Lüllmann, 2000)*.

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

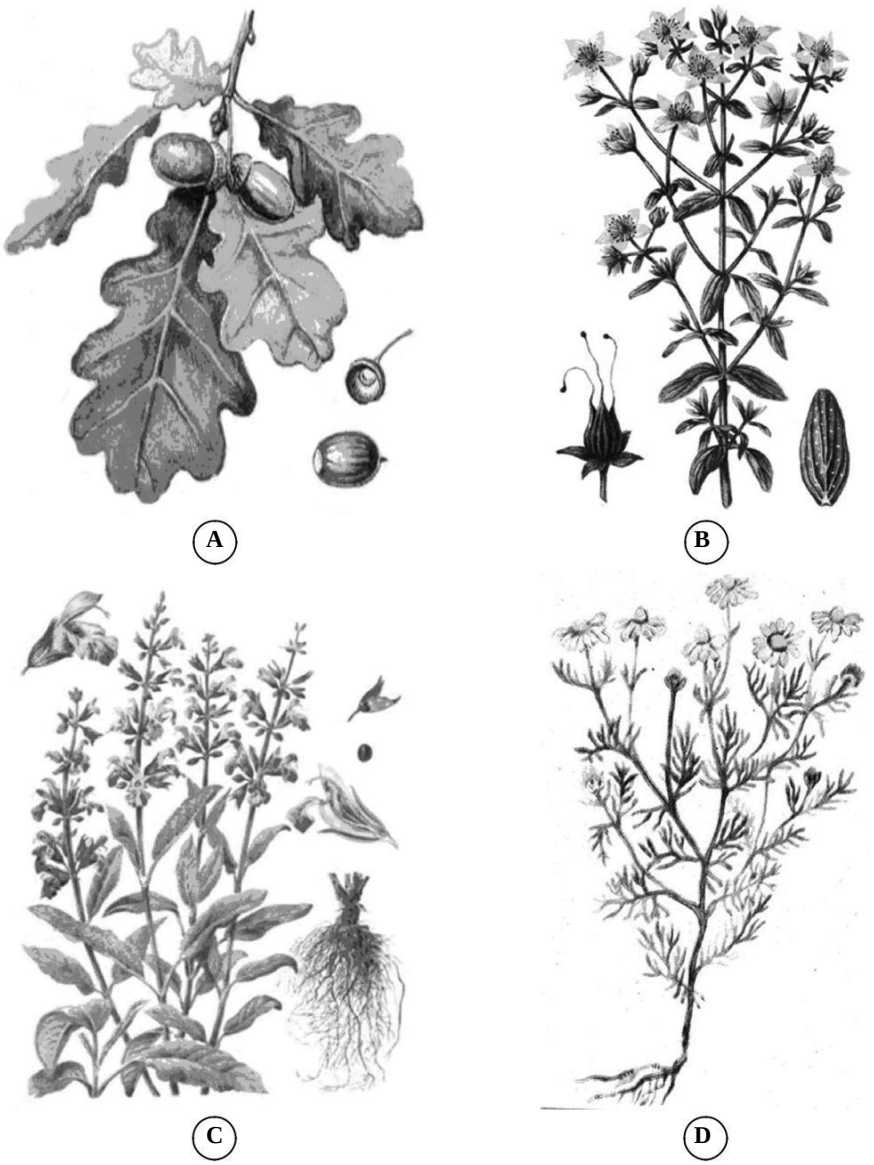


Fig. 3.3. Medicinal plants containing astringent substances:
A – oak; B – sant john's-wort; C – salvia; D – chamomile.

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

Benzocaine (Anaesthesinum) 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 (Xycainum) is the amide; acts longer than procaine; is more active; is suitable for all types of anesthesia; is used for the treatment of ventricular tachyar-rhythmia (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 protein and form albuminates on the surface of the damaged skin or the mucous membrane, thus protecting the receptors from irritating factors and relieving pain.

CLASSIFICATION

Organic substances
- Tannin
- Tanalbinum
- herb of Saint-John's-wort (*herba Hyperici*)
- flowers of chamomile (*flos Chamommillae*)
- leaves of salvia (*folium Salviae*)
- bark of oak (*Cortex Quercus*)

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 anti-toxic action (is an antidote in poisonings

with alkaloids and salts of metals); is used for gargling in diseases of oral mucose, for processing of burns, for lavage of stomach in acute poisonings; may disturb digestion if it is taken orally.

Tanalbinum 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.

Leaves of salvia (Folium Salviae), herb of sant-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 skin.

ADSORBENTS

Adsorbents are insoluble fine powders which have a large active surface capa-ble 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 char-acterized 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:
Procaine (Novocainum)
Tetracaine (Dicainum)
Benzocaine (Anaesthesinum)
Cocaine
Lidocaine (Xycainum).

№2. Tannin realizes its anti-inflammatory action due to:
The formation of albuminates on the surface of the mucous membrane
The adsorbtion of toxic substances
The formation of colloidal covering on the mucous membrane
Local anesthesia
The irritation of sensitive nerve endings.

№3. Local anesthetics have the following common properties:
They are bases
The anesthetic activity rises at alkaline pH
Ester local anesthetics are metabolized by esterases in blood
Amide local anesthetics are metabolized by hepatocytes
The duration of action of esters is longer than that of amides.

№4. The starch mucus realizes its action due to:
The formation of albuminates on the surface of the mucous membrane
The adsorbtion of toxic substances
The formation of colloidal covering on the mucous membrane
Local anesthesia
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:
The blockage of sodium ion channels
The blockage of calcium ion channels
The opening of potassium channels
The blockage of adrenergic receptors
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)

Expectorants (reflexly acting)

- Herb of *Thermopsis*
- Root of *Althea*
- Mucaltinum

Bitters

- Tincture of Absinthium

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

Laxatives and purgatives

Acting in the small intestine
- Castor oil

Acting in bowels
- Root of *Rheum*
- Leaves of *Senna*
- Bisacodyl

Acting in all the 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 inhala-tions
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 a diminishing a toothache and for 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 (38ºC) myrosin destroys synegrin with release of mustard oil; this oil irritates sen-sitive nerve endings in the skin, dilates blood vessels and improves trophy in the site of application; has reflexive action and decreases pain in internal tissues; reflexly lowers BP, decreases anginal pain, accelerates recovering from pneumonia

indications: myositis, myalgia, peripheral neuritis, neuralgia, arthritis, ar-thralgia, 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.

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

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 the beat of the cotton 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 effect. 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 acute and chronic diseases of 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 grass of Thermopsis (fig. 4.2) also excites the respiratory center. Decoction from the root of Althea and Mucaltinum (fig. 4.2) have a covering effect.

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

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. 4.3. *Arthemisia absinthium* containing bitter.

EMETIC DRUGS

Emetic drugs are medications provoking vomiting.

They are divided into:

Drugs of central action – ***apomorphine hydrochloride*** acting on the chemo- receptors 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, pregnancy.

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 gut motility (fig. 4.4).

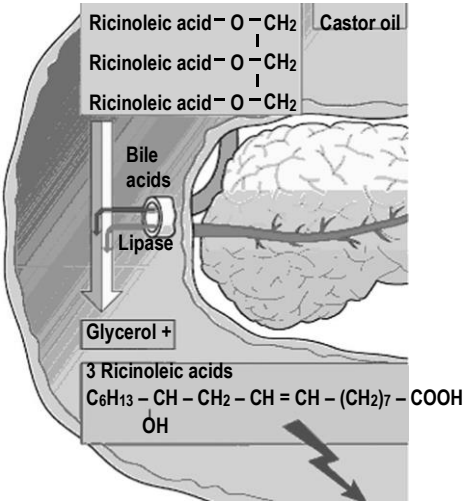


Fig. 4.5. Mechanism of action of Castor oil *(by H.Lüllmann, 2000)*.

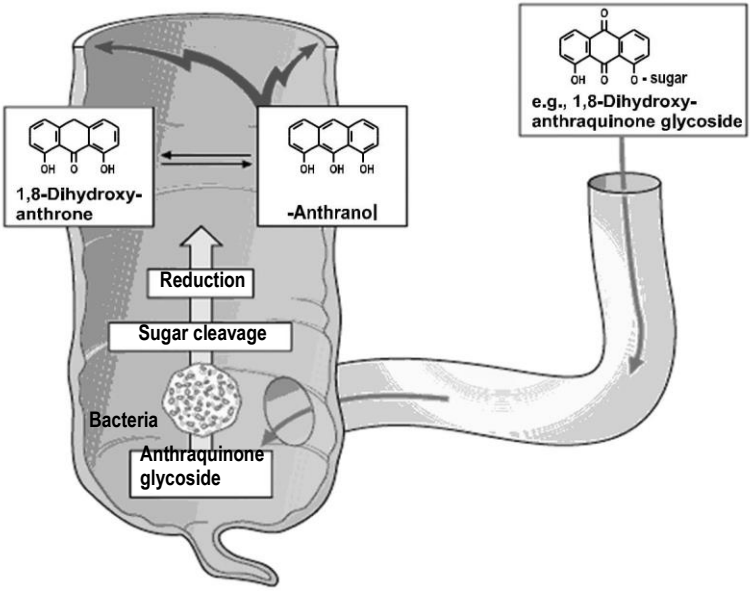


Fig. 4.6. Mechanism of action of anthraquinone derivatives – large-bowel irritant laxatives *(by H.Lüllmann, 2000)*.

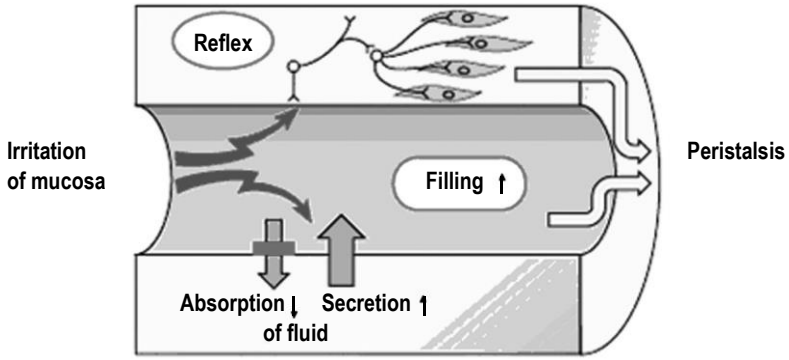


Fig. 4.4. Stimulation of peristalsis by mucosal irritation *(by H.Lüllmann, 2000).*

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 anthraguinone 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 induce an increased fluid secretion and colonic contraction (fig. 4.5). It is used in acute constipation.

Anthraguinone 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 intoxication, acute constipation, before some diagnostic procedures, or in treatment with some antihelminthics.

TESTS FOR SELF-CONTROL

№1. Mustard seeds realize their action by:

The formation of albuminates

The absorption of toxic substances

Ā Ä ˚Ā □ Ā □ Ā
he formation of colloidal covering
Ā Ä ˚Ā □ Ā □ Ā
he stimulation of nerve endings in the gut
Ā Ä ˚Ā □ Ā □ Ā
he irritation of sensitive nerve endings in the skin.

№2. Menthol is characterized by all, except:
The irritation of sensitive nerve endings
A reflexive action on coronary blood vessels
The constriction of blood vessels in the site of application
Vasodilation in the site of application
The improvement of taste and odor of dental powders and pastes.

№3. The reflexly acting expectorants are:
Sodium bicarbonate
Trypsin
Mucaltinum
Infusion from the herb of Thermopsis
Decoction from the root of Althea.

№4. Bitters are:
Stimulants of appetite
Suppressors of appetite
Drugs for replacement therapy
Antimicrobial drugs for treatment of peptic ulcer
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?
Castor oil
Phenolphtalein
Magnesium sulphate
Root of Rheum
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 the function of 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 the 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 tissue of effector organs or near it	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.***

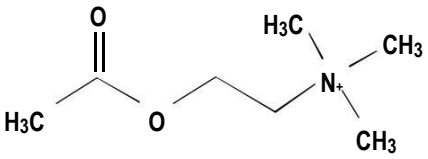


Fig. 5.1. Structure of acetylcholine

Each synapse contains a presynaptic membrane, a synaptic gap (cleft), and a post-synaptic membrane with cholinergic receptors (fig. 5.2). Acetylcholine is synthesized in the presynaptic part of the nerve ending. It is deposited in vesicles, releases 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.

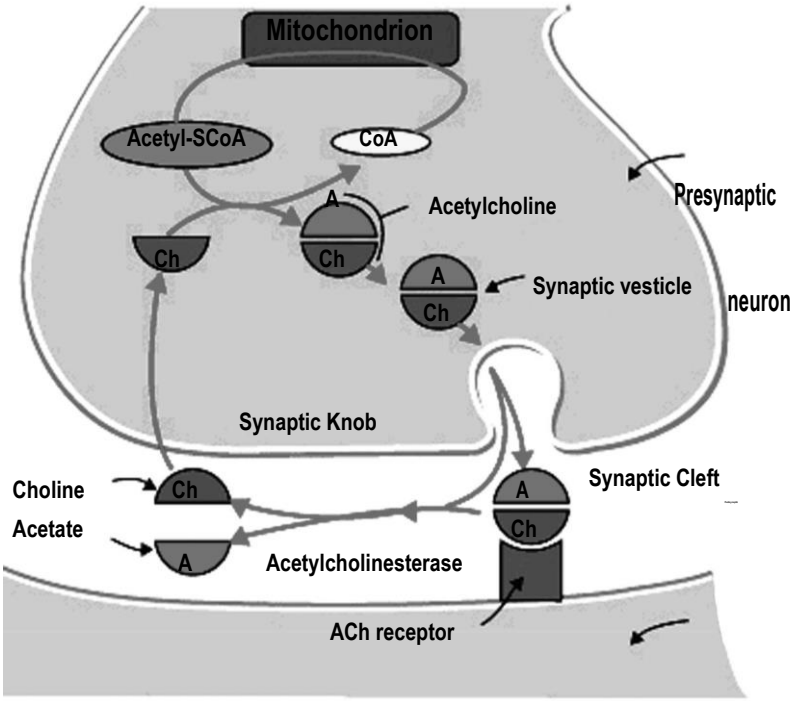


Fig. 5.2. Structure and function of cholinergic synapse *(http://images.yandex.ru)*.

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 (muscarinic)*** 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.

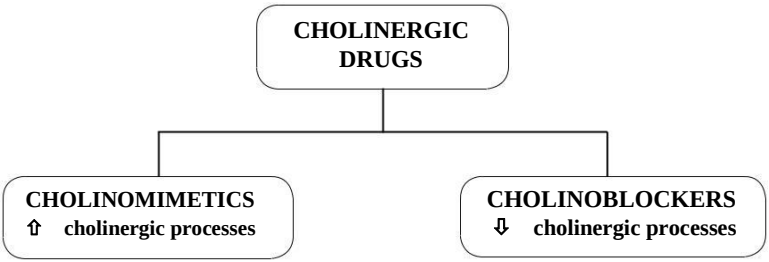


Fig. 5.3. Cholinergic drugs.

CHOLINOMIMETICS

Classification

M-,N-cholinomimetics

Direct-acting
- Acetylcholine
- Carbachol (Carbocholinum)

Indirect-acting (anticholinesterases)
- Neostigmine (Proserinum)
- Physostigmine
- Pyridostigmine
- Galanthamine hydrobromide
- Isoflurophate

M-cholinomimetics
- Pilocarpine hydrochloride

N-cholinomimetics
- Cytitonum
- 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 eye lens for near vision) A decrease in intra-eye pressure	Glaucoma
Stimulation of glands secretion An increase in salivation	Xerostomia
An increase in smooth muscles tone	Atonia of the intestine and urinary bladder after surgeries
Bradycardia Blood vessels dilation	Arrhythmia

Side-effects

Hypersalivation
Pain in the abdomen

Diarrhea
Spasm of bronchi
Bradycardia
Frequent urination
Sweatiness.

Peculiarities of preparations

Carbachol (Carbacholinum) has the chemical structure similar to acetylcholine, but is not destroyed by cholinesterases; is 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 a M-cholinomimetic; has 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.

Aceclidinum 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

Fig. 5.4. *Pilocarpus pinnatifolius* containing pilocarpine

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.

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

Pharmacodynamics

all M-cholinomimetic effects on internal organs (similar to those of carba-chol and pilocarpine)

an increase in neuromuscular transmission resulting from the accumulation of acetylcholine at the neuromuscular junction.

Side-effects

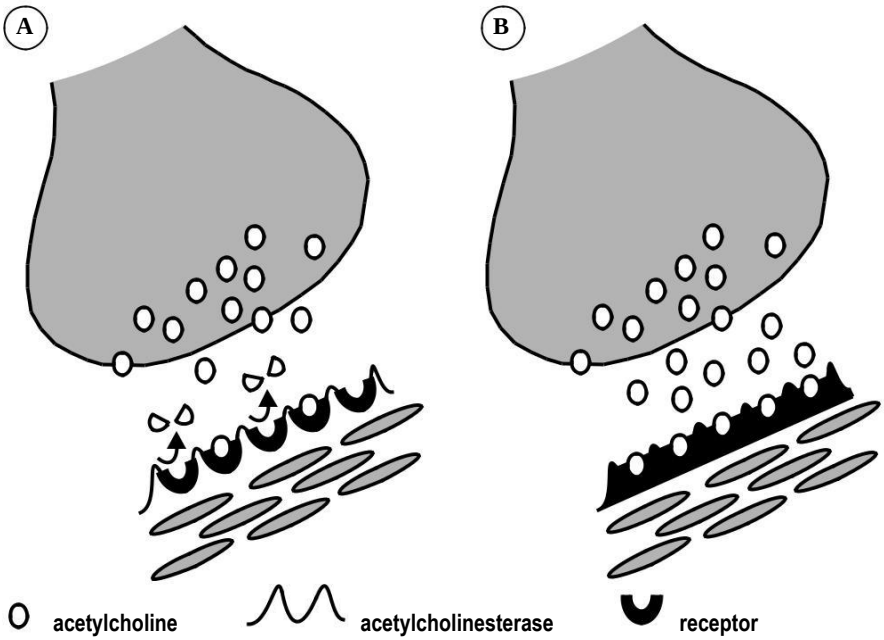


Fig. 5.5. Mechanism of action of anticholinesterases *(http://www.picsearch.com)*.

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

Galantamine is an alkaloid from *Phyzostigma venenosum* (fig. 5.6); is administered SC, IM; penetrates into 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.

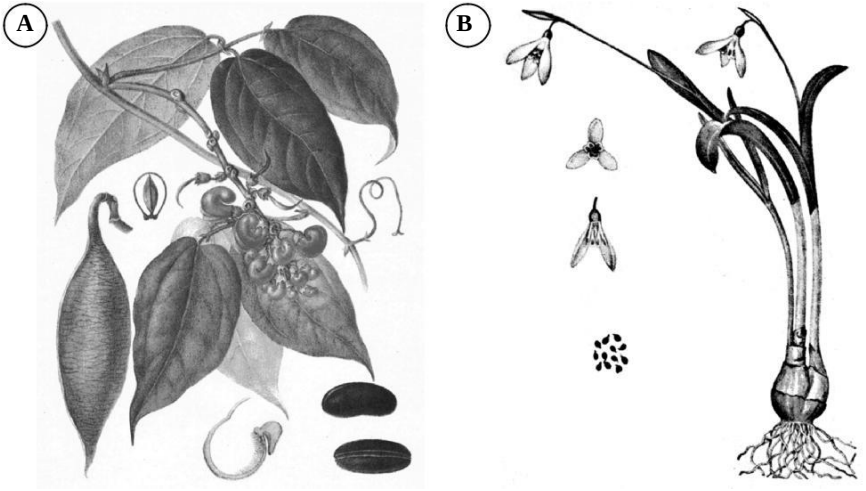


Fig. 5.6. Medicinal plants containing anticholinesterases:
A – *Phyzostigma venenosum*; B – *Galanthus Woronowi*.

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

Phosphacolum 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

- 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

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

Lobeline is an alkaloid; is administered IV and acts during 3-5 min; the mechanism of action is similar to Cytitonum; 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 a decrease in BP resulting from the stimulation of *n.vagus* center.

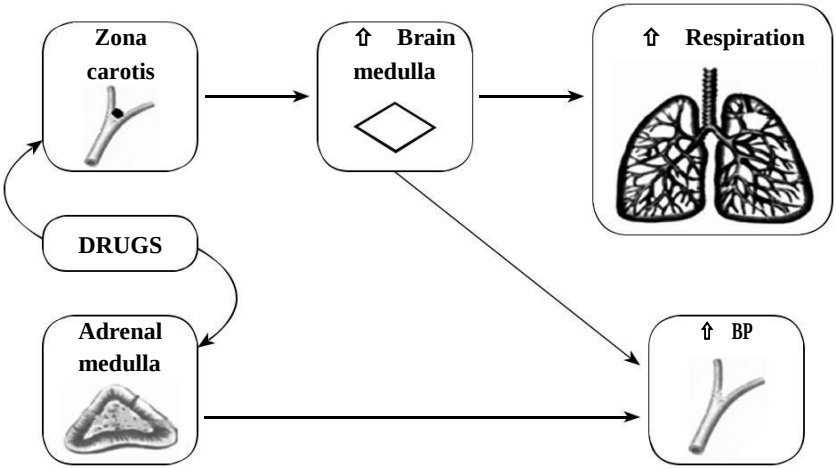


Fig. 5.7. Mechanism of action of N-cholinomimetics.

NICOTINE

It is a tobacco alkaloid with a dose-dependent action on N-cholinoreceptors. Effects of nicotine are manifested in tobacco smoking. Nicotine causes dependence that leads to abuse of tobacco and results in the development of cardiovascular and lungs pathology.

TESTS FOR SELF-CONTROL

№1. Cholinomimetics may cause all the following side-effects, except:
Bradycardia
Bronchospasm
Salivation
Constipation and urinary retention
Sweating.

№2. Only one preparation is N-cholinomimetic:
Carbochol
Lobeline
Neostigmine

Aceclidinum
Pilocarpine.

№3. Anticholinesterases are used for the treatment of:
Atropine (belladonna) poisoning
Postoperative paralytic ileus (atony of intestines)
Overdose of depolarizing myorelaxants
Myasthenia gravis
Glaucoma.

№4. N-cholinomimetics:
Are stimulants of respiration
Are drugs for emergency help
Have long duration of action
Are used for the treatment of glaucoma and atony of the GI tract
Are drugs for relief of tobacco smoking.

№5. In the complex treatment of a child suffering from cerebral palsy, the doctor decided to include anticholinesterase drug penetrating CNS and moderately improving mental development. Choose this drug.
Phosphacol
Neostigmine (Proserinum)
Galanthamine
Pilocarpine
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).

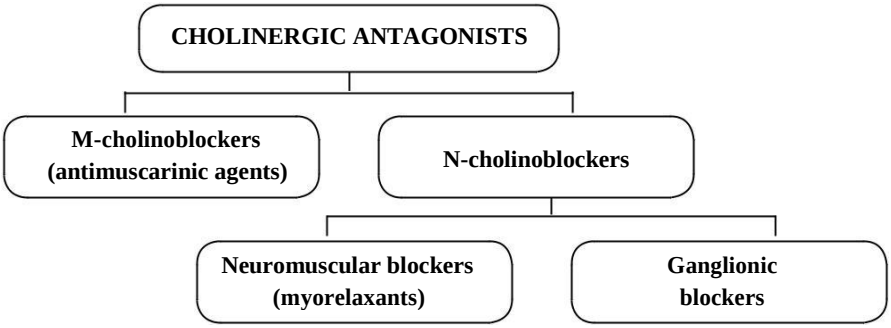


Fig. 6.1. Groups of cholinergic antagonists.

M-CHOLINOBLOCKLERS

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

Classification

A. *Non-selective*

1. Natural agents
   - Atropine sulfate
   - Hyoscine (Scopolamine hydrobromide)
   - Platyphylline hydrotartrate
   - Belldoonna dry extract

   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.

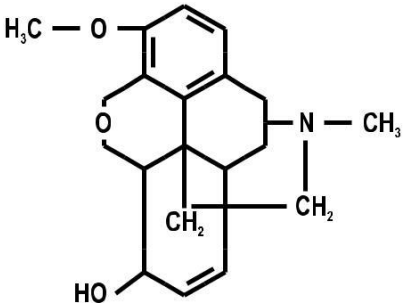


Fig. 6.2. Chemical structure of atropine.

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

Fig. 6.3. *Atropa Belladonna* containing atropine.

Pharmacokinetics

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

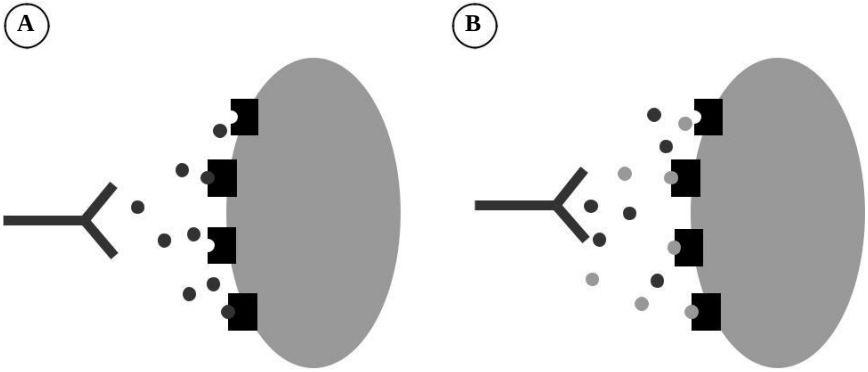


Fig. 6.4. Mechanism of action of atropine: A –normal condition of cholinergic synapse; B – synapse condition in the presence of atropine *(http://www.picsearch.com)*.

Pharmacodynamics

weak local anesthesia in the site of application
in CNS: therapeutic doses – a sedation and antiparkinsonian effect; large doses – excitation, hallucinations, and coma
in the eye: dilatation of pupil (midriasis), 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 blad-der and urinary pathways
the inhibition of sweat secretion
antidote properties in acute poisonings with M-cholinomimetics, anti-cholinesterases 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 midriasis are "pharmacological bandage" producing eye immobilization)
Diagnostics of eye diseases, the measurement of refraction for the correct selection of 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	Contraindications
Dilated pupils resulting in photo-phobia	Glaucoma
Blurred vision	Tachycardia, taciarrhythmia
An increase in intraocular pressure, an attack of glaucoma in someone with latent condition	Atonia of the GI tract, achalasia, ulcerative colitis
Tachycardia	Prostate hyperplasia, adenoma of prostate
Dry mouth	Hepatic insufficiency
Constipation	Hyperthyroidism
Retention of urine	High body temperature
Flushed skin	Toxicosis of pregnancy
A rise in body temperature.	Cerebral pathology in children
	Childhood or old age.

Acute poisoning with atropine

Signs:

— restlessness, disorientation, hallucinations, delirium, coma
— midriasis, 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 contained 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 block-ing, has antiparkinsonian effect; has a strong and short (5-6 hrs) 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 the 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 over-excitation of n. vagus nerve. 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 ex-creted; 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 the 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 gastrointestinal tract. Side effects are dry mouth, mydriasis, disturbances of accom-modation, drowsiness.

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

Pirenzepine is selective M1-cholinoblocker inhibiting gastric secretion; is administered orally, IM, IV; produces maximal concentration in 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 treatment of ulcer of 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 the M-cholinoreceptors of the sphincter in the iris and ciliary muscle, causing short-term mydriasis and accommodation paralysisis; is used in ophthalmology for examination of the ocular fundus, investigation of refraction, as well as in 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 ganglia or in skeletal muscles.

GANGLIONIC BLOCKERS

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

Classification

Quaternary amines
- Hexamethonium (Benzohexonium)
- Hygronium
- Pentamine

Tertiary amines
- Pachycarpine hydroiodide
- Pirilenum.

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 sympathetic and parasympathetic ganglia and disturbs the autonomic regulation of 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 sympatholytic and antisecretory effects.
Under these conditions sensitivity of effector organs to humoral stimuli stays normal or is increased.

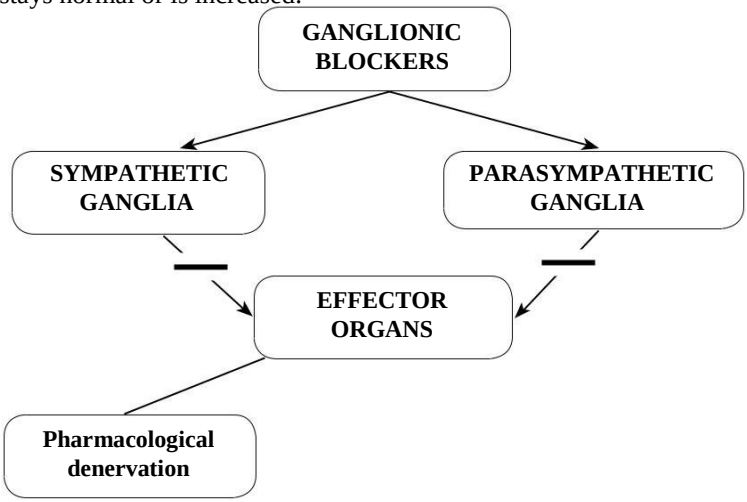


Fig. 6.5. Mechanism of action of ganglionic blockers.

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 intraocular pressure which depends on the type of glaucoma.

Indications

Hypertensive emergence
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 emergence.

Pentamine is less potent than hexamethonium, acts during 1,5 hrs, is administered IV, IM for emergency help in acute hypertension, a bronchial asthma attack, colic, as well as for controlled hypotension in surgeries.

Fig. 6.6. *Sophora pachycarpa* containing pachycarpine.

Pirilenum 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.

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 gangl-iolitis, spasms of blood vessels, nervous diseases, myopathy, may be used for the stimulation of the labor activity; has high toxicity.

MYORELAXANTS

Myorelaxants (neoromuscular blockers) are cholinergic drugs which interfere with the transmission of nervous impulses in the synapses of skeletal muscles caus-ing their relaxation.

Classification

Non-depolarizing agents
– d-Tubocurarine chloride
– Pancuronium bromide
– Pipecuronium bromide
– Rocuronium bromide
Depolarizing agents

Succinylcholine (Dithylinum).

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).

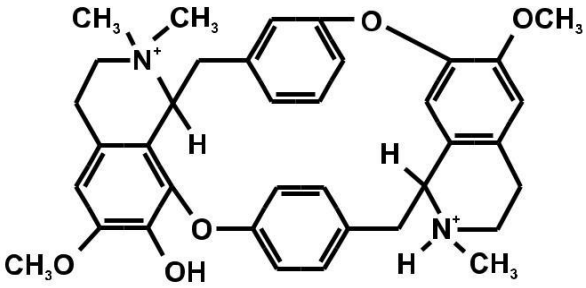


Fig. 6.7. Chemical structure of d-tubocurarine.

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).

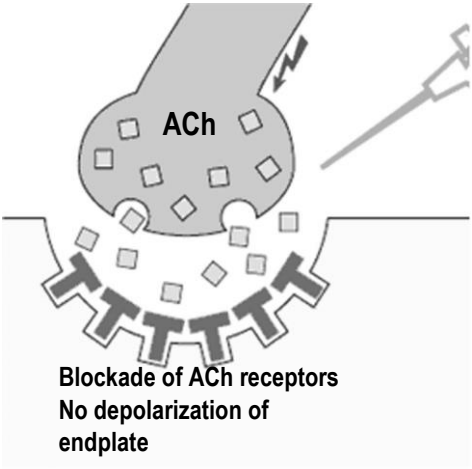


Fig. 6.8. Mechanism of action of d-tubocurarine *(by H.Lüllmann, 2000).*

Pharmacodynamics

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

Indications

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

Side-effects

Spasm of bronchi and urticaria (due to histamine release from mast cells)
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 musculs; inhibits neuromuscular transmission and causes myorelaxation, has weak vagolytic effect, does not affect the release of histamine. The duration of the effect is 22 min in adults.

SUCCINYLCHOLINE

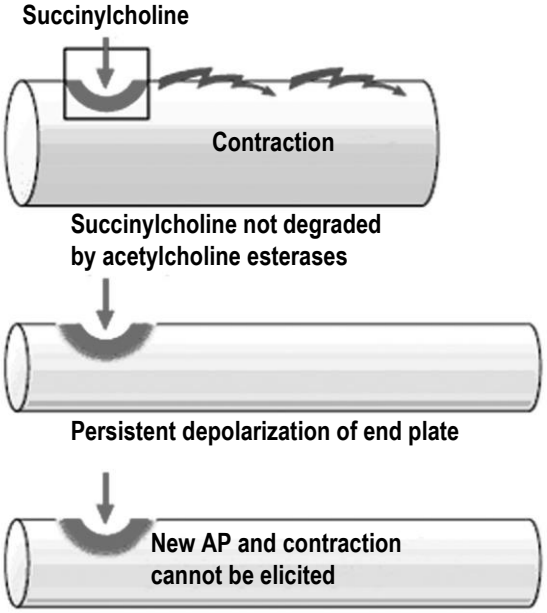


Fig. 6.9. Mechanism of action of succinylcholine *(by H. Lüllmann, 2000)*.

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 ventila-tion; is destroyed by butiryl cholinesrerase in blood

like acetylcholine, acts on 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 (AP). 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 short surgeries, intubation of thrachea, endoscopy, reposition of bone fractures

may cause fibrillation of skeletal muscles at the start of action, hyper-kalemia, cardiac arrhythmia, an increase of intraocular pressure, pain in 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 aminoacid transmitters.

TESTS FOR SELF-CONTROL

№1. Succinylcholine (Dithylinum):

Is depolarizing myorelaxant
Has short duration of action
May cause lasting apnoea in some patients
Is suitable for short surgeries
All the listed.

№2. Ganglionic blockers:

Block N-cholinoreceptors in parasympathetic ganglia
Block N-cholinoreceptors in sympathetic ganglia
Block N-cholinoreceptors in skeletal muscles
Block N-cholinoreceptors in CNS

E. Block N-cholinoreceptors both in parasympathetic and sympathetic ganglia.

№3. Indications to the use of atropine are:
Gastric ulcer
Colic
Atonia of the gut after the surgery
Bradycardia
Preanesthetic medication.

№4. The true statements concerning M-cholinoblockers are:
Atropine is used to treat glaucoma
Scopolamine is used in motion sickness
Plathyphylline dilates blood vessels and lowers BP
Pirenzepine is for the treatment of gastric ulcer
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:
The inability to penetrate through the blood brain barrier
The inhibition of M-cholinoreceptors in the bronchi only
The inhibition of all the types of M-cholinoreceptors
The inhibition of cholinesterase
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).

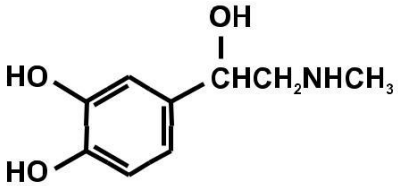


Fig. 7.1. Chemical structure of norepinephrine.

ADRENERGIC SYNAPSE

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

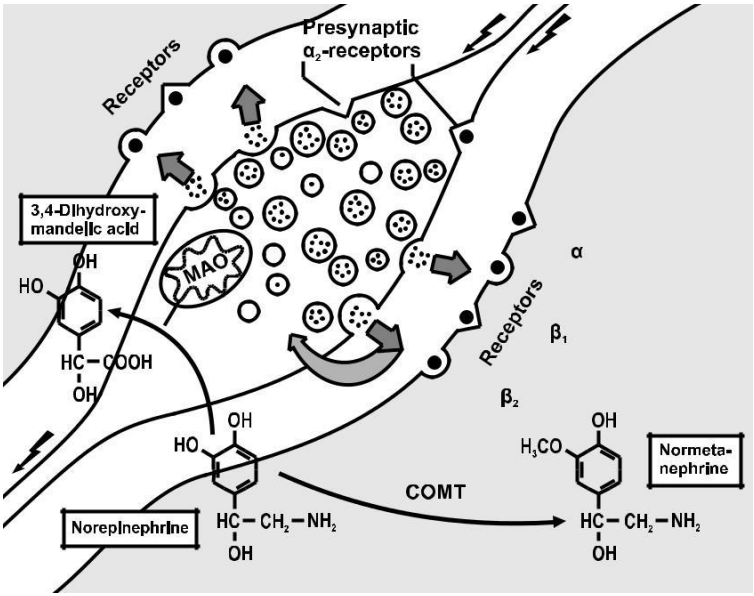


Fig. 7.2. Adrenergic synapse and its function *(by H.Lüllmann, 2000)*.

Norepinephrine is synthesized in the presynaptic part of the neuron. It is depos-ited 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 synaptic gap 20% of norepinephrine is degradated by catechol-O-methyltransferase (COMT). Another part of neurotransmitter (80%) is re-uptaken by the presynaptic membrane.

ADRENOCEPTORS

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

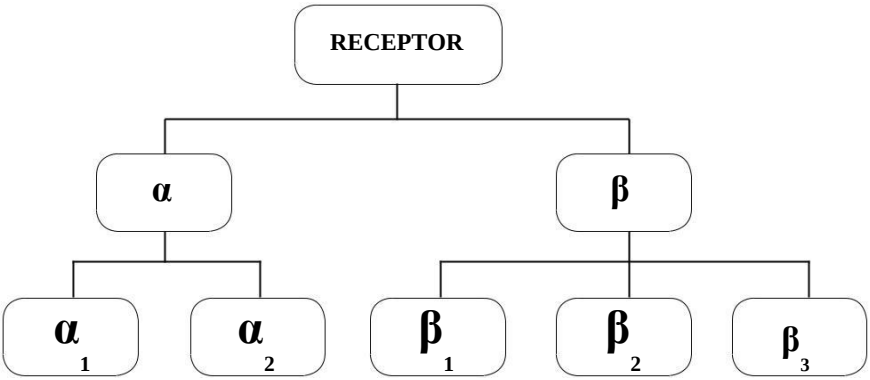


Fig. 7.3. Types and subtypes of adrenoceptors.

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

ADRENERGIC DRUGS

Drugs acting on adrenergic synapses are named ***adrenergic drugs***. They are divided into two groups: ***adrenergic agonists*** and ***adrenergic antagonists (adreno-blockers and sympatholytics)*** – fig.7.4.

Adrenergic agonists are also named adrenopositive drugs or adrenomimetics. Adrenergic antagonists are also named adrenonegative agents. Among them there are substances inhibiting adrenergic receptors (adrenoblockers) and substances influencing the store and re-uptake of norepinephrine (sympatholytics).

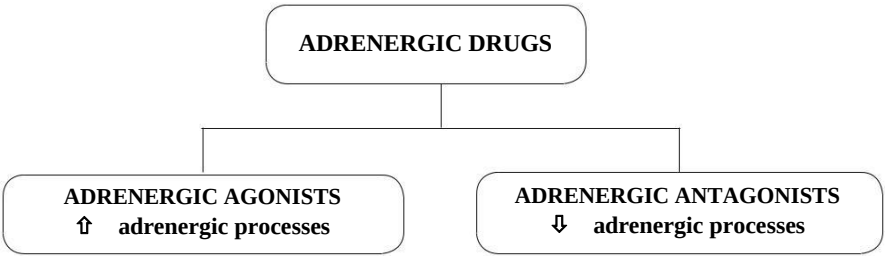


Fig. 7.4. Drugs influencing adrenergic synapses.

ADRENERGIC AGONISTS

Adrenergic agonists are drugs stimulating adrenergic neurotransmission. **Classification**

α-, β-adrenomimetics
- Direct-acting
  - Adrenaline hydrochloride (Epinephrine)
- Indirect-acting
  - Ephedrine hydrochloride

α-adrenomimetics
- Non-selective
  - Noradrenaline hydrotartrate (α_1, $\alpha_2 > \beta$)
- Selective
  - Phenylephrine (Mesatonum) (α_1)
  - Naphazoline (Naphthyzinum) (α_2)
  - Halazolin (Xylometazoline) (α_2)

β- adrenomimetics

Non-selective
– Isoprenaline (Isadrinum) (β_1, β_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 CNS
is biotransformed by enzymes in blood
acts during 15 min on intern organs and during 30 min on metabolic proc-esses.

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 the eye
Elevation of blood	Shock, collapse
pressure Bronchodilation	Bronchial asthma attack
An increase in glucose concentration in blood	Hypoglycemic coma
Inhibition of allergy	Anaphylactic shock
Mydriasis	Pupil dilatation.
A decrease in intra-eye pressure.	Open-angle glaucoma.

Side-effects

Excitement, tremor
Hypertension
Arrhythmia
Hyperglycemia.

Contraindications

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

EPHEDRINE

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

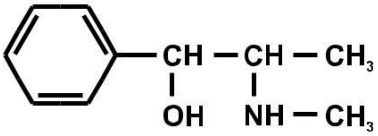


Fig. 7.5. Chemical structure of ephedrine.

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

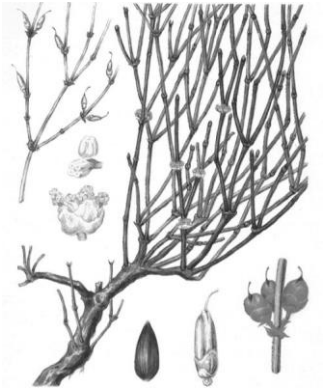


Fig. 7.6. *Ephedra equisetica* containing ephedrine.

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 noradrenaline, inhibits the re-uptake of noradrenaline (indirect action) (fig. 7.7).

It has a weak direct action on adrenoceptors.

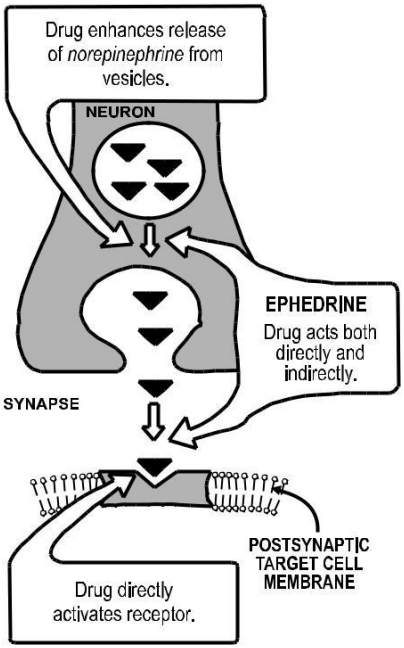


Fig. 7.7. Mechanism of ephedrine's action
(adapted from R.Finkel et al., 2008).

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
Anaphylactic shock
Bronchial asthma
Bronchospasm
AV block, bradycardia
Acute rhinitis
Acute conjunctivitis
For pupil dilatation
Pathological narcolepsia
Myasthenia
Enuresis.

Side-effects

Insomnia
Anxiety, restlessness, insomnia
Tachycardia
Palpitation
Hypertension
Rash on the skin
Tolerance and tachyphylaxis
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 *e*ffects	**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 adrenocep-tors 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 the necrosis of soft tissues, if it is administered SC or IM; is contraindicated in blood loss, cardiogenic shock, long-lasting shock.

Phenylephrine (Mesatonum) 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 midriasis, 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 neurotrans-mission 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 bronchi	Bronchial asthma, spasm of bronchi
An increase in the heart rate	Heart block, bradycardia
An increase in the heart work	Danger of pregnancy interruption.
A decrease in the myometrium tone.	

Peculiarities of preparations

Isoprenaline (Isadrinum) 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 a bronchial asthma attack, heart block, some types of cardiogenous 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 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 cardiogenous shock.

COMPARISON OF ADRENOMIMETICS-CATECHOLAMINS

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

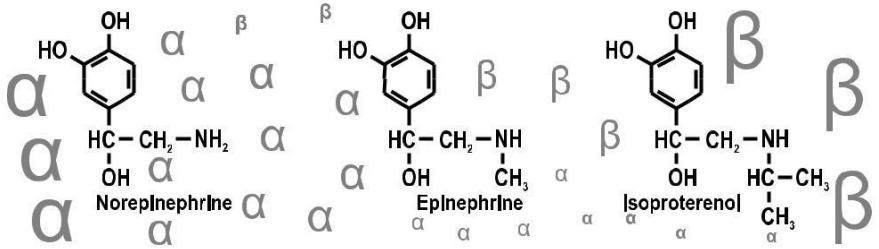


Fig. 7.8. Chemical structure of catecholamines and their affinity to α- and β-adrenoceptors *(by H.Lüllmann, 2000)*.

This affinity depends on the structure of substitute radicals. They may be methyl in adrenalin or isopropyl in isoproterenol. 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. **Dependance of catecholamines' effects on their chemical structure**

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

Dobutamine
Metoprolol
Isadrinum
Adrenaline
Partusisten (Fenoterol).

№3. Ephedrine:

Releases stored noradrenaline from nerve terminals
Produces bronchodilation
Stimulates CNS
Rises systolic blood pressure
Produces AV block.

№4. Isoprenaline (Isadrinum) is:

Contraindicated in tachyarrhythmia
Synthetic catecholamine
Bronchodilator
Stimulant of the heart function
Cardioselective adrenomimetic.

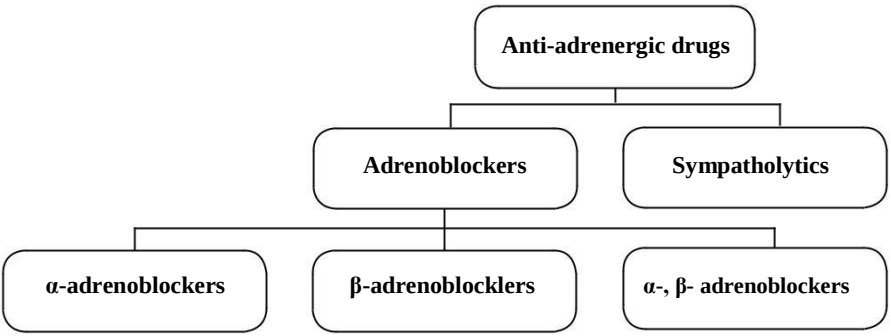


Fig. 8.1. Groups of anti-adrenergic drugs.

№5. To perform fundoscopy, ophthalmologist instilled in the eye an agent capable of causing midriasis without cycloplegia. Point out this agent.
Phenylephrine (Mesatonum)
Noradrenaline
Atropine
Pilocarpine
Isoprenaline (Isadrinum).

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).

Classification

α-adrenoblockers

Non-selective

– Phentolamine hydrohloride

Selective

– Prazosin

– Doxazasin

β-adrenoblockers

Non-selective

– Propranolol (Anaprilin)

– Oxprenolol
Selective
– Metoprolol
– Atenolol
– Nebivolol
– Bisoprolol

α-, β-adrenoblockers
– Labetalol
– Carvedilol

Sympatholytics
– Guanethidine (Octadinum)
– 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 peripheral resistance, an increase in venous capacity
a decrease in BP
the improvement of trophy of peripheral tissues
the stimulation of gut motility
the stimulation of the salivary, lacrimal, pancreatic, and respioratory tract secretions
a decrease of urine retention in patients with prostate hyperplasia.

Indications

Hypertension
Spasms of peripheral blood vessels (Raynaud's disease)
Frostbites, trophic ulcers
Pheochromacitoma (diagnostics and treatment)
Prostate hyperplasia.

Side-effects

Headache, vertigo
Hypotension
Weakness
Insomnia
Orthostatic collapse
Tachycardia
Vomiting, nausea, diarrhea
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 back-cross regulation of norepinephrine liberation in 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.

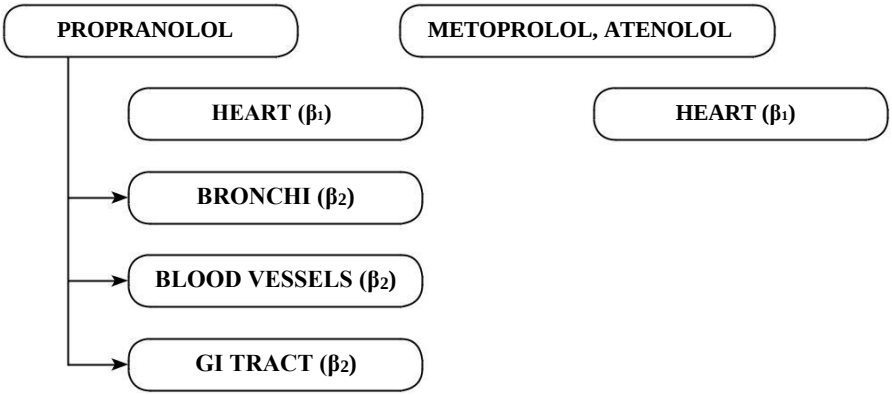


Fig. 8.2. Targets of action of propranolol and cardioselective β-adrenoblockers.

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 blood serum
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 myocardium
a decrease in excitability of myocardium
a decrease in conductivity of myocardium
a decrease in the heart rate (*anti-arrhythmic* effect)
decreases 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 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 taken orally for the treatment of hypertension, angina pectoris, and arrhythmia; does not cause spasm of 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 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_1-adrenoceptors.

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

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

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 a bronchi, pregnancy.

CARVEDILOL

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

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

h
s an alkaloid from *Rauwolfia serpentine*

h
ecreases the storage of norepinephrine that leads to destruction of neurotransmitter by MAO in axonal cytoplasma resulting in a decrease of neurotransmission in adrenergic synapses (fig. 8.3)

h

enetrates CNS, has a central and peripheral action (table 8.1)

has an antihypertensive, sedative and antipsychotic action
is administered orally, IM or IV
acts during 8–12 hrs
is indicated in hypertension
may cause disturbances of sleep, depression, bradycardia, spasm of bronchi, stimulation of gastric secretion, diarrhea.

GUANETHIDINE (OCTADINUM)

is a synthetic compound of simple structure
produces active storage and uptake instead of norepinephrine, decreases neurotransmitter release
does not penetrate CNS, has only peripheral action (table 8.1)

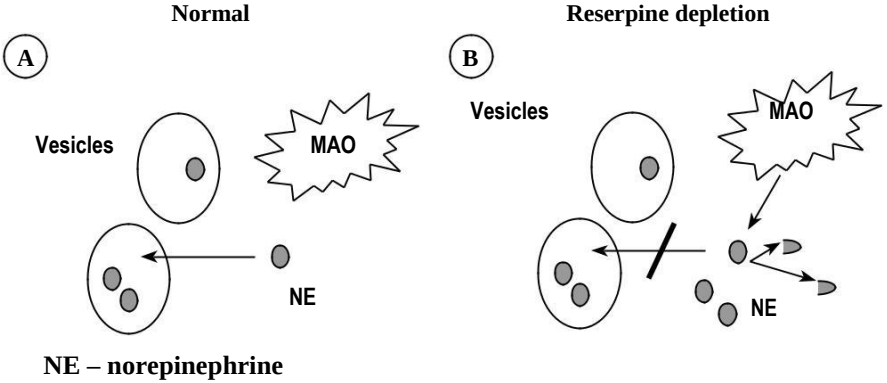


Fig. 8.3. Mechanism of reserpine's action: A – normal condition of adrenergic synapse; B – adrernergic synapse in the presence of reserpine.

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 bronchi, stimulation of gastric secre-tion, diarrhea, enlargement of salivary glands).

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

HISTAMINERGIC DRUGS

Histaminergic agents include histamine and antihistamines.

HISTAMINE

Histamine is biologically active amine which regulates the tone of smooth mus-cles, allergy, inflammation, and secretion of exocrine glands. It realizes its action by the binding with histamine receptors. In a 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

Drugs stabilizing mast cells membranes
— Cromolyn sodium (Sodium cromoglycate, Intal)
— Ketotifen (Zaditen)

Blockers of H_1-histamine receptors
— Diphenhydramine (Dimedrol)
— Clemastine (Tavegil)
— Chloropyramine (Suprastin)
— Promethazine (Diprazin)
— Mebhydroline (Diasolinu
— Quifenadine (Phencarol)
— Loratadine
— Fexofenadine

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 the bronchial asthma attack, allergic rhinitis, and conjunctivitis
may cause the irritation of respiratory pathways, spasm of 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).

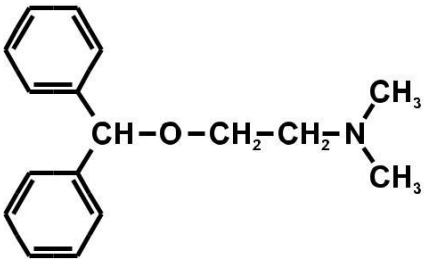


Fig. 8.4. Chemical structure of diphenhydramine.

Pharmacokinetics

Ā ÄĀᵀĀ □ Ā □
s administered orally, IM, IV, rectally, topically (ointment, eye drops)

Ā ÄĀᵀĀ □ Ā □
s absorbed in the GI tract

Ā ÄĀᵀĀ □ Ā □
enetrates CNS and placenta

Ā ÄĀᵀĀ □ Ā □
s metabolized in the liver, is the inductor of microsomal oxidation

Ā ÄĀᵀĀ □ Ā □
s excreted by urine

Ā ÄĀᵀĀ □ Ā □
as 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 a histamine action
a decrease of allergic reactions
a decrease in edema of tissues due to histamine
a decrease in permeability of blood vessels wall
a decrease of inflammation
a decrease in spasms of smooth muscles
ganglia blocking effect
sedative and hypnotic effect
anti-emetic effect
potentiative action.

Indications

Allergic diseases (angioneurotic edema, hay fever, urticaria, vasomotor rhinitis, serum sickness)
Allergic complications of blood transfusion
Allergic complications of pharmacotherapy
Hemorrhagic capillary toxicosis
Radiation sickness

Motion sickness
Insomnia
The potentiation of general anesthesia.

Side-effects

1. Weakness, fatigue, psychomotor impairment, depression

Dry mouth
Blurred vision
Urinary retention
Gastro-intestinal disturbances
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 antihista-mine and weak sedative effect.

Chloropyramine (Suprastin) is taken orally, IM, IV; has an overage antihista-mine 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 a 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 action.

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, gastroe-sophagitis. 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.

SEROTONIN-ERGIC DRUGS

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

SEROTONIN ADIPINATE

is administered IV or IM
is the agonist of serotonin receptors
decreases the permeability of the blood vessels wall
is used as an anti-hemorrhagic agent in hemorrhagic vasculitis, hypo- and aplastic anemia, thrombocytopenia, hemorrhagic syndrome accompanied the anti-cancer chemotherapy
may cause pain in 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 recep-tors 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-HT1D and 5-HT1B agonist
causes vasoconstriction of dilated cranial and basilar arteries, decreases the activity of the trigeminal nerve
is efficactive in the treating cluster headaches and migraine.

DOPAMINERGIC DRUGS

DOPAMINE HYDROCHLORIDE

is the agonist of dopamine receptors
has cardistimulant, 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. Carbochol

Adrenaline hydrochloride
Prazosin
Propranolol
Guanethidine.

№2. All the drugs are used for the treatment of hypertension, except:
Prazosin
Anaprilinum
Diphenhydramine
Labetalol
Reserpine.

№3. The following statements concerning guanethidine are correct
It is a potent antihypertensive agent
It causes vasodilatation
It blocks β-adrenoceptors
It acts presynaptically
It blocks α-adrenoceptors.

№4. Dimedrolum is applied in a clinic for:
The treatment of bronchial asthma
Allergic diseases
Allergic complications of pharmacological therapy
Hemorrhagical diathesis
Hypertension.

№5. An adrenoblocking drug was prescribed for the treatment of angina pectoris, but bradycardia, 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?
Labetalol, propranolol for its replacement
Propranolol, metoprolol for its replacement
Propranolol, prazosin for its replacement
Phentolamine, metoprolol for its replacement
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, anti-convulsants, and antiparkinsonian drugs.

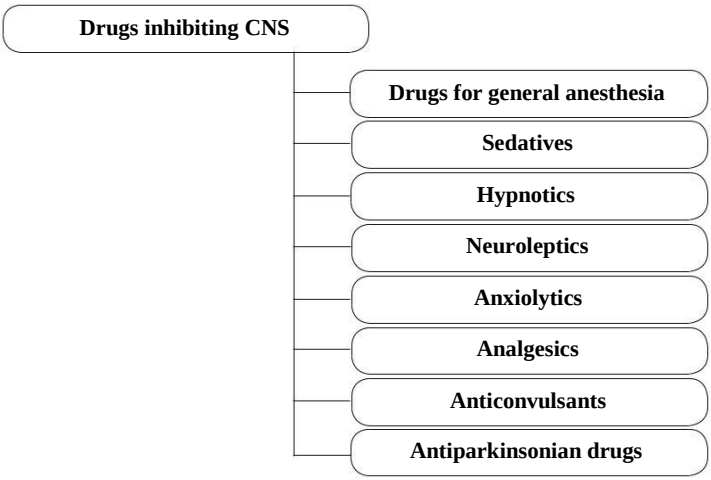


Fig. 9.1. Main groups of CNS inhibitors.

GENERAL ANESTHESIA

General anesthesia (narcosis) is a reversible suppression of CNS with the aboli- shing of pain and all kinds of sensitivity, with myorelaxation and unconsciousness (fig. 9.2).

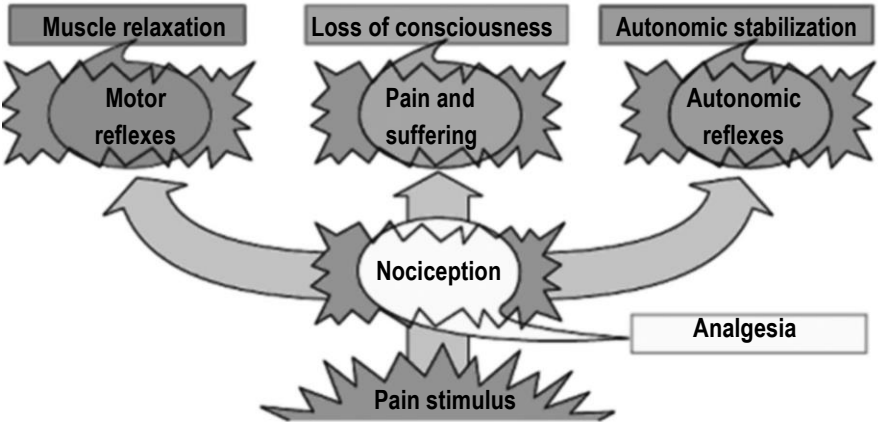


Fig. 9.2. Main goals of general anesthesia *(by H. Lüllmann, 2000).*

Disparities between general and local anesthesia

General anesthesia and local anesthesia both are used for abolishing of pain in 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	– Local abolishing of pain
– A loss of consciousness	– Normal consciousness
– Relaxation of skeletal muscles	– Normal muscular tone
– Abolishing of reflexes	– Normal reflexes
– Usage for all kinds of surgeries	– Usage for uncavitary surgeries

Main concepts of general anesthesia

Induction to anesthesia (inductive narcosis) is the start of narcosis which should be pleasant for the patient

Basis narcosis is the maintenance of narcosis for all the periods of surgery
Mixed narcosis is the combined usage of general anesthetics from one pharmacological group (Halothane + Nitrous oxide)
Combined narcosis (balanced anasthesia) is the combined usage of general anesthetics and preparations from another pharmacological group (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
Premedication (preanesthetical madication) is the administration of prepa-rations for the potentiation of narcosis, as well as for the prophylaxis of side-effects of general anesthesia.

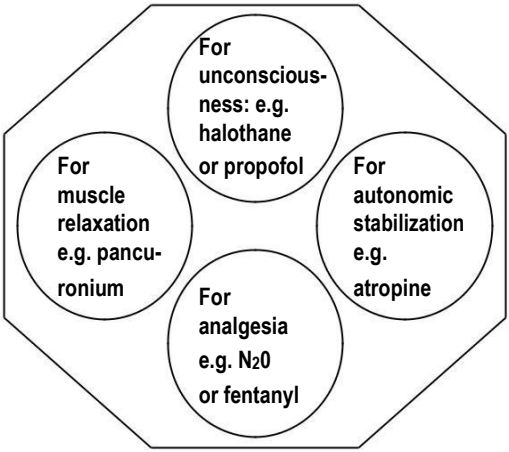


Fig. 9.3. Balanced anesthesia *(by H.Lüllmann, 2000)*.

DRUGS FOR GENETRAL ANESTHESIA

According to their routs 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).

INHALATION ANESTHETICS

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

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
– Strong myorelaxation	– Weak myorelaxation
– Well managed anesthesia	– Unmanaged anesthesia
– Usage for cavitary surgeries	– Usage for short uncavitary surgeries

CLASSIFICATION

Volatile liquids
– Ether for narcosis (Aether pro narcosi)
– Halothane (Phthorothanum)
– Isoflurane
– Sevoflurane
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).

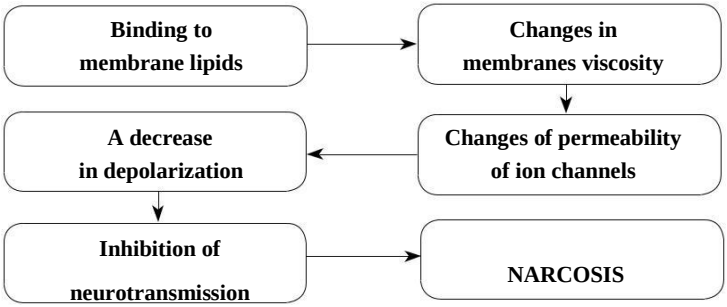


Fig. 9.4. Mechanism of action of inhalation general anesthetics.

Stages of narcosis

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

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 bronchi, spasm of larinx, vomiting, hypersalivation), which make surgerical 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 a volatile inflammable liquid with specific odor; 80% of 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 narco-sis; irritates the upper respiratory pathways; may cause pneumonia after the surgery.

Halothane (Phthorotanum) is a volatile liquid; contains fluorine; is not inflammable; has a strong narcosis action , but weak analgesia; has long stage of analgesia without the excitement stage; dilates bronchi (may be used for the termination of a 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 lesion; 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.

Sevoflurane is a sweet-smelling, nonflammable, highly fluorinated methyl isopropyl ether used as an 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, It 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; a 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 concentration about 80%.

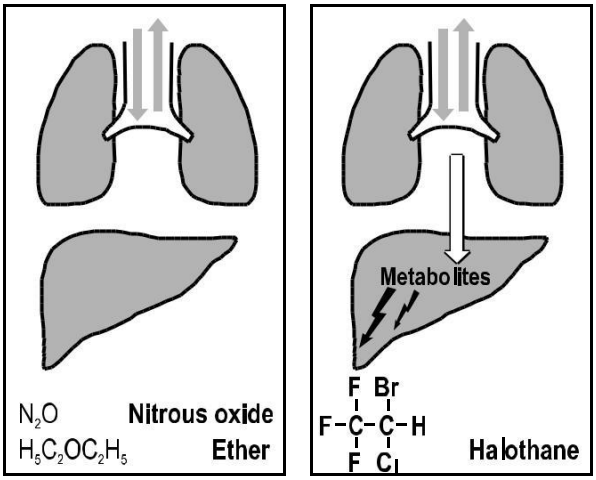


Fig. 9.5. Routes of elimination of inhalation anesthetics *(by H. Lüllmann, 2000)*.

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

Long-acting (more than 60 min)
– Sodium hydroxibutyrate
Intermediate-acting (20-30 min)
– Thiopental-sodium
Short-acting (10–20 min)
– Ketamine (Ketamini hydrochloridum, Kalipsol)
Ultra-short-acting (3-5 min)
– Propofol

According to the mechanism of action

GABA-ergic
– Sodium hydroxibutyrate
– Propofol
Barbiturate-ergic
– Thiopental-sodium
Glutamateergic
– 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).

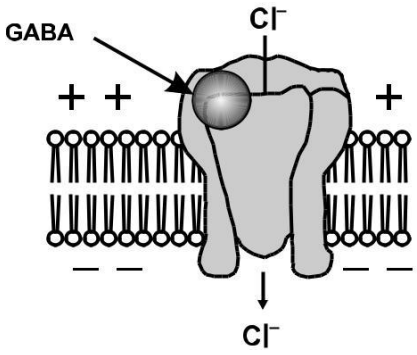


Fig. 9.6. Cloride channel *(adapted from R. Finkel et al., 2008)*.

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 IV administration
acts during 2-4 hrs
is completely metabolized in the body.

Mechanism of action

Sodium oxibutyrate 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 mem-brane and more difficult depolarization.

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

Pharmacodynamics

General anesthesia
A sedative action
A hypnotic action
An anti-seizure action
An antihypoxic action
A nootropic action (after a long-term treatment).

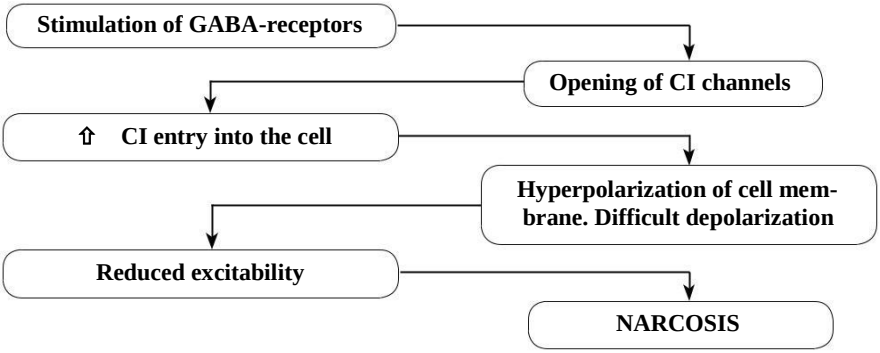


Fig. 9.7. Mechanism of action of sodium hydroxibutyrate.

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-ion channels; displays a rapid onset of ac-tion; has potent anesthesia, poor analgesia, and little myorelaxation; has a hypnotic action; is used for the induction to narcosis, general anesthesia in short-term surger-ies and diagnostic investigations; may cause the suppression of respiration, apnea, bronchospasm, laryngospasm, hypotension, arrhythmia, liver lesions, lowering 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 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, an ionotropic glu-tamate receptor. Also it is an agonist of different subtypes of opioid receptors, the agonist of dopamine D2 receptor and potentiator of 5-HT receptor, The drug causes “dissociate 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 field conditions in war zones, and to supplement spinal or epidural anesthesia. Ketamine causes such side effects as muscles regidity, block of 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 GABAA receptor and acting as a sodium chan-nel 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. Maximum 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

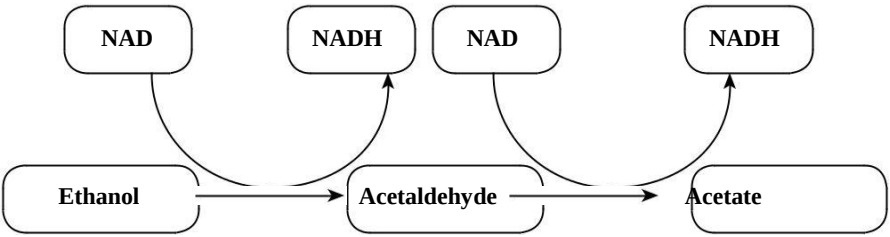


Fig.10.1. Hepatic metabolism of ethanol.

№1. The III stage of general anesthesia (a stage of surgical anesthesia) is mani-fested by all, except:
4 planes of its
development B. Excitement
C. A progressive a decrease in the muscular tone
D. A progressive a decrease in reflexes
E. Stability of BP (at planes 1-2).

№2. Only one IV general anesthetic has antihypoxic and nootropic properties:
Ketamine
Propofol
Sodium oxibutyrate
Kalipsol
Thiopental-sodium.

№3. Nitrous oxide is characterized by the following properties:
Good analgesia
Good anesthesia
Poor muscle relaxation
High liver toxicity
Usage in obstetrics.

№4. Ketamine is:
A long-acting general anesthetic
An increasing cardiac output
Producing profound analgesia
Not abolishing reflexes
Used for short operations.

№5. Lowering of BP has been developed during the surgery under the combined general anesthesia including halothane. The anesthesiologist chooses Mesatonum for the correction of the patient's condition because adrenaline or noradrnaline are contraindicated in this case. What is the ground of such contraindications?

Halothane's liver toxicity
Halothane's neurotoxicity
A combined action of general anesthetics
Halothane's ability to dilate blood vessels
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. ANTI-EPILEPTIC AND ANTIPARKINSONIAN DRUGS

ETHANOL

(Alcohol, Spiritus aethylicus)

Ethanol's chemical structure is C_2H_5OH. It is a water and lipid-soluble liquid with a 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), 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 the surfactant in the lungs.

Effects

an antiseptic action
a disinfective action
an irritating action
a tannic effect
an antifoam action (after inhalation).

The processing of the surgeon's hands and the 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).

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

Shock (20%, IV)
Abscess or gangrene of 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:

– 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.

Emergency help:

– the lavage of the stomach with a solution of potassium permanganate
– analeptics (Bemegridum)
– glucose, insulin, and vitamins preparations (IV)
– nootrops (pyracetam, 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.

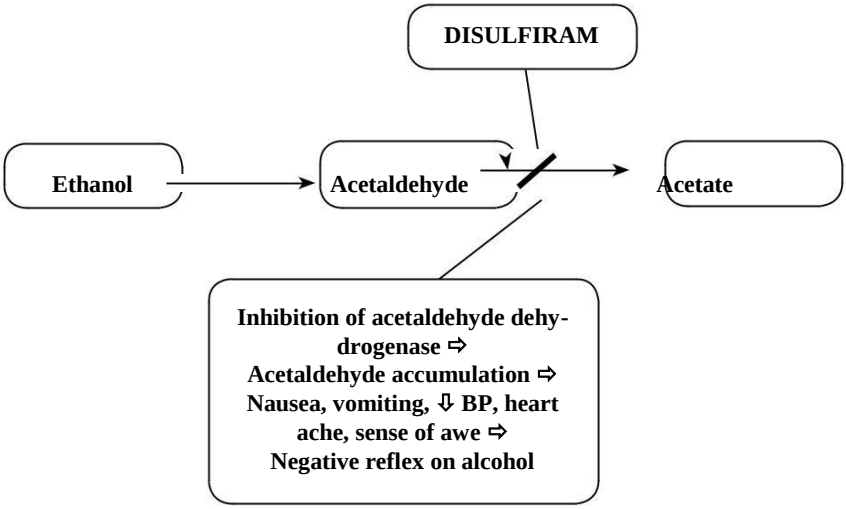


Fig. 10.2. Mechanism of action of disulfiram.

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 (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).

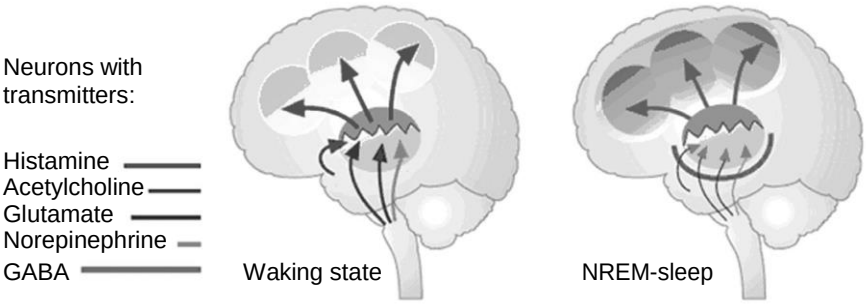


Fig. 10.3. Neurotransmission in the brain in the waking state and NREM sleep *(by H. Lüllmann, 2000)*.

CLASSIFICATION

Barbiturates
– Phenobarbital
– Barbital
– Ethaminal (Aethaminalum-natrium)
Benzodiazepines
– Nitrazepam
Aliphatic compounds
– Chloral hydrate
Other preparations
– Donormyl
– Zopiclone
– Zaleplon.

PHENOBARBITAL

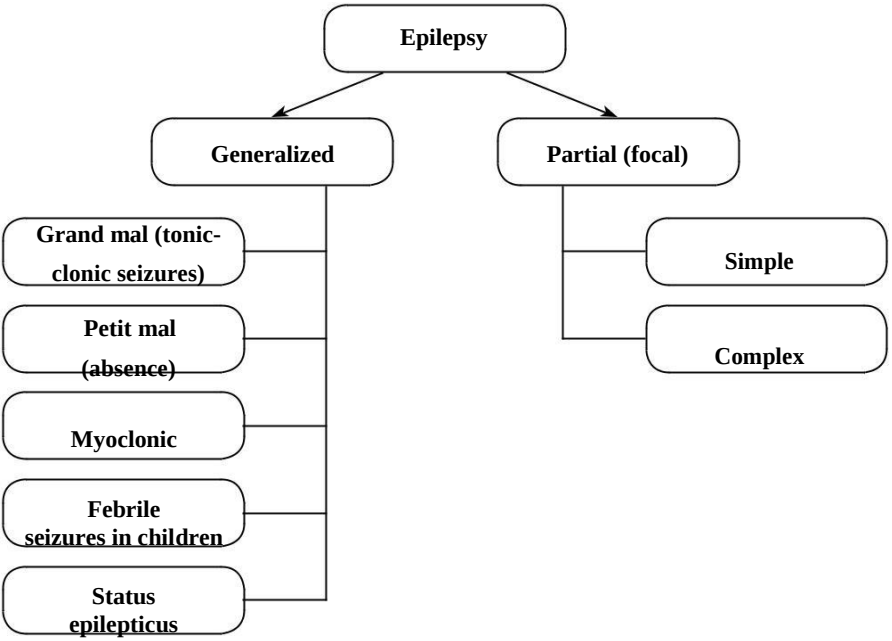


Fig. 10.5. Types of epilepsy as the basis for differential pharmacotherapy.

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

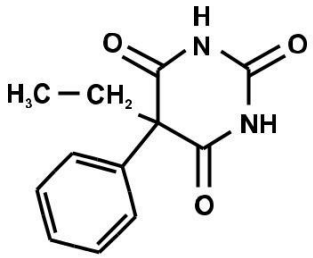


Fig. 10.4. Chemical structure of phenobarbital.

Pharmacokinetics

is taken orally
is absorbed in the small intestine
is strongly bound to proteins in 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 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 anti-epileptic 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

The after-action syndrome (weakness, drowsiness, apathy, slow motor reaction in the morning)
The return-syndrome after rapid cancellation of the drug
Tolerance due to the induction of microsomal oxidation (fig. 10.4)
Drug dependence
Changes in pharmacokinetics of other drugs due to the induction of micro-somal oxidation (fig. 10.5)
The suppression of respiration
Hypotension
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.

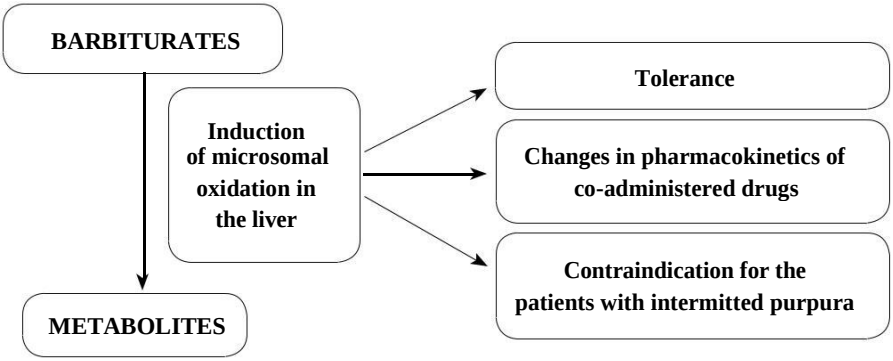


Fig. 10.5. Inhibition of microsomal oxidation by phenobarbital and its result.

Acute poisoning with barbiturates

Main signs:	**Emergency help:**
– sleep, coma	– the lavage of the stomach
– hyporeflexia	– activated charcoal
– a decrease of the muscles tone	– laxatives (magnesium sulfate)
– suppression of respiration	– hemodilution and forced diuresis
– hypotension	– hemodialysis
– hypothermia	– alaleptic Bemegridum (antagonist of barbiturates).

PECULIARITIES OF OTHER PREPARATIONS

Nitrazepam is a benzodiazepine derivative; is the agonist of benzodiazepine receptors of Cl^- ion 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 trichloretha-nol; has an anti-seizure 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 H1-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 hours.

Zopiclone is cyclopirrolone derivative, which interacts with ω1- and ω2 -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 hours. 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 derivative of pyrazolopyrimidine, which selectively binds to ω0 -benzodiazepine receptors and excites them, that leads to the opening of chlorine 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 the disease of the brain with attacks of seizures. There are some types of epilepsy (fig. 10.5).

Principles of the treatment of epilepsy

The choice of the drug according to the type of epilepsy
A long-term treatment
The oral administration of drugs
An equal dose of a new drug, if the change of preparation is needed
Slow cancellation of the drug.

ANTI-EPILEPTIC DRUGS

Anti-epileptics are drugs of a different chemical structure which prevent attacks of epilesy (fig. 10.6).

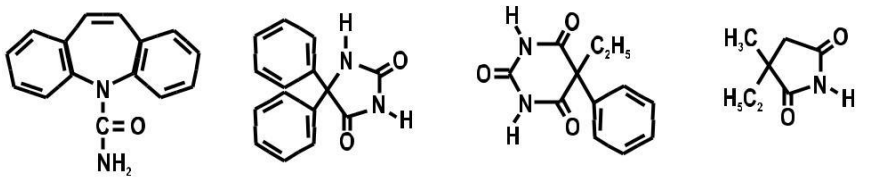


Fig. 10.6. Chemical structure of anti-epileptics.

CLASSIFICATION

Preparations for the treatment of epilepsy with grand mal
- Phenobarbital
- Phenytoin (Dipheninum)
- Carbamazepine (finlepsin)
- Valproic acid, Sodium valproate
- Clonazepam
- Lamotrigine

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 he greatest therapeutic importance. N-metyl-D-aspartrate (NMDA) is a synthetic selective agonist. The stimulation of these receptors permits the entry of both Na^{+} and Ca^{++} into the cell.

Phenytoin, phenobarbital, and a lamotrigine inhibit release of glutamate (fig.10.7).

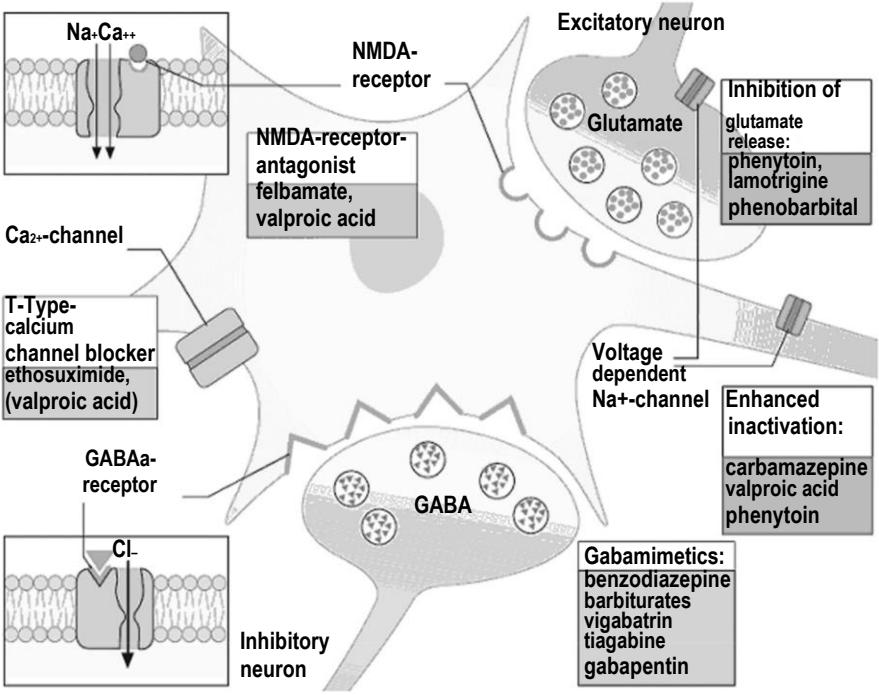


Fig. 10.7. Sites of action of antiepileptic drugs *(by H. Lüllmann, 2000)*.

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 antagonism to glutamate, a direct GABA-mimetic action, regulation of GABA re-uptake.

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 anti-epileptic action; an anti-arrhythmic action; a weak sedative action

is used in epilepsy with grand mal, tachyarrhythmia (especially in acute poisoning with cardiac glycosides), Menier's disease

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 the agonist of benzodiazepine receptors of CL^{-} ion channels; has anti-epileptic and anxiolytic effects, decrease pain syndromes and vestibular disturbances; is indicated in epilepsy with grand mal, petit mal, mixed forms, hyper-kinesis, 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 GABAA receptor, which increases its sensitivity to GABA, reducing the excitability of neurons. It is used for epilepsy with focal and general-ized seizures, absences (typical and atypical small epileptic attack), panic disorder, phobias, bipolar disease, and hyperkinesia. Like other benzodiazepines group, clon-azepam has sedative, anxiolytic, and central myorelaxing effect.

Sodium valproate (or valpoic acid) inhibits GABA transaminase and produces accumulation of GABA in brain, is used for 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 A SEIZURES ATTACK

Diazepam (IV or IM)
Sodium oxibutyrate (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 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. 10.8).

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

The stimulation of dopaminergic processes with

– Levodopa
– Nacom
– Madopar
– Midantan
– Selegelin

Inhibition of central cholinergic processes by

– Trihexyphenidyl (cyclodol.)

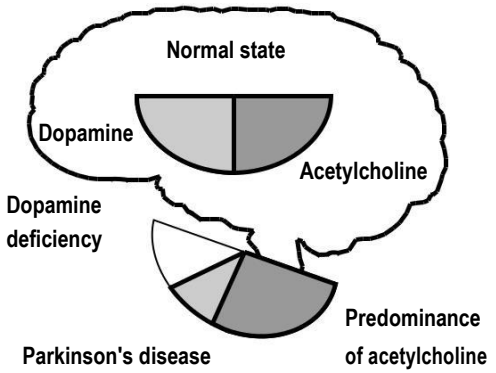


Fig. 10.8. Main disorders in CNS resulting in Parkinson's disease *(by H. Lüllmann, 2000)*.

Peculiarities of preparations

Levodopa is the precursor of dopamine (fig. 10.9). It is administered with the pur-pose 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 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 preparation (fig. 10.9).

Madopar is combined remedy for the treatment of Parkinson's disease and restless legs syndrome, contains levodopa and benserazide, an inhibitor of peripheral

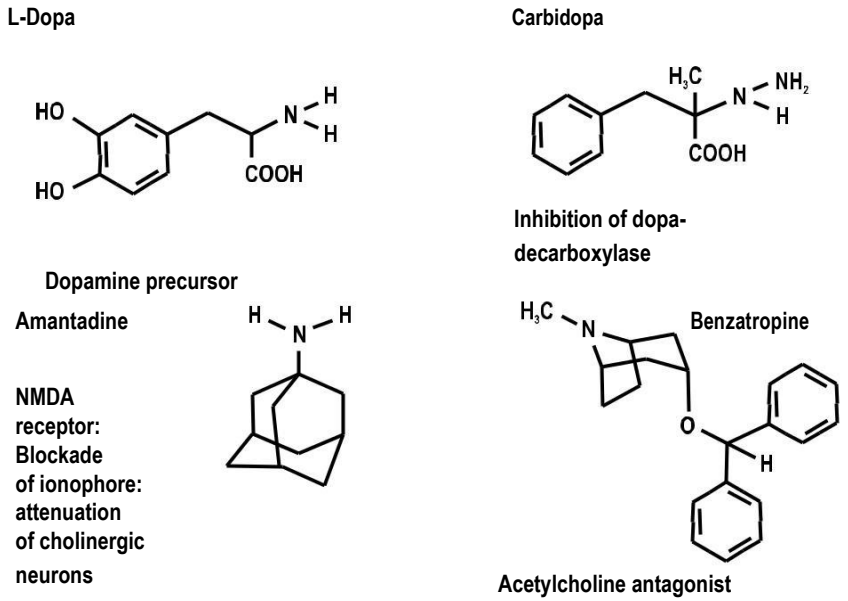


Fig. 10.9. Chemical structure and mechanism of action of levodopa, carbidopa, midantan, and benzatropine *(by H.Lüllmann, 2000)*.

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.

Midantan blocks glutamate receptors in the cortex (fig. 10.9), decreases their influence on the neostriatum, protects neurons in substantia nigra, increases the sensitivity of dopamine receptors to the mediator; 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, loss of balance, insomnia, agitation, arrhythmia, bradycar-dia, hypertension, angina pectoris, and syncope. Due to the structural similarity to amphetamine, selegiline is a controlled substance.

Trihexyphenidy (cyclodol) blocks cholinoreceptors in basal ganglia of the brain; avoids hypokinesia, regidity, and hypersalivation; is used for 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:
Phenobarbital
Zolpidem
Zopiclon
Thiopental sodium
Nitrazepam.

№2. The concentration of ethanol for IV administration in cachexia is:
40%
96%
70%
Absolute ethanol
20%.

№3. Phenytoin exerts the following useful effects:
A. Anti-epileptic

Gum hypertrophy
Coarsening of facial features
Hyperglycemia
Anti-arrhythmic.

№4. Ethanol is:
A long acting general anesthetic
A neuronal depressant with local antimicrobial action
Causing acute and chronic poisonings
Is used mainly as antiseptic
Used for short operations in a polyclinic.

№5. An antiparkinsonian drug influencing dopaminergic processes in basal ganglia of the brain was prescribed to 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?
Levodopa
Nacom
Cyclodol
Amantadine (midantan)
Carbidopa.

Answers:

№ 1 – E; № 2 – E ; № 3 – A, C, 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.

ANTIPSYCHOTIC DRUGS

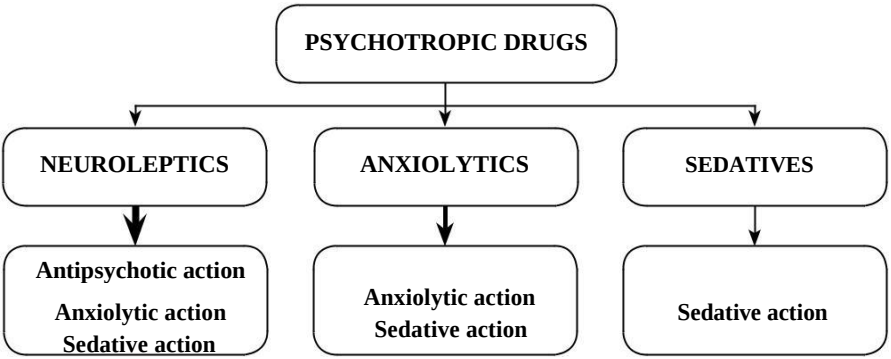


Fig. 11.1. Main groups of psychotropic drugs and their potency.

SCHIZOPHRENIA

Schizophrenia is the 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*

Phenothiazines
- Chlorpromazine (Aminazinum)
- Trifluoperazine (Triftazinum)
- Flunazine (Phthorphenazinum)

Butyrophenones
- Haloperidol
- Droperidol

Thioxanthenes
- Chlorprothixene

B. *Atypical neuroleptics*

Dibenxzodiazepines
- Clozapine

Benzamides
- Sulpiride.

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 (AMINAZINUM)

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

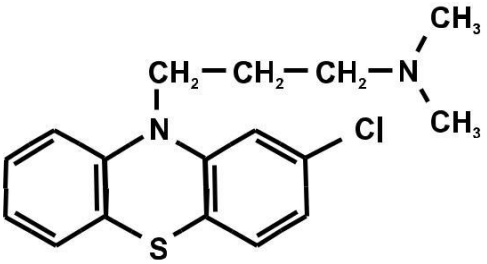


Fig. 11.2. Chemical structure of chlorpromazine.

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 a receptor, decreases an intracel-lular 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).

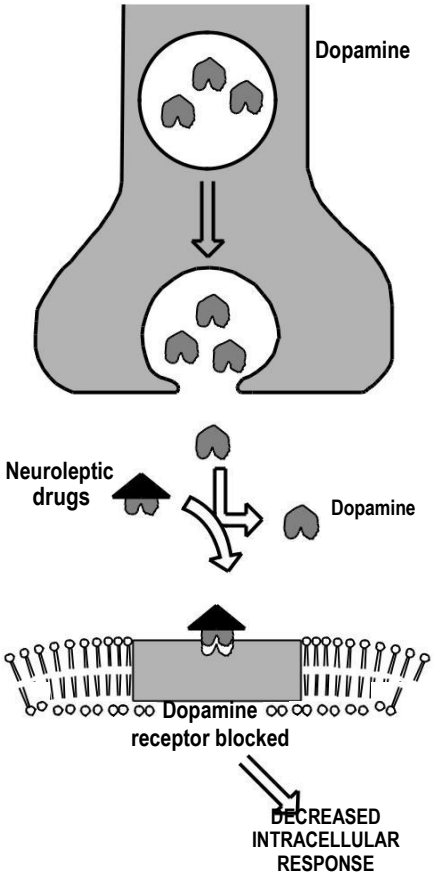


Fig. 11.3. Dopamine-blocking mechanism of action of neuroleptics *(by R.Finkel et al., 2008).*

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 psycho-motor excitement
ahypnotic action
an anti-seizure action
cataleptic effect (absence of active movements under the conditions of the normal muscle tone)
an anti-emetic 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

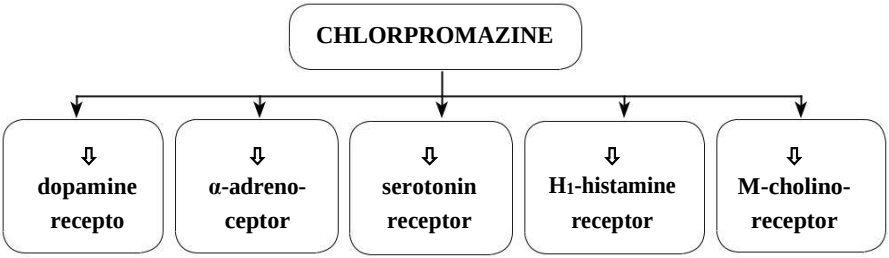


Fig. 11.4. Receptors which are blocked by chlorpromazine.

Indications

h
sychosis, schizophrenia
h
sycho-motor excitement
h
eizures attack
h
remedication
h
evere vomiting of central origin
h
ypertensive crisis
h
yperthermia
h
ibernation (a decrease in normal body temperature during surgeries on the brain or on the heart)
h
ombined therapy of pain syndromes
h
kin 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)

Contraindications

1. Diseases of the liver and kidney
2. Diseases of blood
3. Hypothyroidism
4. Thromboembolism
5. Organic diseases of the

5. Hypotension, orthostatic reactions, lightheadedness (due to the blockage of α-adrenoceptors)
6. Liver lesions, icterus
   Inhibiting in hemopoiesis (leukopenia, agranulocytosis)
   Dermatitis, phototoxicity
   Parkinsonian symptoms, such as akathisia and tardive dyskinesia (due to the blockage of dopaminoreceptors in the nigrostriatal pathway)
   Neuroleptic syndrome (apathy, depression, parkinsonism)

brain and spinal cord (trauma, cancer, insult)

6. Gastric ulcer
7. Pregnancy and lactation.

The aggravation of acute agitation
accompanying withdrawal from alcohol
The aggravation of epilepsy
Amenorrhea, galactorrhea, infertility, impotence (due
to the depression of hypothalamus)
Allergy
Tolerance.

PECULIARITIES OF OTHER PREPARATIONS

Typical neuroleptics

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

Flunazine (Phthorphenazinum) contains fluorine; has strong antipsychotic and anti-emetic 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, anti-emetic 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, anti-arrhythmic, 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 weak anti-seizure 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 anti-emetic action and a weak cataleptic action; has no sedative, anti-seizure 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 (droperi-dol) and narcotic analgesic (fentanyl) are administered together (IV). In this case neuroleptic produces psychic suppression and a narcotic analgesic causes abolishing of pain. Co-administered, they display a synergic action.

ANTI-ANXIETY DRUGS

ANXIETY

Anxiety is the 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, ataractics.***

CLASSIFICATION

Benzodiazepines
- Chlordiazepoxide (Chlosepidum)
- Diazepam (Sibasonum)
- Phenazepam
- Medazepam (Mezapam, Rudotel)
- Gidazepam

Preparations of another chemical structure
- Buspirone
- Benactyzime (Amizilum)
- Meprobamate (Meprotanum).

Antagonist of benzodiazepines is Flumazenil.

CLORDIAZEPOXIDE

The drug is a benzodiazepine derivative (fig. 11.5).

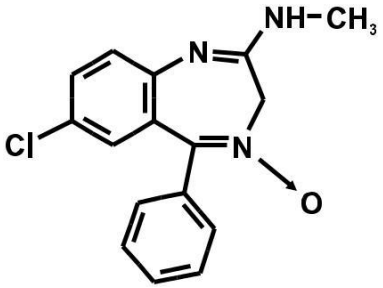


Fig. 11.5. Chemical structure of chlordiazepoxide.

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, T½= 24-48 hrs.

Mechanism of action

Benzodiazepine-receptor is the 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 cell membranes. Depolarization gets worse and decreasing of neurons excitement in the limbic system and midbrain developes. It results in an 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 anti-seizure action
A potentiative action (a drug addition, if analgesics, general anesthetics, or other CNS inhibitors are administered together with this drug).

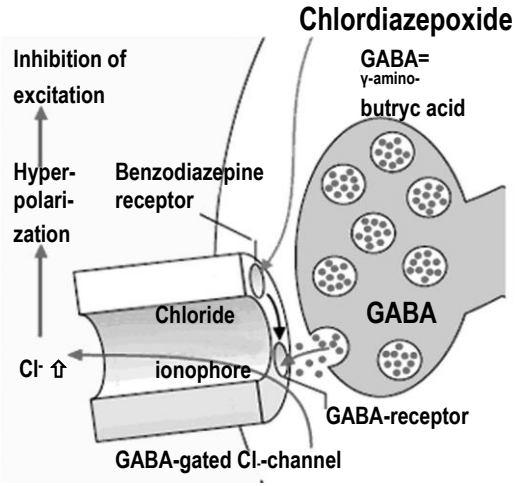


Fig. 11.6. Mechanism of action of chlordiazepoxide *(by H. Lüllmann, 2000)*.

Indications

Neuroses
Stress, emotional overstrain
Sleeping disorders induced by emotional overstrain
Neurological diseases with muscle spasticity
Seizures
Abstinence in chronic alcoholics
Psychosomatic diseases
Premedication.

Side-effects

1. Weakness
2. Drowsiness
3. A decrease in attention and rapidness of motor reactions

Ataxia
Skin itch
Amenorrhea
Impotence
Drug addition
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 (Sibazonum) is administered orally, IM, IV; maximal concentration after 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 T½= 48 hrs); is more potent than clordiazepoxide, especially in an anti-seizure effect; causes a decrease in night gastric secretion and arrhythmia; is suitable to treat a seizure attack; may be used in combined therapy of ulcerative disease and heart arrhythmia.

Phenazepam is administered orally; maximal concentration is in 1-2 hrs; has T½ = 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 T½ = 87 hrs; has an anxiolytic action, psychostimu-lating 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 the kind of general anesthesia when the tranquilizer and the narcotic analgesic are administered together (IV).

SEDATIVES

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

Classification

Non-organic preparations
- Sodium bromide
- Potassium bromide

Vegetable preparations
- Tincture from valerian
- Tincture from Leonurum

3. Metabolic sedatives
   - Melatonin
   - Glicised

Combined preparations
– Corvalolum
– Valocormidum.
– 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 blood plasma
accumulates in the body.

Mechanism of action

It increases inhibition in 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 anti-epileptic 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 meals

— 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 stomach and intestine.

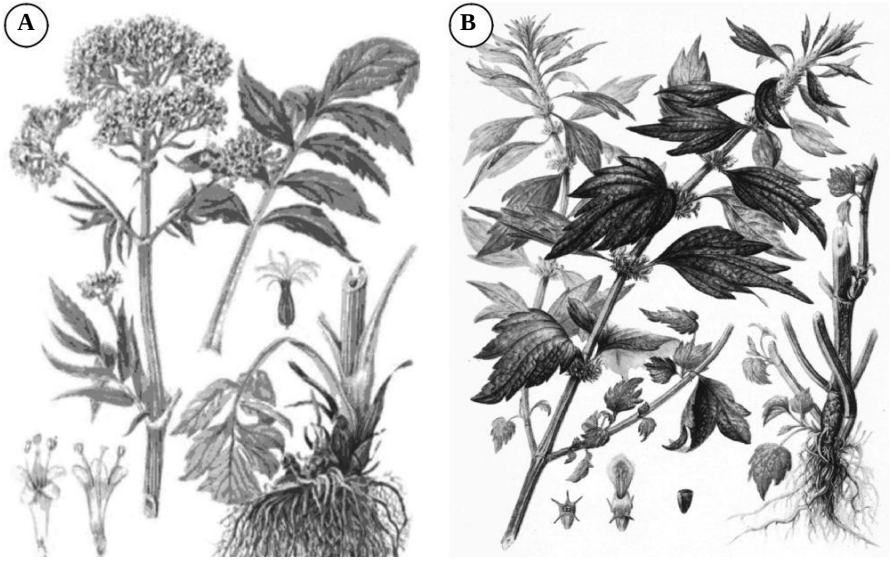


Fig. 11.7. Medicinal plants containing sedatives:
A – *Valeriana*; **B** – *Leonurum*.

METABOLIC SEDATIVES

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

Glycised has a mild sedative, anti-anxiety, nootropic and antitoxic action. The 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. improvement of memory and education, psychoemotional stress, depression, sleep disorders, increased irritability. It well tolerated by patients

COMBINED SEDATIVE PREPARATIONS

Corvalolum is 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 action; is used in neuroses, spasms of coronary blood vessels, tachycardia, spasms in the gut.

Valocormidum 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 ef-fect; It is used for light neuroses, after the abolition of potent sedatives; 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 cardio-vascular 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

Lithium salts
– Lithium carbonate
– Lithium oxibutyrate
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 the dose is excreted with urine and 5% – with sweat
T½ = 19 hrs
therapeutic effect developes in 1-3 weeks after the start of the 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 re-uptake 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

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

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

TESTS FOR SELF-CONTROL

№1. Only one preparation in the list belongs to “day-time” tranquilizers:
Chlorpromazepine
Chlorprothixene
Chlordiazepoxide
Gidazepam
Diazepam.

№2. All of the following are observed in patients taking neuroleptics, except:
Increased BP
Orthostatic hypotension
Parkinsonian symptoms
Altered endocrine function
Phototoxicity.

№3. Anxiolytics:

Are the drugs to treat a manic-depressive disorder
Are the drugs to treat panic and phobia
Bind to dopamine receptors in the brain
Bind to benzodiazepine receptors of chloride ion channels
Act in the limbic system, midbrain, and hypothalamus.

№4. Lithium salts are characterized by:
Complete and durative absorption in the gut
Competition with sodium in cells of the brain
A small therapeutic index
Minimal side-effects and low toxicity
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 (Aminazinum). She was troubled with tremor and disturbances of movements. What is the mechanism of these side-effects?
The activation of hyppocampus
The inhibition of reticular formation (α_1-adrenoceptors)
The inhibition of neostriatum (D_2-receptors)
The inhibition of hypothalamus
The inhibition of neocortex.

Answers

№ 1 – D; № 2 – A; № 3 – B, D, E; № 4 – A, B, C; № 5 – C.

Chapter 12 OPIOID (NARCOTIC) ANALGESICS

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 the cortex of the brain (fig. 12.1).

Thalamus is the main collector of pain impulses. Strong nociceptive stimuli irradiates on the medulla of the brain resulting in a 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 ar-rival of the action potentials causes the opening of voltage-gated Ca^{++}channels in the pre-synaptic membrane. An increased influx of Ca^{++} causes vesicles containing

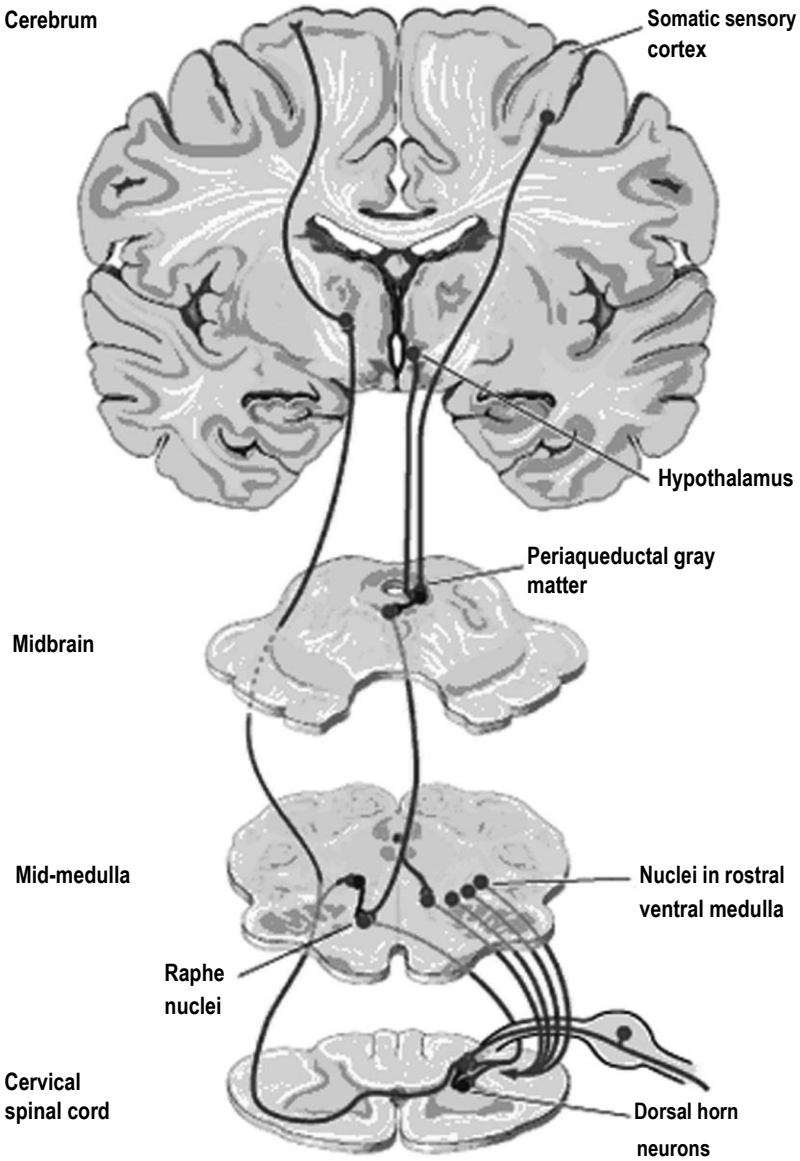


Fig. 12.1. Anatomy structures connected with nociception *(http://www.picsearch.com).*

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 post-synaptic 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.

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), delta (δ)-receptors (fig. 12.2).

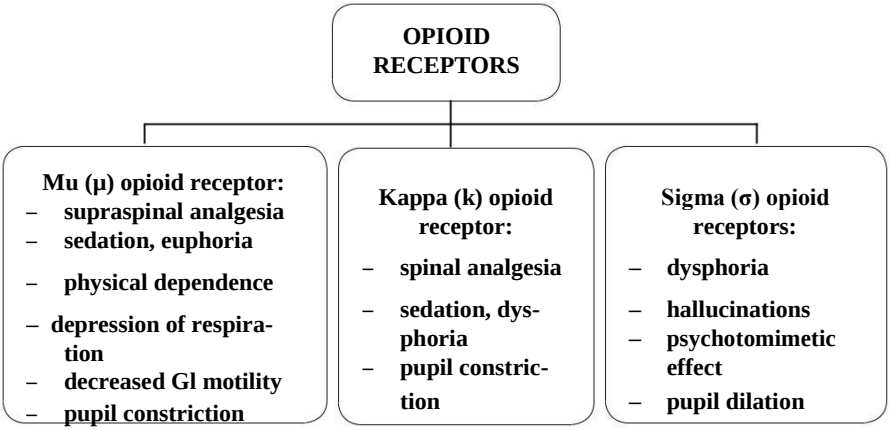


Fig. 12.2. Subtypes of opioid receptors and processes mediated by them.

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

Ligands of opioid receptors are endorphins, enkephalins, 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, 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^+ chan-nels 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^+ 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).

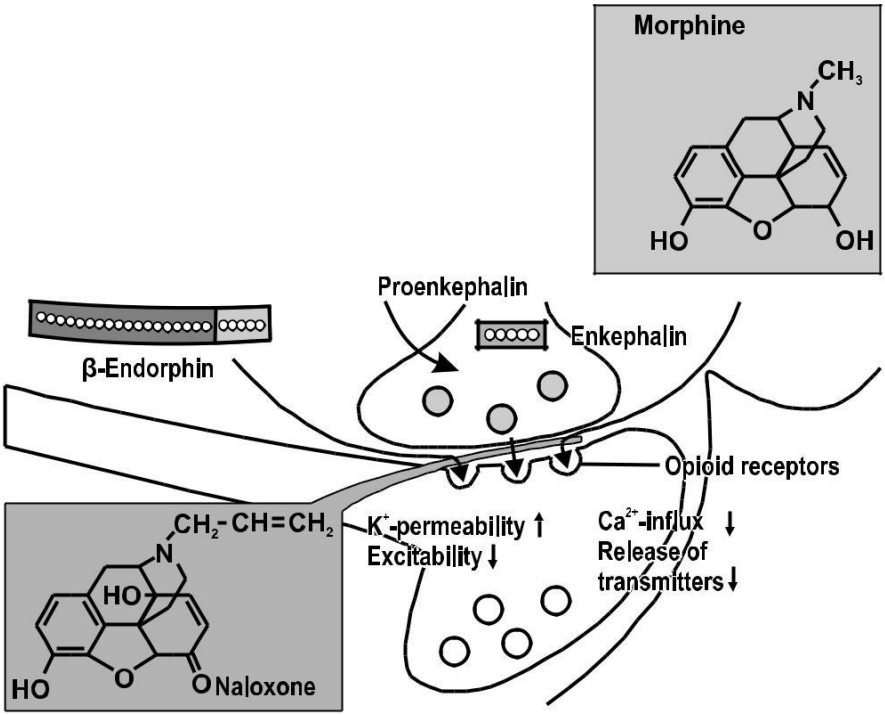


Fig. 12.3. Mechanism of action of endogenous opioids, exogenous opioids (morphine) and their antagonists (naloxone) *(by H. Lüllmann, 2000)*.

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 antagonists 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*

Natural compounds

– Morphine hydrochloride
– Codeine phosphate
– Omnoponum

Synthetic compounds

– Tremeperidine (Promedolum)
– Fentanyl

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

– Pentazocine
– Buprenorphine
– Butorphanol
– Nalbuphine
– Nalorphine hydrochloride

– Tramadol hydrochloride

Antagonists of opioid receptors

– Naloxone hydrochloride
– Naltrexone.

MORPHINE

Morphine is an alkaloid of opium. ***Opium*** is a 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).

Fig. 12.4. *Papaver somniferum* containing morphine.

Morphine is a phenanthrene derivative (fig. 12.5).

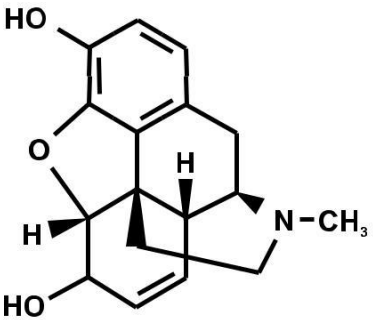


Fig. 12.5. Chemical structure of morphine.

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 recep-tors (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 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 the 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, bile 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
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 CNS.

Contraindications

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

— The lavage of stomach 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

OMNOPONUM

is the 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

an is 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 depend-ence.

TRIMEPIRIDINE (PROMEDOLUM)

is a synthetic preparation with a structure unrelated to morphine
is administered orally, SC, IM, IV; begins to act in 10 min after IV admin-istration 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 a negative influence on the fetus
is indicated in acute severe pains, premedication, myocardial infarction, colic, 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, 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 opi-ate 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, 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 (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
ompared with morphine has a lesser ability to cause physical dependence, less often causes constipation.

NALBUPHINE

is 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-ffect is sedation; other reactions are: feeling sweaty/ clammy, 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 the agonist-antagonist of opioid receptors; is a weak narcotic analgesic and competitor of morphine in 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 a narcotic analgesic, because may cause psychic excitement, anxiety, hallucination
in higher dose may cause nausea, vomiting, headache, miosis, drowsiness, 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, 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 re-uptake 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 GI 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, 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 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 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.

TESTS FOR SELF-CONTROL

№1. The incorrect statement about morphine is only:
It is an antagonist of opioid receptors
It is the most effective by parenteral administration
It causes euphoria and sedation
It causes respiratory depression
Its effects are antagonized by naloxone.

№2. The side-effects of opioid analgesics include all, except:
The inhibition of respiration
Stimulation of anti-diuretic hormone release
Drug dependence
Tolerance
The suppression of hemopoiesis.

№3. Pentazocine is:
An agonist-antagonist of opioid analgesics
A less potent analgesic than morphine
The most potent in its ability to cause drug dependence
Agent caused dysphoria
The antagonist of opioid receptors used in acute poisoning with morphine.

4. Naloxone is used in acute poisoning with opioid analgetisc due to:
A. Agonism to opioid receptors
B. Competitive antagonism with opioid agonists
C. A rapid onset of action
D. A 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. The 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?

It increases intracranial pressure
It stimulates the vagal center
It decreases intraocular pressure
It causes miosis
It depresses the center of a 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 lipooxygenases (fig. 13.1).

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

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)

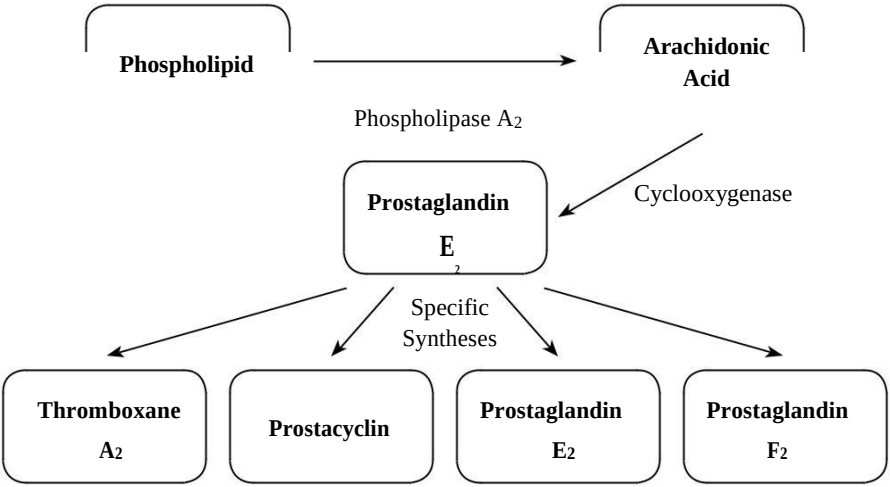


Fig. 13.1. Synthesis of prostaglandins (http://www.picsearch.com).

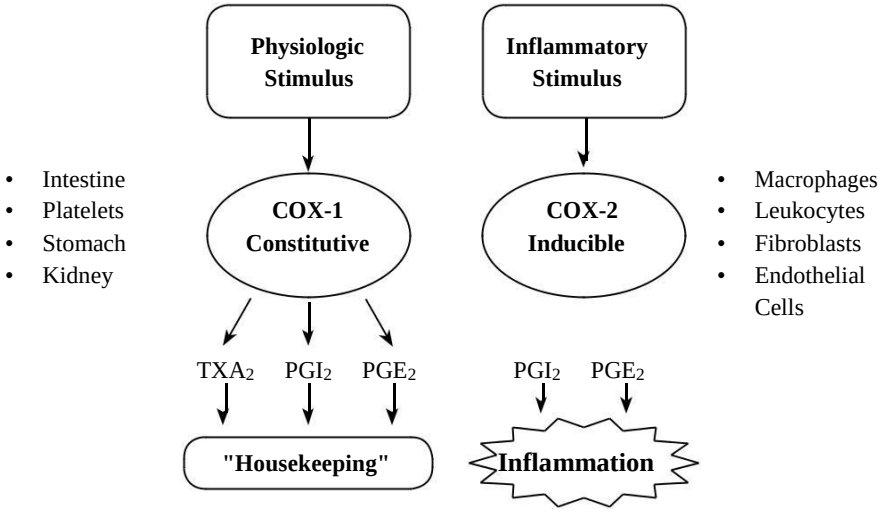


Fig. 13.2. Peculiarities of COX-1 and COX-2 *(http://www.picsearch.com)*.

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 the gastric mucus and reduce the formation of the 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.

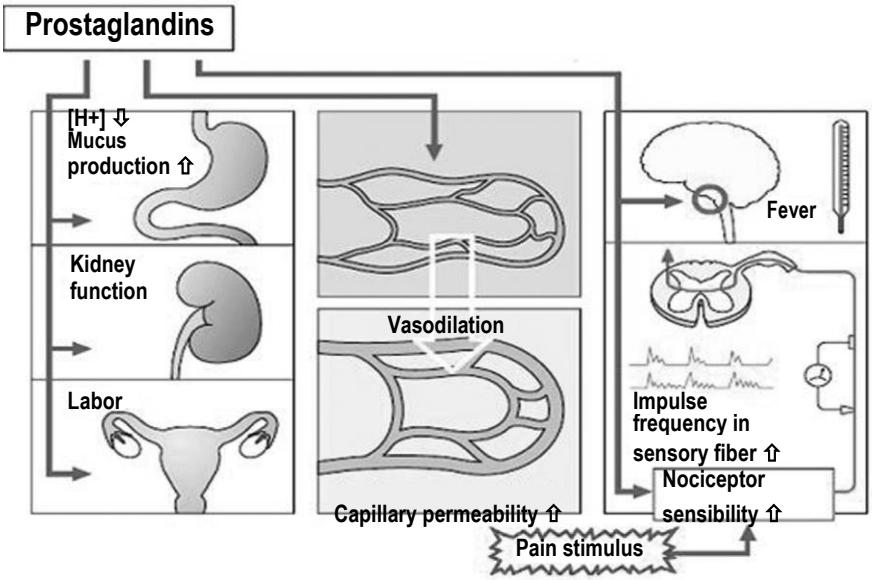


Fig. 13.3. Biological effects of prostaglandins *(by H.Lüllmann, 2000)*.

NON-OPIOID ANALGESICS

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

They always have:

an analgesic action

an anti-inflammatory action

an antipyretic action

Drugs with the prevalence of anti-inflammatory activity are named ***non-steroidal anti-inflammatory preparations (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.

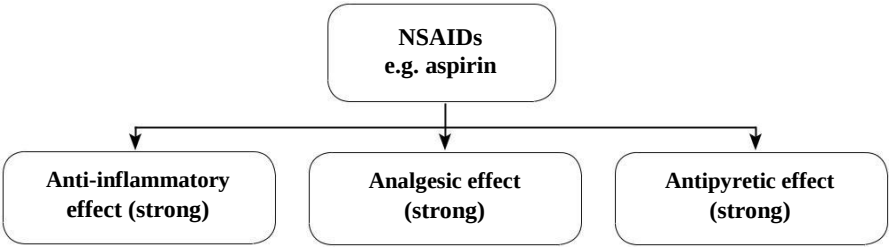


Fig. 13.4. Expression of effects of NSAIDs.

Drugs with the prevalence of analgesic and anti-pyretic activity are named ***analgesics-antipyretics*** (fig. 13.5).

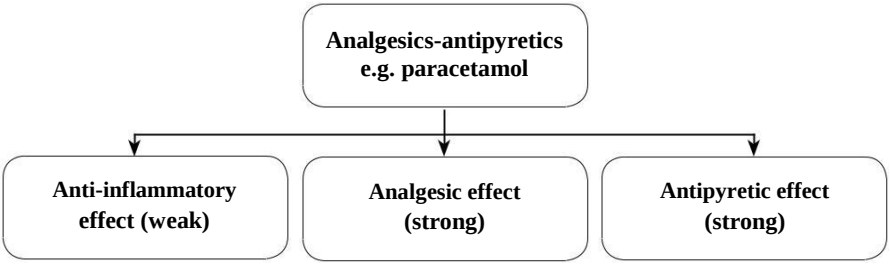


Fig. 13.5. Expression of effects of analgesics-antipyretics.

CLASSIFICATION

According to the chemical structure

Salicylates

– Acetylsalicylic acid (Aspirin)

Pyrazoles

– Metamizole (Analgin)
– Phenylbutazone (Butadione)

Fenamates
– Mefenamic acid

Indolacetic acid derivatives
– Indomethacin

Phenylacetic acid derivatives
– Diclofenac-sodium

Propionic acid derivatives
– Ibuprofen

Para-aminophenol derivatives
– Paracetamol (Acetominophen)

Oxicams
– Piroxicam
– Meloxicam (Movalis)

Coxibs
– Celecoxib

According to the mode of action

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

Mainly with a peripheral action
– Acetylsalicylic acid
– Phenylbutazone
– Metamizole
– Mefenamic acid
– Indometacin
– Diclofenac-sodium
– Ibuprofen
– Piroxicam

Mainly with a central action
– Paracetamol

– 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. indometacin) inhibit fibroblasts' activity and decrease the proliferation stage of inflammation.

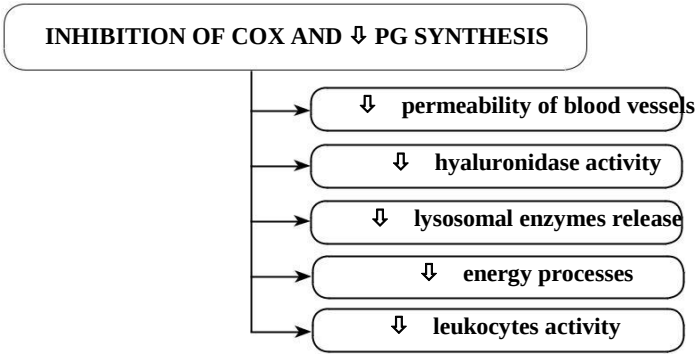


Fig. 13.6. Mechanism of anti-inflammatory action of non-opioid analgesigs

Mechanism of anti-pyretic action

The 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 CNS and relief of pain.

Mechanism of anti-platelet action

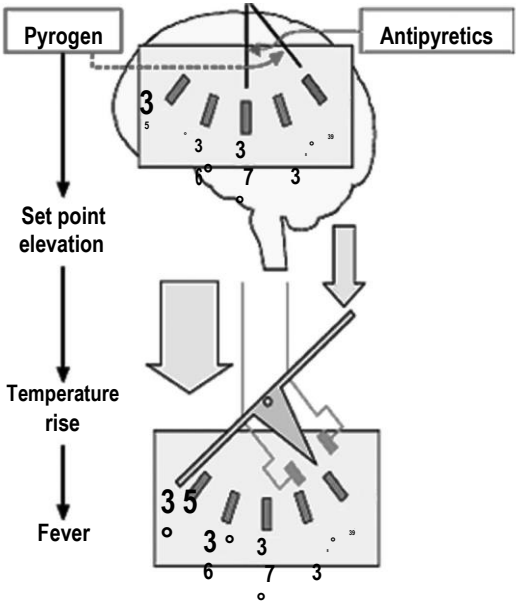


Fig. 13.7. Mechanism of antipyretic action of non-opioid analgesics *(by H. Lüllmann, 2000)*.

Some non-narcotic analgesics (e.g. the acetylsalicylic acid) may cause the inhibition of COX-1 in 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.

Some other mechanisms of action

In high concentrations NSAIDs influence nitric oxide-dependent processes, in-hibit 5-lipoxigenase, and reduce the production of leukotrienes. They activate PPAR connected with colorectal carcinogenesis, 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)

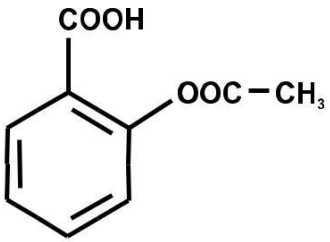


Fig. 13.8. Chemical structure of acetylsalicylic acid.

is absorbed in the stomach and the small intestine by passive diffusion (absorption is increased by acidic pH in the stomach)
binds to albumins in 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, lungs
at normal low doses, is hydrolyzed to salicylate and the acetic acid by esterases present in tissues and blood (fig. 13.10)
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 anti-platelet action of 7 days
at normal low dose of 600mg/day, has a half-life of 3,5 hrs; at anti-inflamma-tory doses (>4g/day), has a half-life of 15 hrs or more due to the saturation of hepatic metabolic pathway.

Mechanism of action

Aspirin is a non-selective inhibitor of COX-1 and COX-2 in peripheral tissues and in CNS.
It irreversibly acetylates and thus inactivates COX (fig.13.9). All other non-opioid analgesics are reversible COX inhibitors.

Pharmacodynamics

an anti-inflammatory action (a decrease in exudation)
an anti-pyrexiae action (a decrease in high body temperature)
an analgesic action (a decrease in intermediate and weak pain)

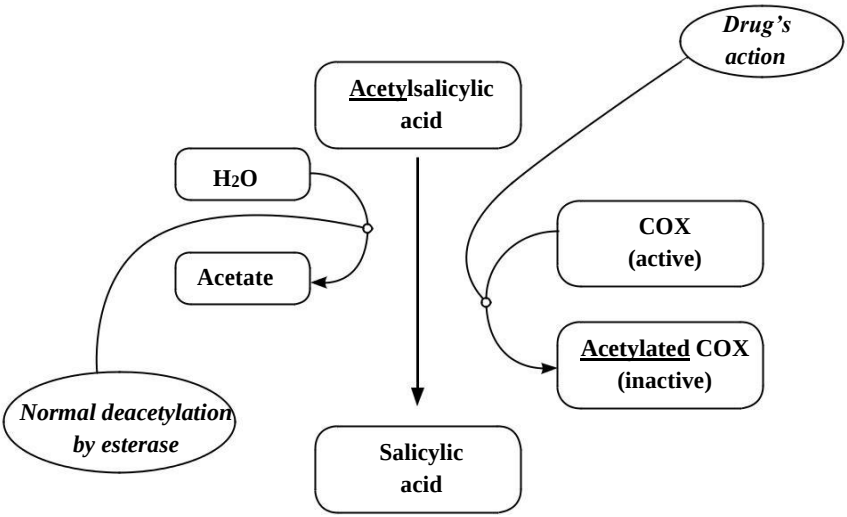


Fig. 13.9. Acetylation of COX by acetylsalicylic acid.

an anti-platelet 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)
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, neuralgia
Gout
Dysmenorrhea
Prophylaxis of re-thrombosis, myocardial infarction, or insult
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 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

Thrombocytopenia
Hypocoagulation, bleeding
A decrease in renal blood flow, the retention of so-dium and water
Disturbances in normal development of pregnancy, prolonged labor, bleeding tendency in the mother and infant, a premature closure of ductus arteriosus
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 anti-pyrexia

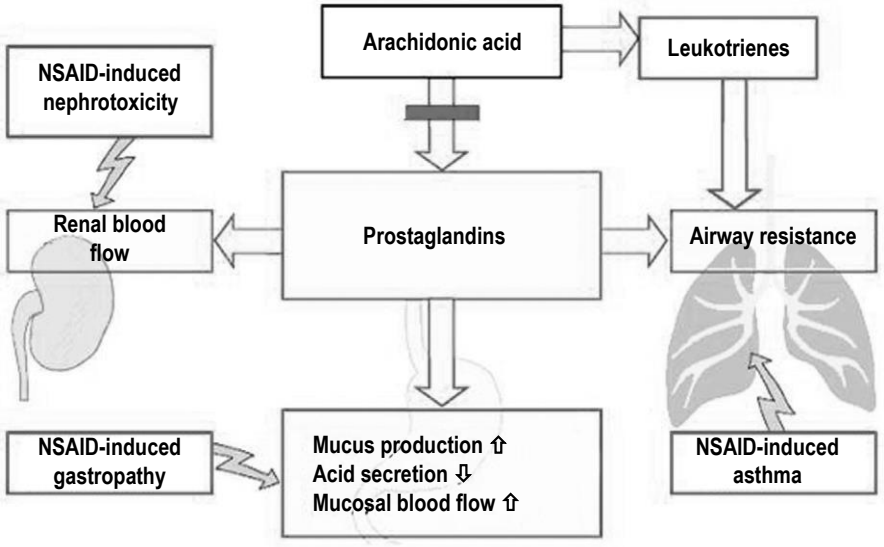


Fig. 13.10. Group-specific side-effects of aspirin and other NSAIDs *(by H. Lüllmann, 2000)*.

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 (typically 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, anemia.

DICLOFENAC-SODIUM

is a phenylacetyc acid dervative
anti-inflammation is the strongest effect
belongs to NSAIDs, exceeds aspirin and indomethacin
is administerefd orally, IM, topically (gel, ointment)
displays maximal concentration in plasma in 1-2 hrs after the oral administration; binds to proteins in 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 indometacin; 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 epigastric area, meteorism, constipation, diarrhea, rarely ulceration in the stomach, gastro-intestinal bleeding, headache, drowsiness, thrombocytope-nia, 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, osteoarthritids, acute gout
may cause such side-effects as gastric ulceration, skin rash, the inhibition of blood formation, toxic action on CNS.

MEFENAMIC ACID

is 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, diarrhea associated with the inflammation of the bowel.

METAMIZOLE (ANALGIN)

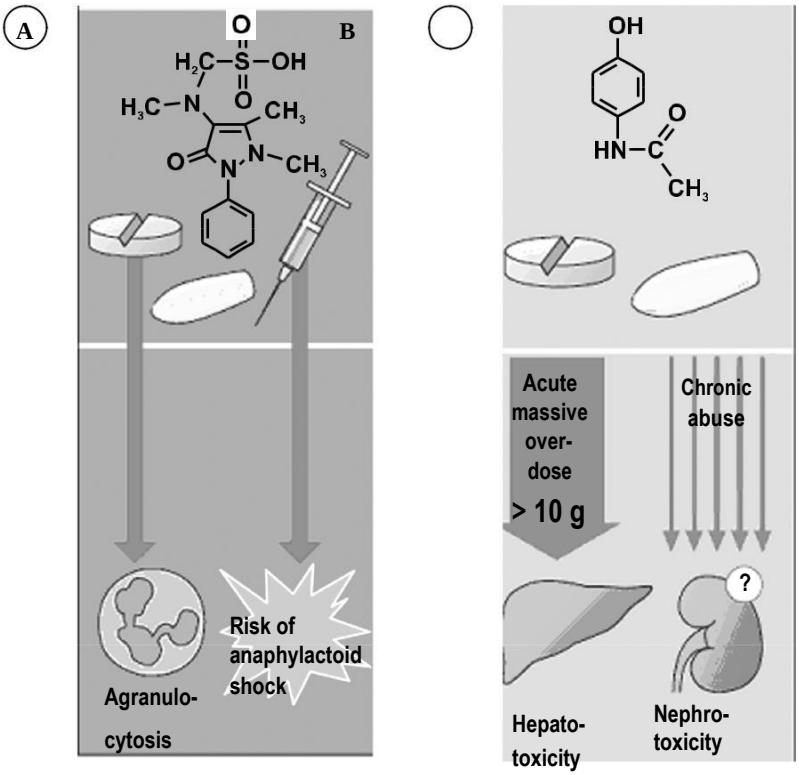


Fig. 13.11. Chemical structure, routs of administration, and side-effects of analgesics-antipyretics: A – metamizole; B – paracetamol *(by H. Lüllmann, 2000)*.

is a pyrazole derivative (fig. 13.11)
belongs to analgesics-antipyretics; has strong analgesic and anti-pyretic activity, but weak anti-inflammatory activity
is administered orally, IM, IV, rectally (fig. 13.11)
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 pans, control of intermediate post-operative pain, fever, 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 anti-pyretic 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 over to the patient 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 a mainly 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 plasma in 3-5 days after the start of treatment; has concentration in synovial fluid which is more than that in 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, gastro-intestinal 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 gastro-intestinal diseases, heart failure, cirrhosis of the liver, chronic renal diseases.

CELECOXIB

belongs to the group of coxibs
is 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 plasma in 2-3 hrs after the administration; is bound to plasma proteins, has 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, stoma-titis, ulcer of the stomach, dysphagia, gastro-intestinal bleeding, headache, vertigo, insomnia, depression, an increase in intracranial pressure, hyper-tension, 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 administration: has half-elimination from tissues of 2-3 hrs and half-elimination from blood of 13-14 hrs; is metabolized in the liver and excreted with urine

has anti-inflammatory, anti-pyretic, and analgesic actions resulting from inhibition of Pg synthesis; has antiviral activity resulting from direct influ-ence on viruses, as well as from interferon induction; is 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:

The inhibition of prostaglandins synthesis
The inhibition of cyclooxygenase
The inhibition of monoaminooxidase
An increase in noradrenaline release
The inhibition of dopamine reuptake.

№2. All the listed drugs are non-selective inhibitors of COX, except:

Indomethacin
Diclofenac sodium
Ibuprofen
Acetaminophen
Celecoxib.

№3. Non-opioid analgesics exert the following effects:

An antipyretic action
Immunity suppression
An anti-inflammatory action
An analgesic action
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
an 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 (Analginum). Point out another useful effect of this drug that contributes to the improvement of the patient's condition:
A sedative effect
An anti-inflammatory effect
An anti-platelet effect
An antioxidative effect
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).

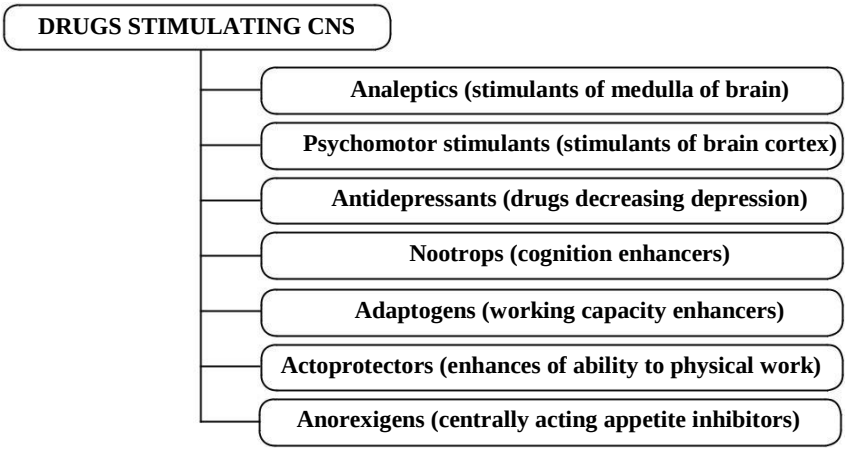


Fig. 14.1. Main groups of CNS stimulants.

ANALEPTICS

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

Direct-acting
- Bemegride
- Etimizol
- Strychnine nitrate
- Caffeine (Caffeine-sodium benzoate)

Indirect-acting (M-cholinomimetics)
- Cytizin (Cytitonum)
- Lobeline

Mixed-acting
- Camphor
- Sulfocamphocaine
- Nikethamide (Cordiaminum)
- Carbogenum.

According to the mechanism of action

Membrane-tropic
- Camphor
- Sulfocamphocaine

Barbituratergic
- Bemegride

Benzdiazepinergic
- Nikethamide

Purinergic
- Caffeine
- Etimizol

Glycinergic
- Strychnine.

CAMPHOR

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

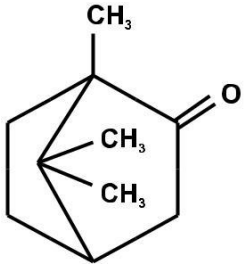


Fig. 14.2. Chemical structure of camphor.

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

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

Fig. 14.3. Camphor tree containing natural camphor.

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 results in an increase of Na^+ concentration in the cells that leads to the maintenance of the excitement of neurons in the me-dulla 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).

Pharmacodynamics

a local action (antiseptic, irritating, trophic, whitening)

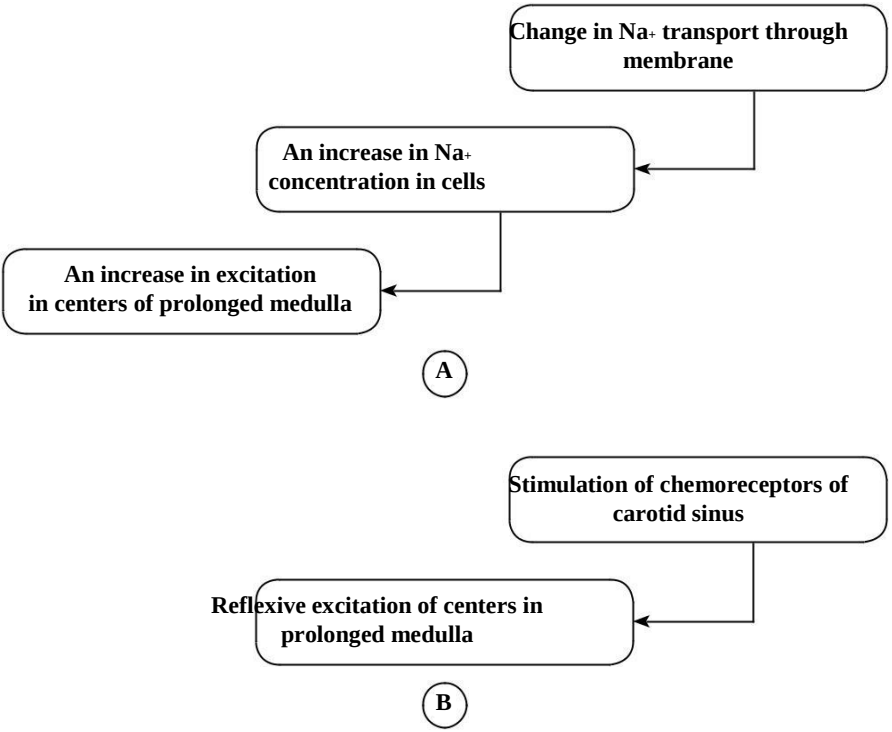


Fig. 14.4. Mechanism of camphor's action: A – direct action; B – indirect action.

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
the stimulation of lactation.

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 suppres-sion of respiration, collapse, shock, overdose of drugs inhibiting CNS, heart failure; is contraindicated to patients with allergy to procaine.

Nikethamide (Cordiaminum) 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, 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, 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 Bemegridum (by this action Bemegridum is more potent than other analeptics); is indicated in acute poisonings with barbiturates, alcohol, narcotic analgesics; overdose of general an-esthetics; suppression of respiration; may cause seizures, tremor, hyperventilation, arrhythmia; is contraindicated in epilepsy, psychomotor excitement, intoxication with seizure poisonings.

Etimizol is a synthetic preparation, an imidazole derivative; is administered IV, IM, and orally; has short action; is a direct-acting analeptic inhibitinig adenosine receptors; decreases phosphodiesterase activity, thus increases cAMP in 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, 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 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 en-cephalytis, 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).

Carbogenum 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.

Fig. 14.5. Vomiting nut containing strychnine.

PSYCHOMOTOR STIMULANTS

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

CLASSIFICATION

Purinergic

Methylxantines
– Caffeine (Cofeinum natrii-benzoas)
– Theophylline

Phenilalkilamines
– Amphetamine (Phenaminum)
Piperidine derivatives
– Meridile
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 (Coffeine sodium benzoate) are better soluble than caffeine.

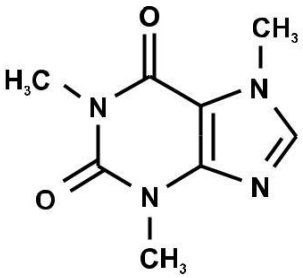


Fig. 14.6. Chemical structure of caffeine.

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; T½ = 3,9 – 5,3 hrs, is completelly eliminated for 24 hrs.

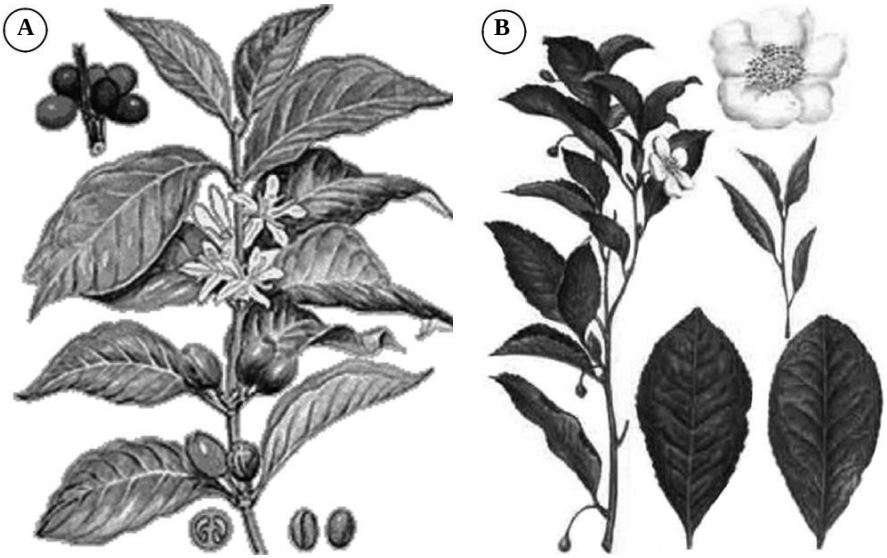


Fig. 14.7. Plants containing caffeine: A – *Coffe arabica*; B – *Thea chinensis*.

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 cells.
It inhibits phosphodiesterase and increases cAMP concentration in cells.
The drug also increases the activity of phosphorilase resulting in an increase of glycogen metabolism and forming of the energy.

Pharmacodynamics

a psychostimulant action (an increase in the excitement in the cortex of the brain; 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 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 heart rate)
action on blood vessels, which is the sum of the central action (vasoconstric-tion) and the peripheral action (vasodilation): blood vessels in the heart, lungs, kidney, skeletal muscles are dilated; blood vessels in the brain cov-ers 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
Diagnostic of the gastric secretory function
Headache (as the an ingredient of combined preparations for headache).

Side-effects

1. Agitation, anxiety
2. Insomnia
3. Tachycardia, arrhythmia
4. Hypertension
5. Pain in stomach
6. Drug dependence
   Withdrawal syndrome (lethargy, irritability, headache in users who have consumed more than 600mg per day).

Contraindications

1. Psychomotor excitement
2. Hypertension
3. Arrhythmia
4. Atherosclerosis
5. Hyperthyroidism
6. Gastritis, ulcer of stomach.

PECULIARITIES OF OTHER METHYLATED XANTINES

Theophylline is taken orally; has a half-life about 8,5 hrs; has a cellular mecha-nism 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 adrenergic psychomotor stimulant, 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 adreno-mimetic action
is indicated for an increase of mental and physical capacity to work, narco-lepsy, 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, addition
causes psychic and physical dependence, “amphetamine psychosis”
the treatment of overdose includes the acidification of urine, administration of chlorpromazine, labetalol for cardio-vascular normalization.

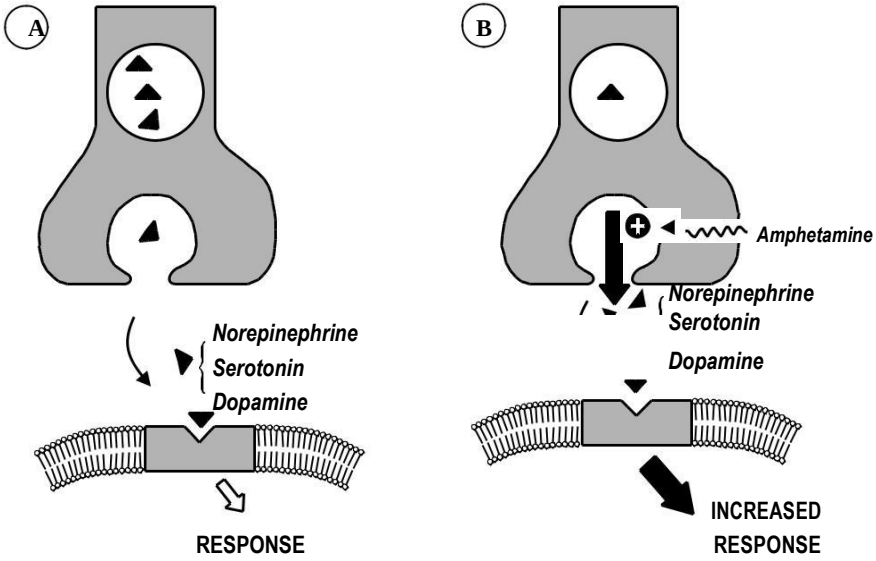


Fig. 14.8. Mechanism of amphetamine's action *(by R.Finkel et al., 2008)*.

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 CNS effects, except:

An increase in BP
Sedation
Psychic stimulation
An increase in gastric secretion
A decrease in fatigue.

№2. Bemegridum is:
The antagonist of adenosine receptors
The antagonist of barbiturate receptors
The agonist of barbiturate receptors
A psychomotor stimulant
The stimulant of ACTH secretion.

№3. The correct statements concerning nikethamide are:
It is analeptic
It has a mixed action
It suppresses respiration
It increases BP
It stimulates the respiratory center.

№4. Psychomotor stimulants are used for:
Relief of pain
Asthenia
Attention deficit in children
Increase the capacity to mental and physical work
Insomnia.

№5. For the prophylaxis of pneumonia after the inhalation general anesthesia mixed acting analeptic was used. This analeptic is administered by inhala-tion and includes two gaseous ingredients. What drug was most probably used?
Nitrous oxide
Cyclopropane
Carbogenum
Nikethamide
Camphor.

Answers:

№ 1 – B; № 2 – B; № 3 – A, B, D, E; № 4 – B, C, D; № 5 – C.

Chapter 15

ANTIDEPRESSANTS. ADAPTOGENS. NOOTROPS. 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, 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 CNS.

ANTIDEPRESSANTS

Antidepressants are the drugs for the treatment of depression.

CLASSIFICATION

According to the mechanism of action

A. *Inhibitors of monoamine re-uptake*

Non-selective inhibitors of the monoamines re-uptake
- Imipramine (Imizinum)
- Amitriptyline

Selective inhibitors of the serotonin re-uptake
- Fluoxetine
- Sertraline

Selective inhibitors of the norepinephrine re-uptake
- Maprotiline

B. *MAO inhibitors*

Non-selective (MAO-A and MAO-B)
- Phenelzine
- Tranylcypromine
- Nialamide

Selective (MAO-A)
- Pirlindole (Pirazidolum)
- Moclobemide

C. *Atypical antidepsessants*
- Trazodone
- Mianserin
- Agomelatine
- Ademetionine

According to the additional action

A. *Thymoleptics* (+ a sedative effect)
- Amitriptyline

B. *Thymoerectics* (+ a psychostimulating effect)
- Nialamidum

C. *Mixed acting*
- Imipramine
- Pirlindole.

IMIPRAMINE

It has a tri-cyclic 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 the treatment).

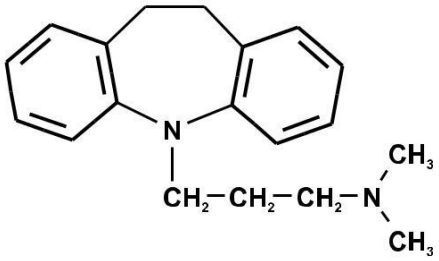


Fig. 15.1. Chemical structure of imipramine.

Mechanism of action

The mechanism of action includes the inhibition of the norepinephrine re-uptake resulting in an increase of adrenergic processes in brain structures (fig.15.2).

It is also connected with the inhibition of the serotonin re-uptake 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 tri-cyclic 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 anti-depressive action
a thymoleptic action in the emotional sphere (a sedative or weak psycho-stimulant action)

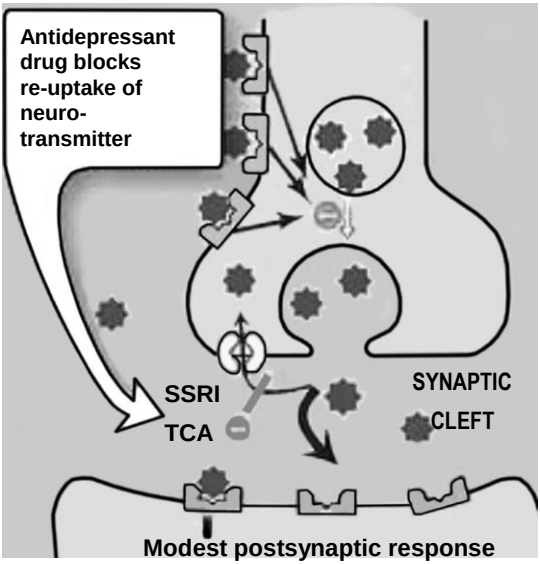


Fig. 15.2. Mechanism of action of monoamine re-uptake inhibitors: TCA – tri-cyclic antidepressants; SSRI – selective serotonin re-uptake inhibitors *(by R.Finkel et al., 2008)*.

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
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.

Contraindications

1. Psychic excitement
2. Schizophrenia
3. Glacouma
4. Adenoma of prostate
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 RE-UPTAKE INHIBITORS

Amitriptyline has a tri-cyclic structure; is administered orally or IM, manifests an antidepressant action in 10-14 days after the start of the treatment; is a non-selective inhibitor of the monoamines re-uptake; is a thymoleptic; does not provoke agitation and hallucinations, does not cause insomnia; may be taken in the evening; is indi-cated to patients, in whom depression is accompanied by panic and anxiety; has a M-cholinoblocking action and side-effects resulting from an antimuscarinic effect.

Maprotiline is a tetracyclic antidepressant. an inhibitor of monoamines re-uptake, but inhibits the re-uptake 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 re-uptake 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, premenstrual syndrome; has low toxicity, but may cause headache, nervousness, insomnia, appetite disturbances, skin

rash, 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 thymoerectic

increases the effects of adrenomimetics and sympathomimetics, is a reser-pine antagonist

decreases pain syndromes

is used in depressions unresponsible to tri-cyclic antidepressants, depressions accompanied by severe anxiety, phobic states, pain syndromes, neuralgia of n.trigeminus

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 cerebro-vascular accidents; needs IV injection of α-adrenoblocker as emergency help).

PECULIARITIES OF OTHER MAO-INHIBITORS

Pirlindole has a tetra-cyclic structure; is a selective inhibitor 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, some types of schizophrenia, has low toxicity; may be used in patients with glaucoma, adenoma of prostate, myocardial infarction.

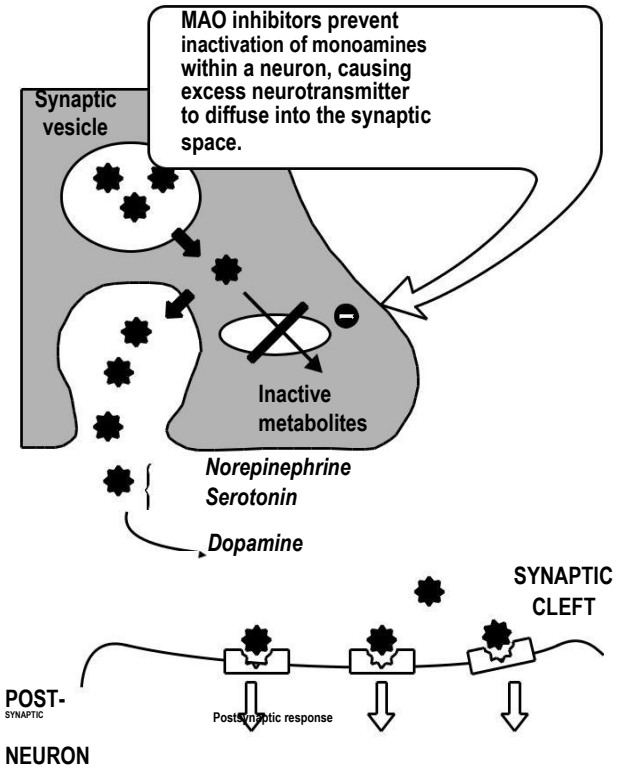


Fig. 15.3. Mechanism of action of MAO-inhibitors *(by R. Finkel et al., 2008)*.

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 the norepinephrine release, by inhibition of serotonin receptors etc.

PECULIARITIES OF PREPARATIONS

Agomelatine is a melatonergic 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-HT2C

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 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

Pyrolidon derivatives
- Piracetam (Nootropil)
- Pramiracetam

GABA derivatives
- Aminalon
- Sodium oxibutyrate
- Phenibutum
- Pantogamum
- Picamilonum

Neuropeptides
- Sinacten-Depo
- Thyroliberin
- Melatonin
- Cerebrolysin

Cerebrovascular drugs
- Vinpocetin (Cavinton)
- Nicergoline (Sermion)
- Pentoxyphylline
- Cinnarisine

Pyridoxine derivatives

– Pyritinol (Pyriditolum, Encephabol)

Antioxidants

– Mexidol.

PIRACETAM

By its chemical structure piracetam is similar to a cyclic form of GABA (fig.15.4).

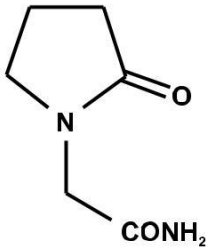


Fig. 15.4. Chemical structure of piracetam.

Pharmacokinetics

is administered orally, IM, IV
is well absorbed from the GI tract, has bioavailability of 90%
develops maximal concentration 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 cells, thus dilates blood vessels in the brain and has an anti-platelet 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 anti-seizure action in some forms of epilepsy
an increase in the efficacy of the treatment by neuroleptics and antidepres-sants, 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 Alzheieimer'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 10g/kg of the body weight). Rarely it can cause nervousness, anxiety, insomnia.

The drug has no significant contraindications.

PECULIARITIES OF OTHER PREPARATIONS

Pramiracetam is piracetam derivative, has simiar action and indications, but is more active and is used in saller 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, anticonvalsant, antihypoxixc, and light antihypertesive effects; is used afer the disturbunces of cerebral blood circulation, for encephalopathyt, cerebral pulthy and mental retardation in children and kinetosis; has low toxicity.

Vinpocetin (cavinton) is an alkaloid; is administered orally and IV (by IV infu-sion); 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 anti-platelet 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 an arterial type; has an anti-platelet 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, is-chemic stroke, diabetic angiopathia, angiopathia of ocular blood vessels; has such side-effects as hypotension, weakness, vertigo, hyperemia of the skin, dyspepsia; is contraindicated to patients with myocardial infarction, bleeding, hypotension, severe atherosclerosis, 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 CNS; has indications similar to that of pentoxiphylline; may cause hypotension, a decrease in cardiac output, vertigo, weakness, hyperemia of the skin, 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

Preparations from medicinal plants
- Tincture of *Ginseng*
- Tincture of *Schizandra*
- Tincture of *Aralia*
- Liquid extract of *Eleuterococcus*

Preparations from animal tissues
- Pantocrinum

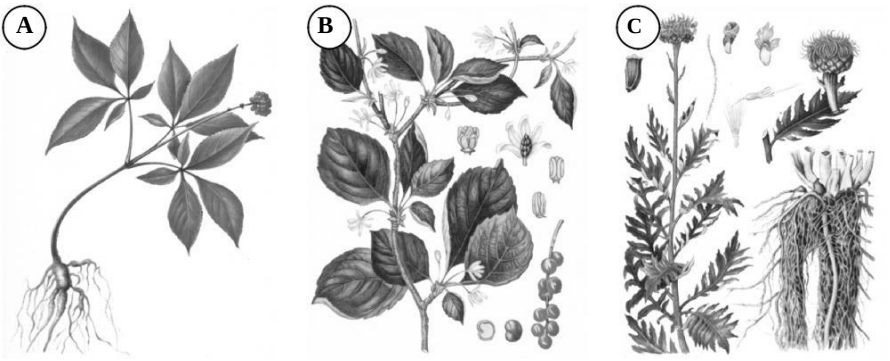


Fig. 15.5. Medicinal plants containing adaptogens:
A – *Panax Ginseng*, B – *Schizandra chinensis*, C – *Leuzea carthamoides*.

All adaptogens have the common mechanism of action and similar pharmacological properties. They are taken orally. Pantocrinum 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

Restlessness, nervousness, insomnia
Hypertension
Hyperglycemia.

Contraindications

Insomnia, hypertension, bleeding, menstruation, severe atherosclerosis, 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.

BEMITHYLUM

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, dyspep-sia, nausea, vomiting, allergy.

ANOREXIGENS

Anorexigens are the drugs decreasing appetite due to their central activity.

CLASSIFICATION

Catecholaminergic (stimulating CNS)
- Amfepranone (Phepranonum)
- Chlorpheniramine (Desopimonum)
- Mazindol

Serotoninergic (suppressing CNS)
- Fenfluramine.

Mechanism of action

The 1st group preparations increase the release and decrease the re-uptake of norepinephrine and dopamine in 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 CNS and inhibit the limbic system influence on the hunger center. In such a way they decrease appetite and limit the meals quantity.

Pharmacodynamics

The inhibiton of appetite, limitation of meals 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 catecho-lamines in CNS synapses is:
An increase in catecholamines release from the presynaptic membrane
An increase in catecholamines synthesis in the presynaptic membrane
The prevention of catecholamines degradation in the synapse
The inhibition of the neuronal re-uptake of catecholamines
The inhibition of MAO.

№2. All the statements concerning adaptogens are true, except:
They are taken orally
They modify the activity of hypophysial-pituitary-adrenal axis
They depresse immunity
They are used to improve non-specific resistance
They increase mental and physical work capacity.

№3. The MAO inhibitors are:
Among thymoerectics
Not influencing the emotional sphere
Causing dry mouth, blurred vision
Causing cheese syndrome
Without dangerous side-effects.

№4. Piracetam is effective in the treatment of:
The disturbance of movement in patients with cerebral stroke
The retardation of mental development in children

Disturbances of memory after stroke
Senile dementia
A memory impairment in alcoholics.

№5. 70-year old patient has vertigo and memory disturbances on the ground 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?

Caffeine
Pentoxiphylline
Diazepam
Phenazepam
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 myo-cardium 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).

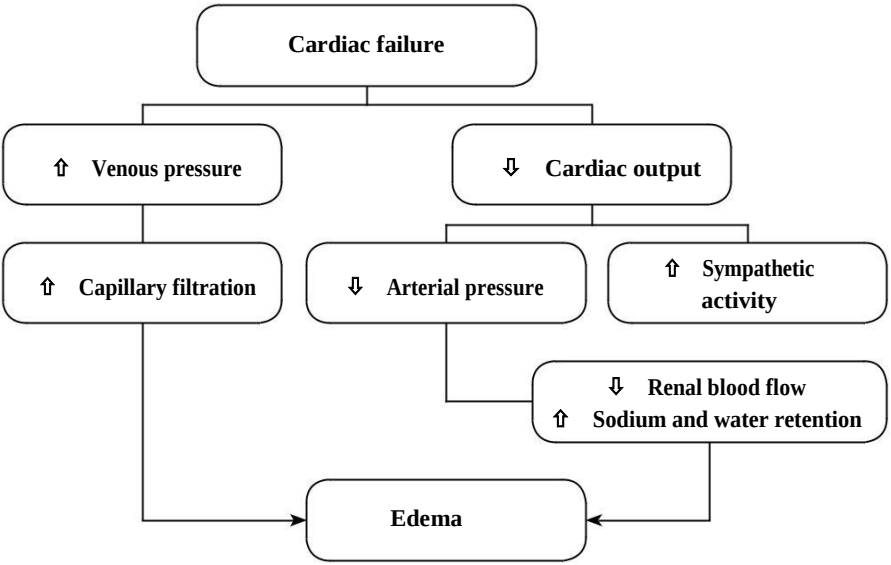


Fig. 16.1. Pathogenesis of congestive heart failure.

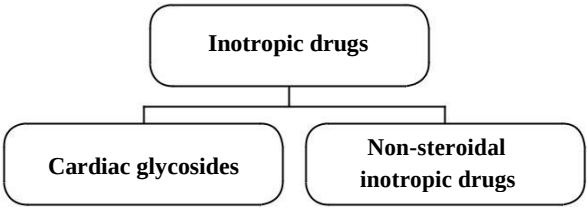


Fig. 16.2. Two groups of inotropic agents.

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
— *Strophanthus gratus* for strophanthin G (Quabain)

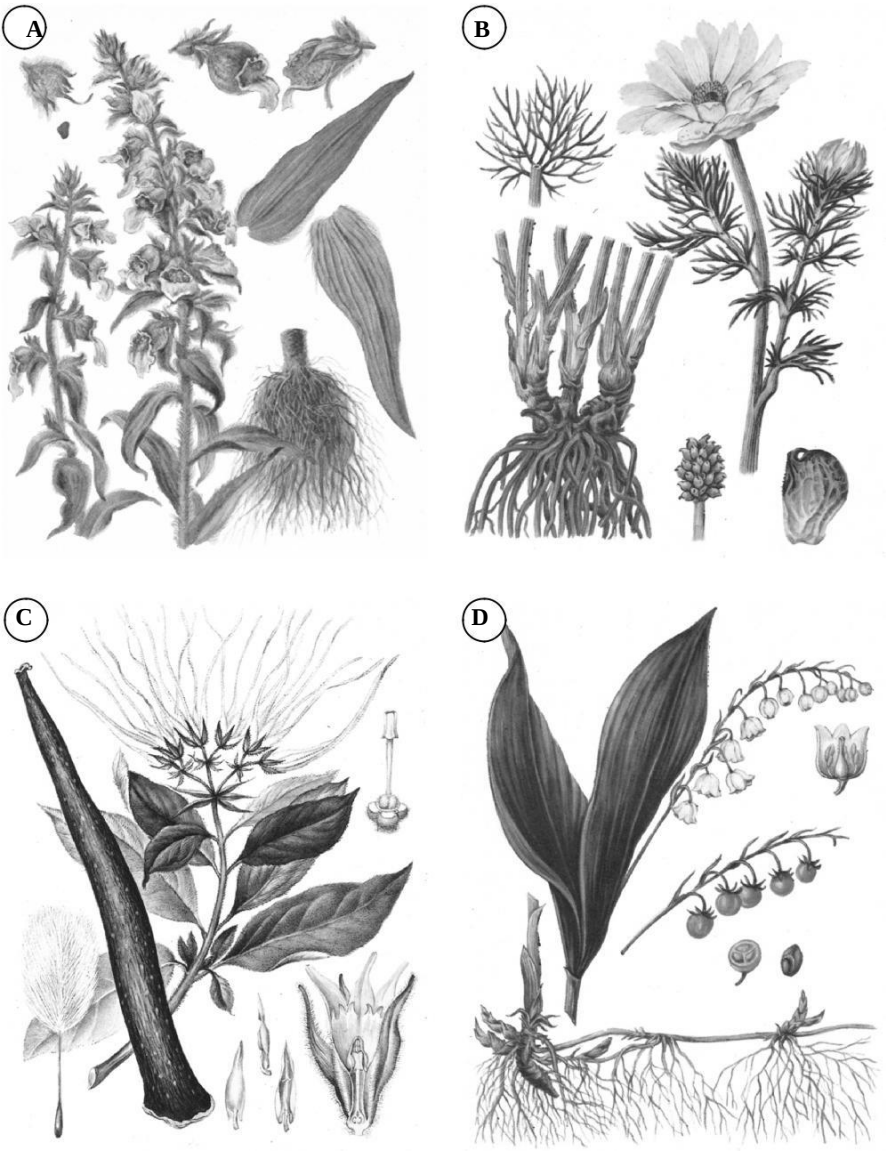


Fig.16.3. Medicinal plants containing cardiac glycosides: A – *Digitalis lanata*; B – *Adonis vernalis*; C – *Strophanthus combe*; D – *Convallaria majalis*.

— *Convallaria majalis* (lily of the valley) for corglycon
— *Adonis vernalis* for adonisidum, 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 digitalis 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).

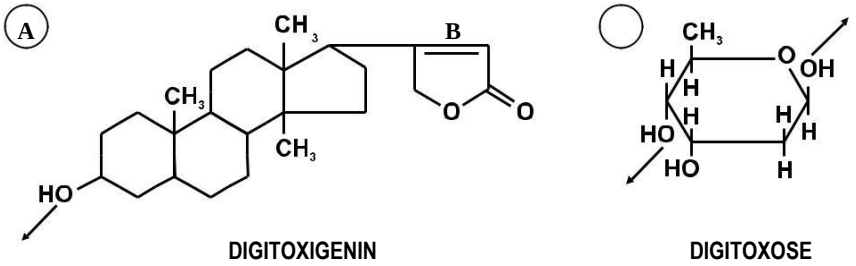


Fig. 16.4. Structural parts of cardiac glycoside digitoxin: digitoxigenin as aglycone (A) and digitoxose as glycone (B).

CLASSIFICATION

According to the origin

Group of *Digitalis*
– Digitoxin
– Digoxin
– Celanidum (Lantosidum C)
– Adonisidum
– Infusion from the herb of adonis (Infusum herbae *Adonidis vernalis*))

Group of *Strophanthus*
- Strophanthin-K
- Strophanthin-G (Quabain)
- Corglycon
- Tincture of Convallaria

According to the duration of action

Long-acting
- Digitoxin

Intermediate-acting
- Digoxin
- Celanidum

Short-acting
- Strophanthin
- Corglycon.

Mechanism of action

Mechanism of a positive inotropic action

Lactone ring binds to SH-groups of Na^+/K^+ ATP-ase that results in the revers-ible inhibition of proton 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.

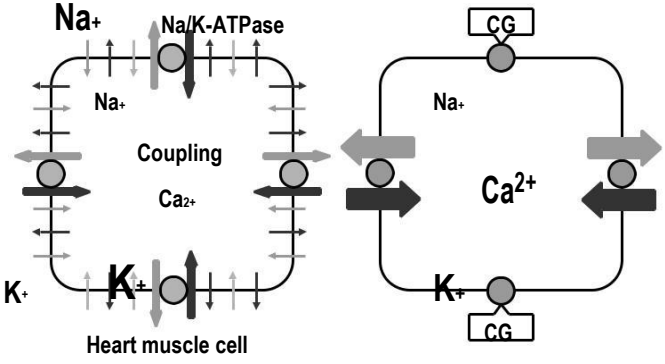


Fig. 16.5. Mechanism of cardiac glycosides' (CG) inotropic action *(by H. Lüllmann, 2000)*.

Mechanism of a 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 SA and the AV nodes and hyper-sensitization of SA node to acetylcholine.

Pharmacodynamics

a positive inotropic effect (an increase in the force of systole, an increase in the myocardial tone)
a negative chronotropic effect (the prolongation of diastole, slowing of heart rate)
a negative dromotropic effect (deceleration of conductivity)
a 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 (durative) 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 minute. 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 signs of heart failure
— changes in ECG
— hypokalemia
— anorexia, vomiting, nausea

— headache, fatigue, hallucinations
— vision disturbances (xantopsia, micropsia, macropsia).

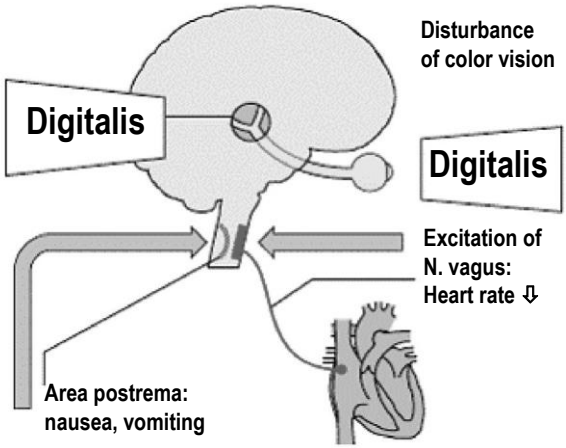


Fig. 16.6. Signs of Digitalis toxicity *(by H. Lüllmann, 2000)*.

Treatment of Digitalis intoxication:
— abolishing of cardiac glycoside
— drugs containing potassium (potassium chloride; panangin)
— SH-group donator (Dimercaprol, or Unithiol)
— anti-arrhythmic agents (phenytoin, lidocaine, propranolol, atropine for AV block)
— digoxin antibodies (digibind)
— glucose, vitamin preparations, oxygen inhalation.

Potassium preparations must be administered for 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, intoxication
is contraindicated in poisoning with cardiac glycosides, bradycardia, AV block, acute myocardial infarction, severe aortal and mitral stenosis, potas-sium deficiency, 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 CHF, an attack of arrhythmia (IV)
is less toxic, may be used in children and in patients with a non-severe AV block.

Celanidum

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, neurosis
(is combined with valerian and bromides)
has low toxicity.

NON-STEROIDAL INOTROPIC DRUGS

These inotrops improve cardiac pump function by adrenergic mechanisms or the inhibition of phosphodiesterase III.

CLASSIFICATION

Adrenomimetics
- Dobutamine (β_1-adrenergic agonist)
- Dopamine (β_1-adrenergic agonist)
- Isoprenaline (β_1-, β_2- adrenergic agonist)
- Ephedrine (α-, β- adrenergic agonist)

Selective phosphodiesterase III (PDE III) inhibitors
- Amrinone
- Milrinone.

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 heart rate; does not cause hypertension
is used in acute heart failure, cardiogenic shock
may cause tachycardia, arrhythmia.

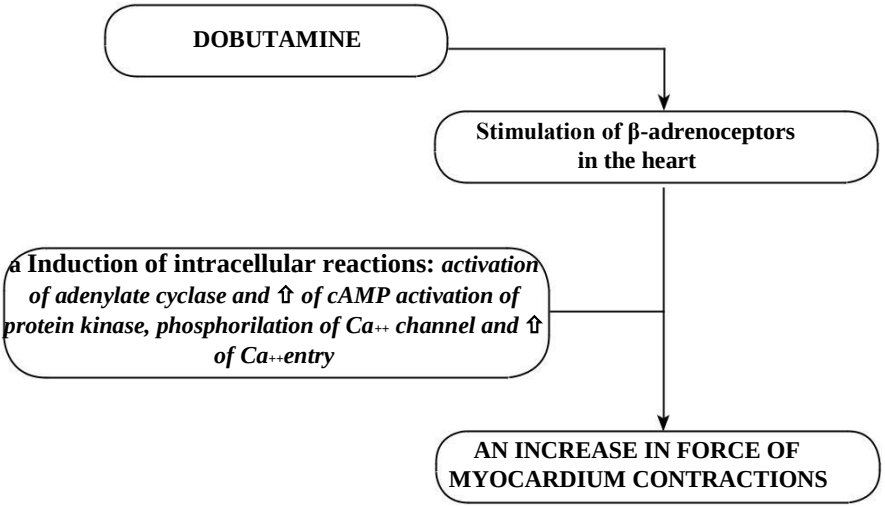


Fig. 16.7. Mechanism of dobutamine's action.

LEVOSIMENDAN

is is 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 vasodilatory effect by opening of ATP-sensitive K+ channels in vascular smooth muscle; 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 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:
Digoxin
Digitoxin
Dobutamine
Corglyconum
Infusion from the herb of adonis.

№2. The main effects of cardiac glycosides include all, except:
An increase in the strength of myocardium contractions
A decrease in heart rate
A decrease in the conductivity of the heart
An increase in neurotransmission in CNS
The improvement of blood circulation.

№3. Digitalis toxicity is characterized by the following:
Disturbances of color vision
Hypokalemia
Heart block
Ventricular tachyarrhythmia
Hyponatremia.

№.4. Acute heart failure may be treated by:
Strophanthin (ampoules)
Corglyconum (ampoules)
Digitoxin (rectal suppositoria)
Digoxin (tablets)
Celanidum (ampoules).

5. Digoxin in tablets was prescribed to a patient with chronic CHF. After 1 month of treatment a decrease in heart rate was noted; the 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.

Potassium chloride
Diphenin
Atropine
Lidocaine
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).

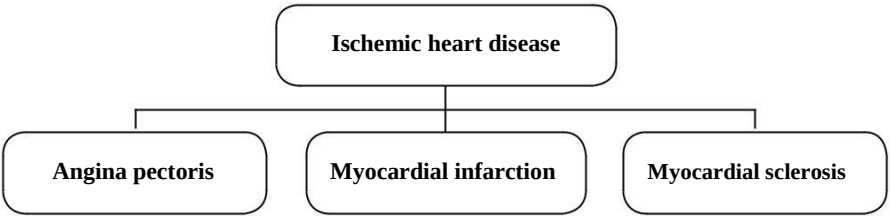


Fig. 17.1. Ischemic heart disease and its forms.

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 ves-sels (fig. 17.2). The coronary blood flow is insufficient to meet the heart's metabolic requirements. It causes the onset of anginal pain.

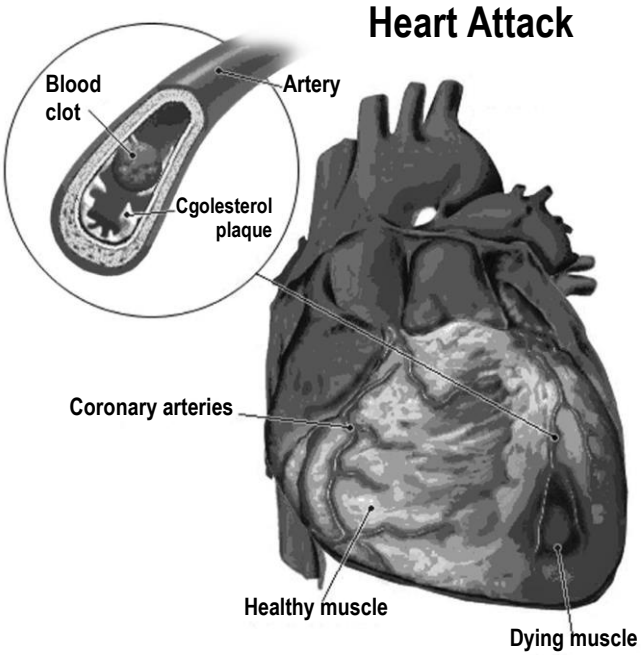


Fig. 17.2. Pathogenic factors of angina attack and myocardial infarction *(http://www.picsearch.com)*.

ANTIANGINAL DRUGS

Antianginal drugs are preparations which delay or prevent angina attack.

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

Calcium channel blockers
– Verapamil
– Nifedipine
– Amlodipine

B. *Drugs that decrease oxygen demand of myocardium*

β-adrenoblockers
– Propranolol
– Metoprolol
– Talinolol
– Atenolol

C. *Drugs that increase oxygen supply*

Substances of myotopic action
– Dipyridamole
– Papaverine
– Drotaverine (No-spa)

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.

Pharmacokinetics

is taken sublingually
is well absorbed from the oral cavity
does not undergo hepatic first-pass metabolism after the sublingual administration

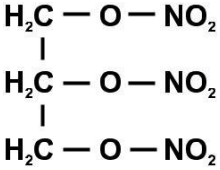


Fig. 17.3. Chemical structure of nitroglycerine.

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 endothe-lial-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).

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 resist-ance, 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.

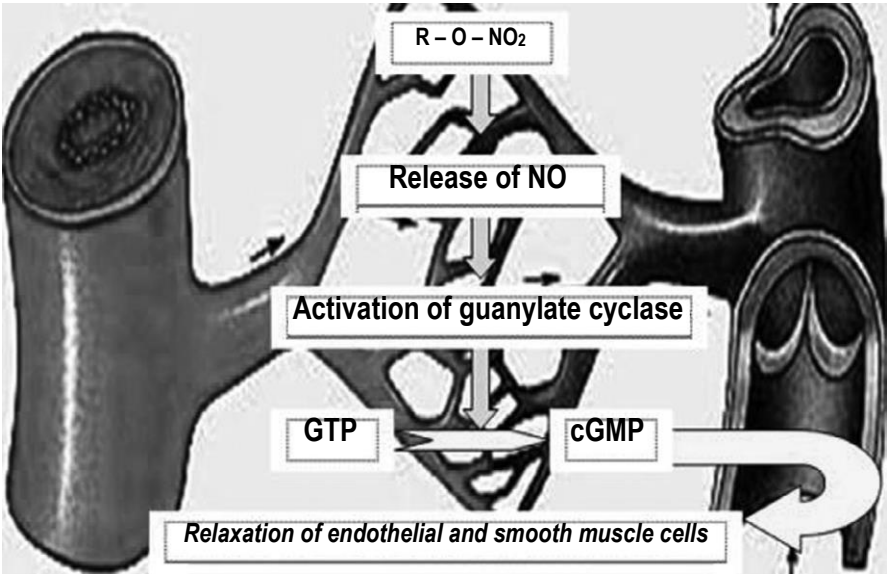


Fig. 17.4. Mechanism of nitroglycerine's action.

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

Headache (as a result of the dilation of blood vessels in brain tunics and increasing of intracranial pressure; may be diminished by the applying of Validolum or non-narcotic analgesics)
Hypotension, postural hypotension, collapse (may be treated by Mesatonum)
Reflex tachycardia
Pain in eyes, an increase in intraocular pressure (as a result of dilation of ocular blood vessels)
Flushing of the skin (as a result of the dilation of blood vessels in the skin)
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)
Overdose (the forming of methemoglobin, hypoxia, collapse, respiratory failure; needs the administration of Methileni coeruleum as an antidote).

Contraindications

Hypersensitivity
Hypotension
Myocardial infarction accompanied by hypotension
Hypertrophic obstructive cardiomyopathy
Aortic and mitral stenosis
Cardiac tamponade
Constrictive pericarditis
An increase in intracranial pressure (trauma of the brain, hemorrhagical insult)
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 preven-tion 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 a clinic; is used for the prevention, as well as for the termination of an angina pectoris attack.

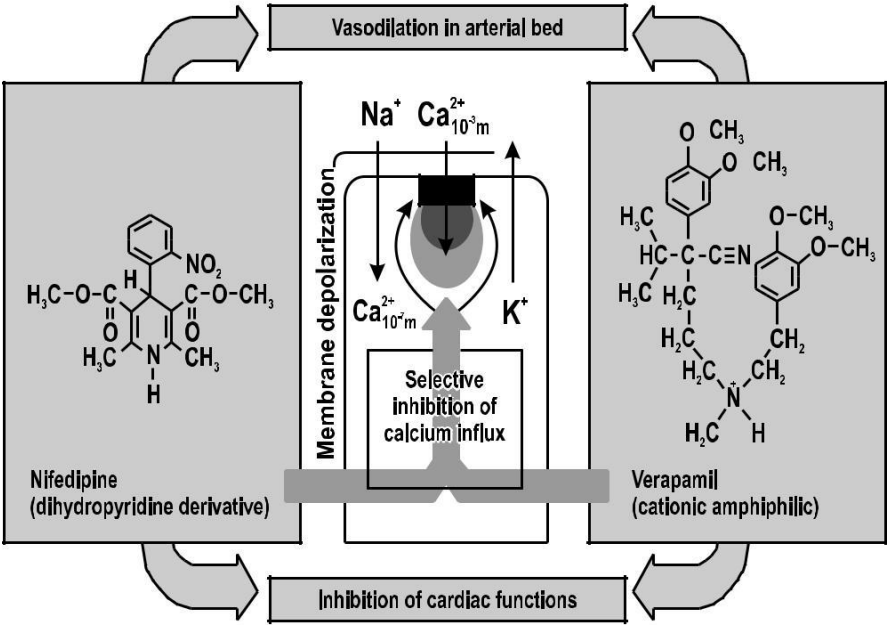


Fig. 17.5. Mechanism of action of calcium channel blockers *(by H. Lüllmann, 2000)*.

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, anti-arrhythmic and antihy-pertensive action.

CLASSIFICATION

According to the chemical structure

Phenylalkylamines
- Verapamil

Dihydropyridines
- Nifedipine (Phenigidine)

– Amlodipine

Benzodiazepines

– Diltiazem

According to generations

The first generation

– Verapamil
– Nifedipine
– Diltiazem

The second generation

– Nifedipine-retard

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 the smooth muscles of blood vessels (fig.17.5).

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 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 the ***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 ***an anti-arrhythmic action***

the dilation of peripheral blood vessels resulting in a decrease of BP and an ***antihypertensive action***

an anti-platelet action and a decrease in blood viscosity

the relaxation of the smooth muscles of uterus, bronchi, and the 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 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 in10 min after sublingual administration; displays peak level in 30 min; has a half-life of 3-6 hrs; has strong vasodilation and weak action on heart rate; is used for angina pectoris, especially for Prinzmetal's angina, for the control of hypertension; may cause reflexive tachycardia, hypoten-sion, 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.

Peculiarities of preparations

Propanolol (Anaprilin) is administered orally, IV; is absorbed in the GI tract; binds to proteins in blood serum; 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 ***(an anti-arrhythmic effect)***; decreases cardiac output and renin's secretion in the kidney, thus lowers BP ***(an 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; glaucoma; has side-effects, such as: brady-cardia, AV block, heart failure, hypotension, worsen of peripheral blood circulation, a spasm of bronchi, gastric ulcer, hypoglycemia (when insulin is co-administered), weakness, drowsiness.

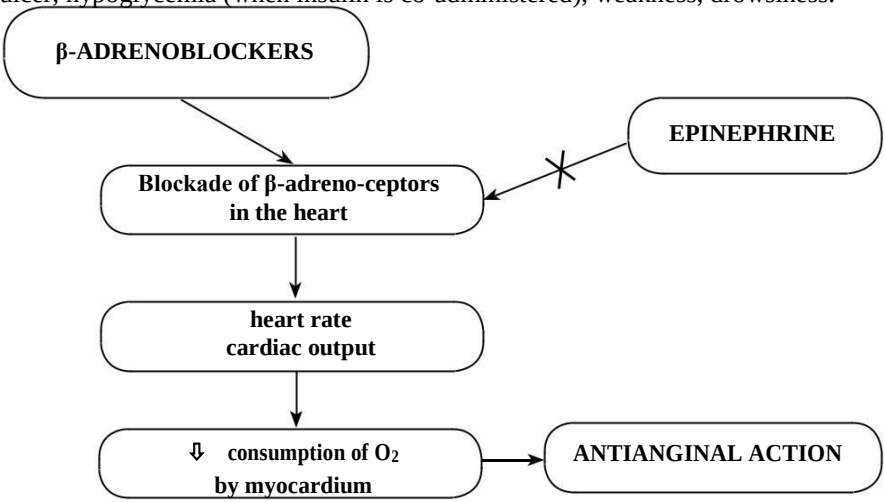


Fig. 17.6. Antianginal action of β-adrenoblockers.

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 a spasm of 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 sympathomi-metic activity and a membrane stabilizing effect (does not inhibits the heart contrac-tility and conductivity), has less side-effects and less contraindications connected with the influence on β_2-adrenoceptors.

Atenolol is a preparation of a cardioselective action (on β_1-receptors), is similar to metopolol in the action, 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

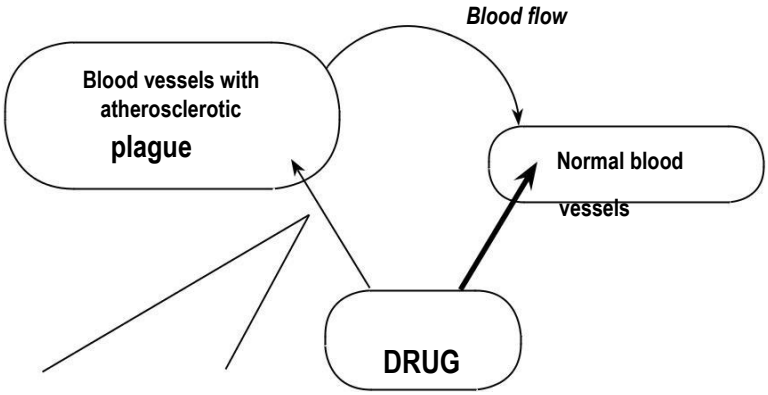
is administered orally or IV
inhibits adenosine desaminase, decreases the re-uptake of adenosine by myocardiocytes and erythrocytes, increases the concentration of adenosine in plasma resulting in the dilation of coronary vessels and ***an increase in the oxygen supply***
produces the dilation of coronary vessels, an increase in the amount of col-lateral vessels in the myocardium, the improving of coronary blood flow; an increase in coronary sinus oxygen saturation, anti-platelet 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 athero-sclerotic 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).

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, colic
may cause weakness, somnolence, constipation, disturbances of AV conduc-tion in high doses, 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.



Different intencity of drug's action on normal and atherosclerotic coronary vessels results in redistribution of blood from ischemic area to normal one

Fig. 17.7. Mechanism of "stealing" syndrome.

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 analogueue of γ-butyrobetaine; inhibits γ-butyrobetaine hydroxi-nase, 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 complica-tions. antihypoxic and anticonvulsant effects; is used in angina pectoris, myocardial infarction, CHF, stroke and cerebrovascular insufficiency, reduced working capac-ity, abstinence syndrome, vascular diseases of the eye; has minimal side effects; is contraindicated to sportsmen as doping.

Trimetazidine is anti-ischemic metabolic agent, which improves myocardial glucose utilization through inhibition of fatty acid metabolism by blocking of g-chain 3-ketoacyl-CoA thiolase (fatty acid oxidation inhibitor): has antianginal, coronarolytic, antihypoxic, ad neuroprotective effects; is used for prevention of angina attacksas well as for the treatment of cardiac ischemia; chorioretinal vascular disorders, vertigo of vascular origin, dizziness in Meniere's disease, tinnitus; has high safety and tolerability profile.

ATP-long is complex compound of ATP and metals (sodium and magnesium); is taken orally; is well absorbed in the gut; enhances ATP content in myocardium; limits ischemia; improves contractility; has anti-arrhythmic action; is the additional drug in prophylaxis of angina attack.

Corvitin contains bioflavonoid quercetin, which modulates the activity of enzymes involving in the degradation of phospholipids, influencing free radical pro-cesses and nitric oxide biosynthesis, has antioxidant, anti-inflammatory, antiallergic, anticancer, and cardioprotective effects, increases force and normalizes the rhythm of heart; effect 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 (table17.1).

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.

PRINCIPLES OF TREATMENT OF MYOCARDIAL INFARCTION

Myocardial infarction is the 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, diaphore-sis, pallor, hypotension, faintness, nausea, vomiting. Myocardial infarction may be complicated by acute heart failure and cardiogenic shock.

Main groups of preparations for 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

For a decrease in arrhythmia: anti-arrhythmics (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. The calcium channel blocker for the treatment of hypertension and angina pectoris is:
Nitroglycerine
Nifedipine
Drotaverine
Papaverine.
Propranolol.

№3. The drugs for emergency help in an angina pectoris attack are:
Propranolol (Anaprilinum)
Verapamil
Validolum
Isosorbide dinitrate
Nitroglycerine.

№4. The following statements concerning antianginal drugs are true:
Isosorbide mononitrate is an active metabolite of isosorbide dinitrate
Calcium channel blockers cause a “stealing syndrome”
Propranolol is a long-acting nitrate
Validolum has a reflexive mode of action
Dipyridamol is a coronarolytic and anti-platelet drug.

№5. A patient with ischemic disease has not informed the doctor that he had had attacks of bronchospasm. The 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

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 ANTI-ARRHYTHGMICS

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 Sino-atrial node (SA node) (fig. 18.1). The impulse initially causes both of the atria to contract, then activates the atrio-ventricular (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 s pecialized action potential (AP) in the heart. There are 5 phases in cardial AP (fig. 18.2).

The resting membrane potential is caused by the difference in ionic concentra-tions 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.

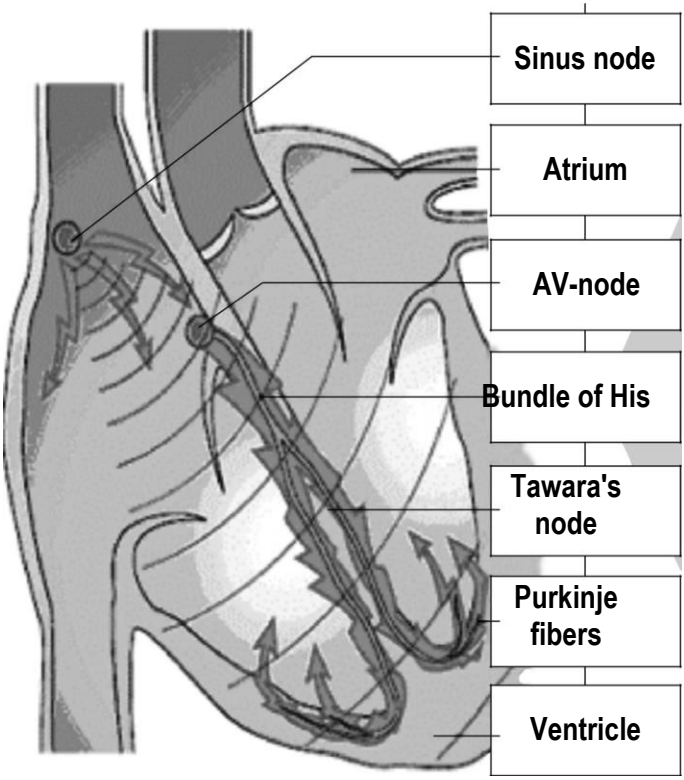


Fig. 18.1. Electrical conduction system of the heart (http://www.picsearch.com).

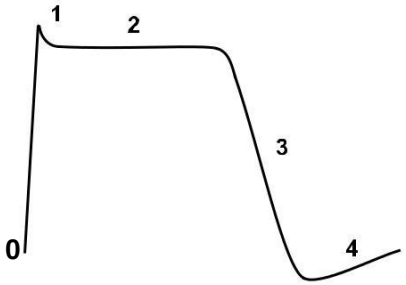


Fig. 18.2. Cardiac action potential (Phases 0-4).

Phase 0 is the 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 slow delayed recti-fier 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_{++}.

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

Cardiac arrhythmia *(also* ***dysrhythmia****)* is a term for any from a large and het-erogeneous 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 heart rate may be achieved by pharmacotherapy or cardioversion (an electrical shock).

ANTI-ARRHYTHMIC DRUGS

Anti-arrhythmics 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 ANTI-ARRHYTHMICS CLASSIFICATION

The ***Vaughan Williams classification*** is one of the most widely used classification schemes for anti-arrhythmic agents. ***Anti-arrhythmics 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 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 anti-arrhythmic effect. However, its dependence on primary mechanism is one of the limitations of this classification, since many anti-arrhythmic agents have multiple action mechanisms. Another limitation is the 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 anti-arrhythmic agents – had no place at all in the Vaughan Williams classification system. This has since been recti-fied by the inclusion of class V.

CLASSIFICATION

A. *Class I. Membrane stabilizing agents (Na^+ channel blockers)*

Subclass IA
- Quinidine
- Procainamide
- Disopyramide

Subclass IB
- Lidocaine
- Phenytoin
- Mexiletine

Subclass IC
- Propafenone
- Flecainide
- Ethacyzin

B. *Class II. β-adrenoblockers*
- Propranolol
- Metoprolol

Class III. K^+ channel blockers
- Amiodarone
- Dronedarone
- Bretylium
- Sotalol

Class IV. Ca^{++}channel blockers (agents affect the AV node)
- Verapamil
- Diltiazem

Class V. Agents of other or unknown mechanisms

Cardiac glycosides
- Digitoxin
- Digoxin

Potassium preparations
- Pananginum.

Magnesium preparations
- Rythmocor
- Magnesium orotate

Adenosine.

CLASS I. MEMBRANE STABILIZING AGENTS

SUBCLASS IA

Mechanism of action

Class IA agents block the fast Na^+channels and inhibit the Na^+ influx. Blocking of these channels depresses the Phase 0 depolarization, which prolongs the AP duration by slowing conduction (fig. 18.3).
Agents in this class also cause decreased conductivity and increased refractoriness.

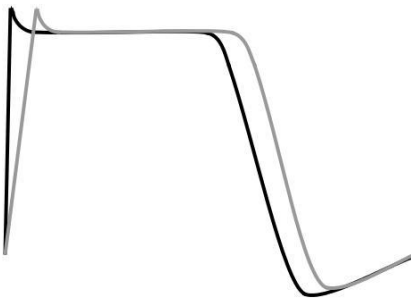


Fig. 18.3. Effect of class IA anti-arrhythmic agents on cardiac action potential.

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 treat-ment 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, itch; is contraindicated to patients with hypersensitivity, AV block, poisoning with cardiac glycosides, serious disturbances of ventricular conduction, hypotension, hypokalemia, 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, allergic reactions; is contraindicated in AV block, denominated bradycardia, heart failure, 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 the 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 the K^+ efflux, accelerates repolariza-tion, inhibits Phase 2, inhibits Phase 4 in Purkinje fibers, that's why decreases their automaticity, decreases the re-entry; unlike quinine, 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, allergy; is contraindicated in hypersensitivity, epilepsy, AV block, bradycardia, weakness of the SA node.

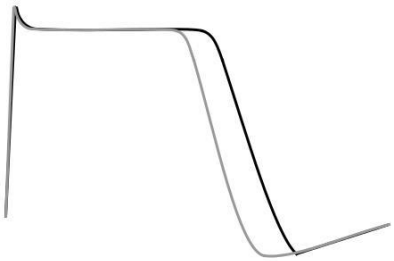


Fig. 18.4. Effect of class IB anti-arrhythmic agents on the cardiac action potential.

Mexiletine is a stable preparation; is taken orally; is used for the chronic treat-ment of ventricular arrhythmias associated with previous myocardial infarction; may cause nausea, vomiting, nistagmus, blurred vision.

Phenytoin is an anti-epileptic drug; is administered orally and IV; in the myo-cardium it decreases the 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, arrhythmias of central origin.

SUBCLASS IC

Mechanism of action

Class IC anti-arrhythmic 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 anti-arrhythmic agents (the class I anti-arrhythmic agents), the class IC agents have the most potent Na_+ channel blocking effects.

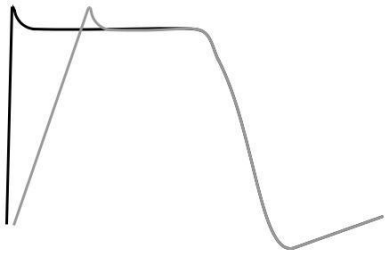


Fig. 18.5. Effect of class IC anti-arrhythmic agents on cardiac action potential.

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 tissue with a minor effect of 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, induction of some kinds of dangerous ventricular arrhythmias.

Ethacyzin is the 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 increase in the 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 extrasystole, paroxysms of fibrillation and atrial flutter, ventricular and supraventricular tachycardia, including in the syndrome of premature ventricular excitation; may cause such side effects as siinus 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 anti-arrhythmic 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

AV block
Bradycardia
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 anti-arrhythmic agents exhibit reverse use dependent prolongation of the AP duration. This means that the refractoriness of the ventricular myocyte increases at lower heart rates. This increases the susceptibility of the myocardium to early after-depolarizations at low heart rates. Anti-arrhythmic 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 anti-arrhythmic agents may paradoxically be more ar-rhythmogenic.

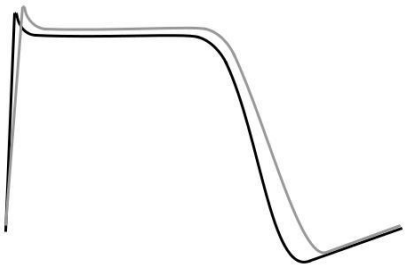


Fig. 18.6. Effect of class III anti-arrhythmic agents on cardiac action potential.

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 anti-arrhythmic 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 anti-arrhythmic 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 tachyarrhyth-mias, 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 anti-arrhythmic 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 lipophi-licity, 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, asthenia; provokes risk of cardiovascular death after the long usage.

Bretylium tosilate is administered IV, IM, is excreted unchanged with urine; has a potent anti-arrhythmic 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 resistance to electrical defibrillation; may cause severe postural hypotension, transitory tachycardia and ectopic beats, nausea, vomiting; is contraindicated in pheochromacytoma, acute disorders of brain blood circulation, hypotension, collapse, severe renal failure, aortal stenosis, pulmonary hypertension, pregnancy, lactation.

Sotalol is a β-adrenoblocker and anti-arhythmic 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 arrhyth-mia 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 anti-arrhythmic 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 the act on conductivity.

Indications

Supraventricular tachyarrhythmia
Fibrillation of atria, atrial flutter
Paroxismal tachycardia.

Common properties of Ca^{++} channel blockers and peculiarities of some prepara-tions 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., ***Pananginum***) 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 tachyar-rhythmias, especially caused by hypokalemia.

Magnesium preparations (***Magnesium orotete***) and combained drugs containing magnesium and potassium (***Rythmiucor***) 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, hypotension.

DRUGS FOR BRADYARRHYTHMIA AND AV BLOCK

CLASSIFICATION

M-cholinoblockers
- Atropine

Adrenomimetics
- Isoprenaline
- Ephedrine.

Peculiarities of preparations

Atropine is a non-selected M-cholinoblocker, has a dose-dependent action on the heart rate. At low doses, the predominant effect is a decreased heart rate (bradycar-dia) 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 a indirect-acting adrenomimetic, has a presynaptic action, stimu-lates the 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 drug, except:
Procainamide blocks Na^+ channels
Amiodarone blocks K^+ channels
Verapamil blocks Ca^{++} channels
Bretylium blocks K^+ channels
Quinidine blocks Ca^{++} channels.

№ 2. Incorrect statement concerning lidocaine is:

It is administered parenteraly
It is class IA anti-arrhythmic
It is metabolized in the liver
It shortens an action potential
It is the drug of choice in ventricular fibrillation.

№ 3. The drugs for the maintenance of the cardiac rhythm after the cardioversion are:
Quinidine
Adenosine
Digoxin
Procainamide
Disopyramide.

№ 4. Adenosine:
Is given only IV
Has the shortest duration of action
Is class III anti-arrhythmic
Stimulates A_1-adenosine receptors
Is used for the termination of acute supraventricular tachyarrhytmia.

№ 5. To maintain the normal sinus rhythm, a patient with atrial fibrillation was prescribed with anti-arrhythmic drug containing iodine. This drug has very long duration of action and may cause reversible pulmonary fibrosis and corneal microdeposits. What preparation was prescribed?
Procainamide
Propranolol
Sotalol
Amiodarone
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 90mm 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 (BP) is the sum of cardiac output and peripheral resist-ance. 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 cardio-vascular 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 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 the 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*

Drugs decreasing vasomotor center activity (centrally acting α_2-adrenomimetics and imidazoline receptor agonists)

– Clonidine (Clophelinum)
– Methyldopa
– Moxonidine

Anti-adrenergic drugs

α-Adrenoblockers
– Prazosin
– Doxazosin
β-adrenoblockers
– Propranolol (Anaprilin)
– Metoprolol
– Atenolol
– Bisoprolol
α,β-adrenoblockers
– Labetolol
– Carvedilol
Adrenergic neuron blocking agents (sympatholytics)
– Reserpine
– Guanethidine (Octadinum)
M-cholinoblocker
– Platyphylline
N- cholinoblockers (ganglionic blockers)
– Hexamethonium
– Pentamine

Ca^{++} channel blockers
– Nifedipine
– Verapamil
– Amlodipine
– Diltiazem
Magnesium salts
– Magnesium sulfate
Phosphodiesterase inhibitors
– Papaverine
– Drotaverine (No-Spa)
– Bendazole (Dibazolum)
Potasium channel openers
– Appressin
– Minoxidil
– Diazoxide
Other vasodilators
– Sodium nitroprusside

C. *Drugs acting on renin-angiotensin system*

ACE inhibitors
– Captopril
– Enalapril
– Lisinopril
– Fosinopril

Angiotensin II receptor antagonist
– Losartan
– Temisaetan

Renin inhibitors
– Aliskiren

– Hydrochlorothiazide
– Furosemide.

DRUGS DECREASING VASOMOTOR CENTER ACTIVITY

CLONIDINE

Pharmacokinetics

is administered sublingually, orally, IV, IM
is completely absorbed in the GI tract
after 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 CNS.
The stimulation of presynaptic α_2-adrenoceptors and imidazoline receptors I1 in the adrenergic synapsis 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 heart rate and cardiac output
a decrease in renin activity
sedation
a decrease in pain
a decrease in intra-ocular 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)
   Constriction of blood vessels in the brain
   Dry mouth
   Inhibition of gastric secretion
   Constipation
   Retention of sodium and water
   Changes in glucose level in blood
   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 chemical structure, that's why acts as "a false mediator" in CNS: stimulates α_2-adrenocepotors and decreases the norepinephrine release in synapses of the vasomotor center; by this mecha-nism it decreases the 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, galac-torrhea
is contraindicated to patients suffering from depression, Parkinson's disease, liver diseases.

MOXONIDINE

is a selective agonist of the imidazoline receptor I1 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 complica-tions 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 a few days and leads to a decrease of diastolic pressure and stable lowering of BP.

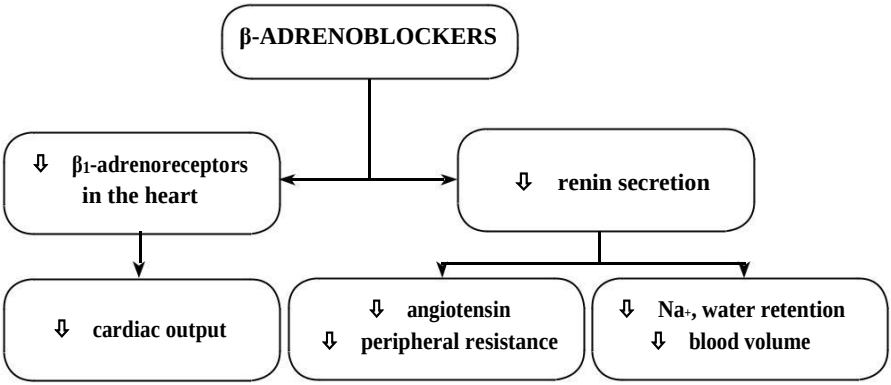


Fig. 19.1. Mechanism of antihypertensive action of β-adrenoblockers.

α,β-ADRENOBLOCKERS

Labetalol and ***carvedilol*** act both on α- and β-adrenoceptors, but action on β-receptors is more significant. They produse lowering BP mediated by the blockade of β-adrenoceptors and vasodilation due to blockade of. α-adrenoceptors

SYMPATHOLYTICS

Reserpine acts in peripheral tissues, as well as in 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 prevanence of PANS.

Guanetidine (Octadinum) 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, a spasm of bronchi, increased activity of the gut).

Adrenoblockers and sympatholytics belong to autonomic and are described in detail in chapter 8. Cholinergic drugs for managment of acute and chronic hypertesion are characterized in the Chapter 6.

MYOTROPIC VASODILATORS

CALCIUM CHANNEL BLOCKERS

Calcium channel blockers (nifedipine, verapamil, amlodipine) have an antihypertensive action resulting from the dilatation 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 and 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 laxative)
is an antagonist of calcium ions in cells
a sedative, hypnotic and narcosis action, the inhibition of the vasomotor center; an anti-seizure action, the dilatation of blood vessels, and a decrease in BP; an anti-arrhythmic action, the dehydratation of tissues, a diuretic ac-tion, a decrease in intracranial pressure; a spasmolytic action; 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, 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 carbogenum (inhalation) should be used.

PHOSPHODIESTERASE INHIBITORS

BENDAZOLE (DIBAZOLUM)

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 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, 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 car-diac 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

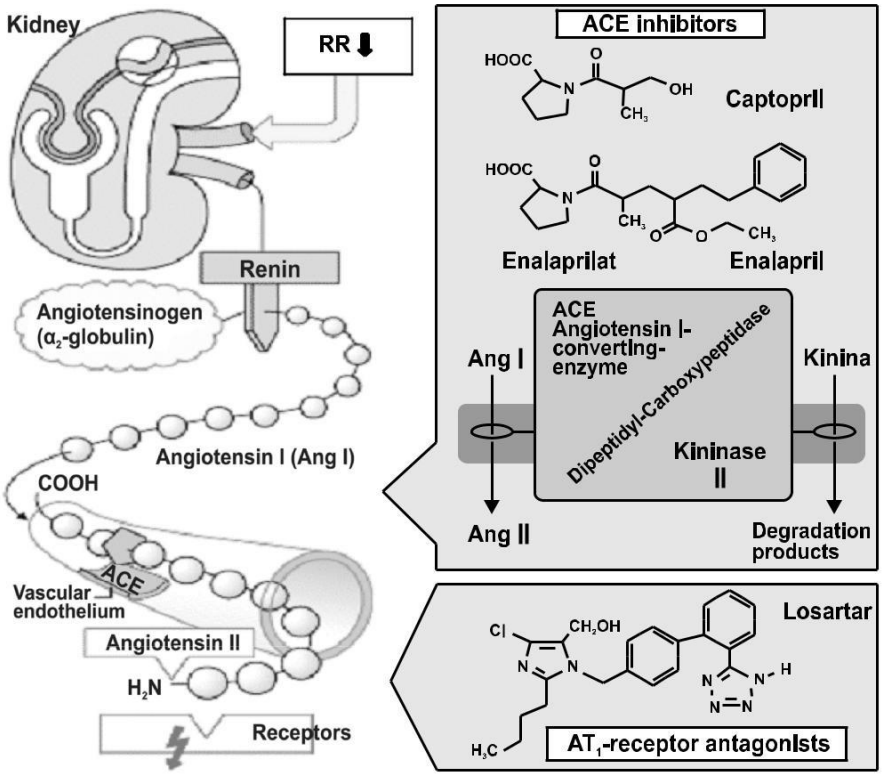


Fig. 19.2. Renin-angiotensin system and mechanism of action of ACE inhibitors and angiotensin II-receptor inhibitors *(by H. Lüllmann, 2000)*.

causes side-effects, such as weakness, headache, tachycardia, worsen in angina, flushing of skin, sweating, reversible lupus-like syndrome, retention of water and salts.

DIAZOXIDE

is administered orally, IV; begins to act in 2-5 min after 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 tone of smooth muscles in the gut and uterus; inhibition of insulin secre-tion, 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, urico-semia, constipation.

MINOXIDIL

is the 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 the Fe, that's why the mechanism of action is the same as the mechanism of nitroglycerine; exceeds nitroglycerine's potency in 1000 times; is a 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, retros-ternal 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, vasodila-tion, 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
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 vasodilatation 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

Dry cough, spasm of bronchi (resulting from an increase in the bradykinin level)
Skin rash
Fever
Hypotension
Hyperkalemia
Disturbance in the renal function
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 the 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 patient with renal failure; has the highest lipophilicity and the best penetration into tissues, so it reliably and for a long time controls 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, 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 a spasm of bronchi.

Telmisartan also is an antagonist of AT1-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 plasma renin activity
can be used either as monotherapy or in combination with other antihypertensive agents; combination therapy with angiotensin receptor blockers may provide additional BP-lowering effects 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 emer-gency.

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*** (no-radrenaline, 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:

Clonidine + furosemide

Metyldopa + dichlothiazide

Reserpine + dichlothiazide
Guanetidine + dichlothiazide
Strophanthin + furosemide.

№2. Only one of following drugs is a potent vasodilator realizing its effects through the –NO group:
Papaverine
Drotaverine (No-spa)
Sodium nitropusside
Prazosin
Captopril.

№3. An antihypertensive action of β-adrenoblockers is due to:
A decrease of cardiac output
The inhibition of the conductivity in the heart
A decrease of the oxygen demand in the myocardium
A decrease of the renin synthesis in the kidney
A decrease of intraocular pressure.

№4. The correct statements concerning antihypertensive drugs are:
Clonidine is the inhibitor of the vasomotor center activity
Diazoxide is K^+-channel opener, arteriolar vasodilator
Guanethidine is sympatholytic for hypertensive emergency
Lisinopril is the active metabolite of enalapril
Diuretics are not combined with other antihypertensive drugs.

№5. Hypertensive patient was treated with the drug that decreases the vascular tone. His treatment was complicated by persistent dry cough. Which drug was most probably used?
Papaverine
Phentolamine
Captopril
Prazosin
Clonidine (Clophelinum).

Answers

№ 1 – A; № 2 – C; № 3 – A, D; № 4 – A, B, D; № 5 – C.

Chapter 20 ANTI-ATHEROSCLEROTIC DRUGS

ATHEROSCLEROSIS

Atheroscleosis is a chronic disease of arteries which results in the forming of an atheromatous plaque. An atheromatous plaque develops in such stages as the infil-tration of the blood vessel wall by cholesterol, local forming of fibrin, development of connective tissue and its calcinosis (fig. 20.1). An atheromathous plaque causes disturbances in blood flow complicated by myocardial infarction, ischemic insult, aneurism of the aorta, and gangrene of extremities.

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.

Hyperlipoprotienemia

The main classes of lipoproteins are:

— chylomicrones (Chy)
— low-density lipoproteins (LDL)

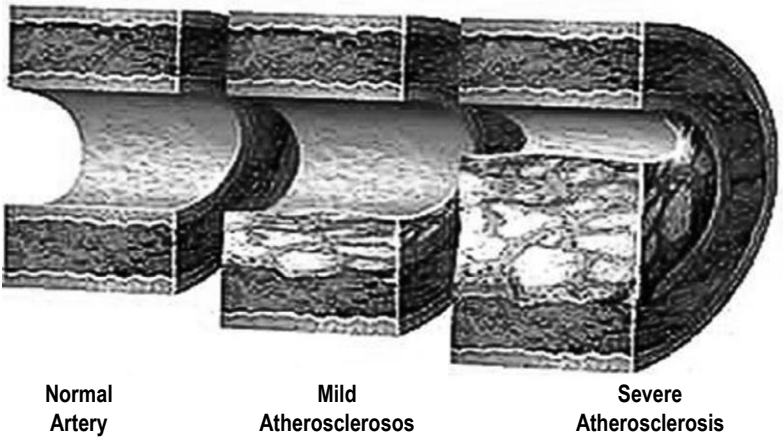


Fig. 20.1. Atheromathous plaque in blood vessel (http://www.picsearch.com).

— very low-density lipoproteins (VLDL)
— high-density lipoproteins (HDL).

Chy, LDL, VLDL are atherogenic lipoproteins. HDL are anti-atherogenic lipoproteins. According to laboratory findingds, there are 5 types of hyperlipoproteinemia. Hyperlipoproteinemia of type II–IV leads to the development of atherosclerosis.

Lipids peroxidation

Lipids peroxidation is non-enzymic oxidation initiated by free radicals of oxygen. It destroys cell membranes and leads to the forming of lipids peroxides. An increase in lipids peroxidation and the inhibition of antioxidant protection results in the injuries of the blood vessels wall. Oxidized lipids are taken by macrophages which are transformed into foam cells (components of an 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 an 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 treatment

A long-durative treatment

Courses of treatment in the periods of worsening of 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 condi-tions of long-lasting therapy

The laboratory control of the effectiveness of treatment.

ANTI-ATHEROSCLEROTIC DRUGS

Anti-atherosclerotic drugs are drugs for the treatment of atherosclerosis. They protect arteries from atherosclerosis and are angioprotectors (fig. 20.2).

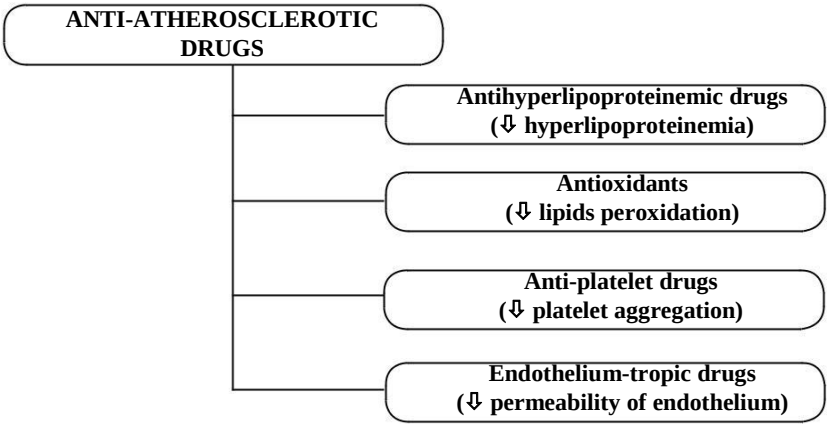


Fig. 20.2. Main groups of anti-atherosclerotic drugs.

ANTIHYPERLIPOPROTEINEMIC DRUGS

Antihyperlipoproteinemic drugs are preparations for a decrease of blood sesum level of atherogenous lipoproteins and cholesterol.

CLASSIFICATION

Drugs interfering with intestinal absorption of cholesterol
- Cholestiramine
- Ezetimibe

Inhibitors of de novo cholesterol synthesis
- Fenofibrate
- Lovastatin
- Simvastatin
- Atorvastatin

- Nicotinic acid (niacin)

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 acid 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 enhanced capture of LDL and cholesterol from blood serum and reduction in serum LDL and the cholesterol level (fig. 20.4)
is indicated in atherosclerosis with hyperlipoproteinemia of II-IV types, cholestasis, and elevated plasma bile acids

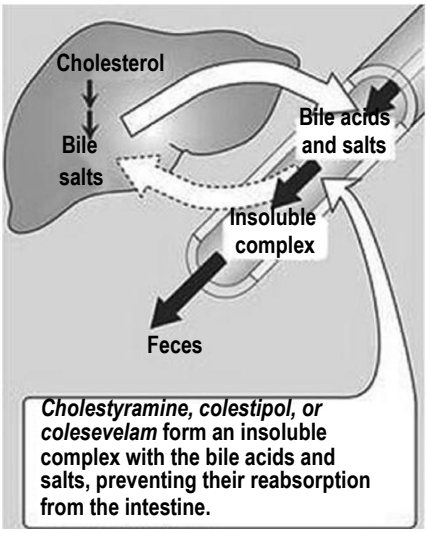


Fig. 20.3. Mechanism of cholestiramine's action *(by R. Finkel et al., 2008)*.

causes side-effects, such as dyspepsia, constipation, a decrease in the absorption of fat-soluble vitamins and other drugs.

EZETIMIBE

is cholesterol-loering agent taking oraly once a day
blocks specific cholesterol transporter in the GI epithelial cells (Niemann-Pick C1-Like1 protein)
acts by decreasing cholesterol absorption in the small intestine, is selective inhibitor of cholesterol absorbtion
is used alone, when other hypolipidemic medications are not tolerated, or together with statins when thet alone do 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 pro-drug (transforms into the active form in the blood)
inhibits HMG CoA reductase and blocks the hepatic synthesis of cholesterol on the stage of the mevalonic acid, increases the expression of hepatic LDL receptors and activates receptor-mediated clearance of LDL (fig. 20.4)
decreases serum levels of LDL, LDL-cholesterol, VLDL-cholesterol; elevates serum level of HDL-cholesterol
is used to treat atherosclerosis with hyperlipoproteinemia of IIa-IIb type, atherosclerosis at a high risk of myocardial infarction; secondary hyperlipi-demia 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 semisynthetic preparation, has pharmacokinetics similar to lovastatin's one, can be prescribed at a normal or moderately elevated baseline level of common cholesterol and LDL-cholesterol; is stronger than lovastatin, but less potent than atorvastatin and rosuvastatin. but greater than atorvastatin, increases HDL-cholesterol.

Atorvastatin is 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 synthetic drug; is not metabolized by the P450 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 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 stimulator of peroxysome proliferator-activated receptor-α (PPAR-α); 3) is an activator of lipoprotein lipase and increases the hydrolysis of triglyc-erides; 4) is an inhibitor of hepatic synthesis of VLDL
reduces the serum level of Chy, VLDL, and triglycerides, lowers VLDL-cholesterol, LDL-cholesterol and increases HDL-cholesterol (less than

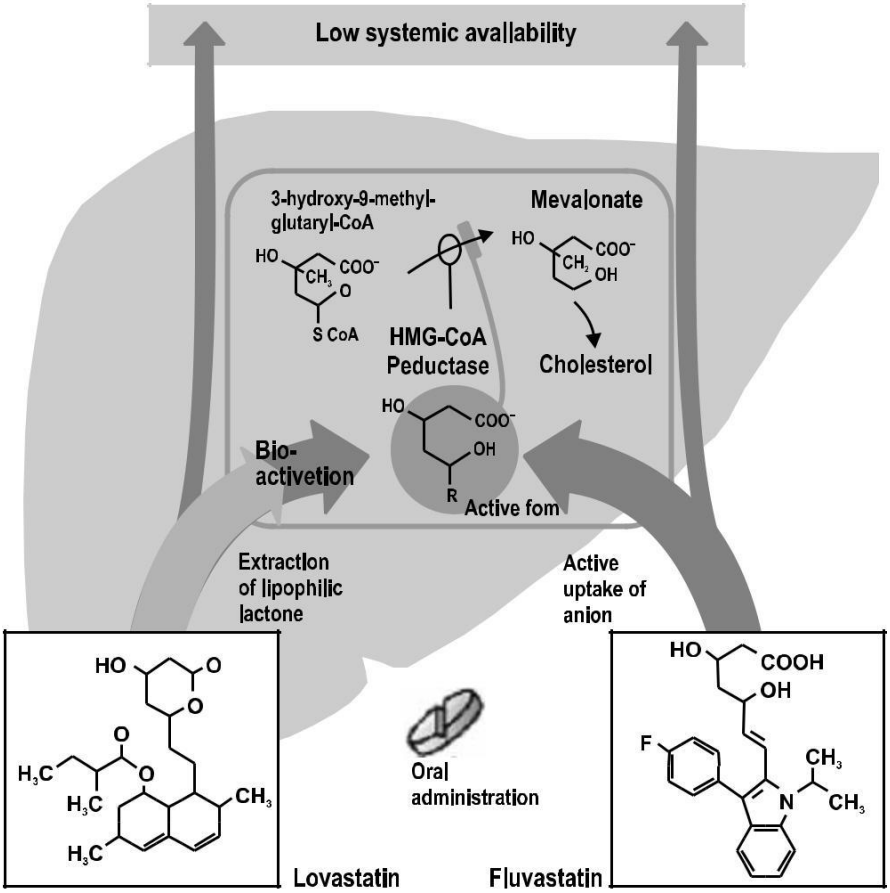


Fig. 20.4. The influence of statins on cholesterol synthesis *(by H.Lüllmann, 2000)*.

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, arrhythmia.

NICOTINIC ACID (NIACINUM)

is a water-soluble vitamin, but an anti-atherosclerotic action is not due to vitamin activity
is taken orally in higher doses (3,0 per day)
inhibits lipolysis in 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 V type
may cause a flush-syndrome, peptic ulcer of the stomach, hepatic lesions, glucose intolerance, hyperuricemia.

ESSENTIALE

contains essential phospholipids, which regulate the metabolism of lipopro-teins, 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 (GI disturbances, diarrhea).

•

LINAETHOLUM

is a plant preparation from oil of flax semen
contains unsaturated fatty acids
is taken orally (1 table-spoon per day)
increases binding of cholesterol to HDL; promotes the transformation of cholesterol into its esters and their transport to the liver; stimulates transformation of cholesterol into bile acids and reduces the serum level of LDL and LDL-cholesterol
is used for the treatment of atherosclerosis with hyperlipoproteinemia of II-IV types
may cause dyspepsia, an increase in lipids peroxidation (tocopherol acetate should be given together with Linaetholum).

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 Linaetholum, but acts stronger, protects hepatic cells, can dissolve fat emboli
is used in atherosclerosis with hyperlipoproteinemia, liver diseases, fat embolism.

ANTIOXIDANTS

Antioxydants are natural or synthetic substances which inhibit free-radical lipids peroxidation.

CLASSIFICATION

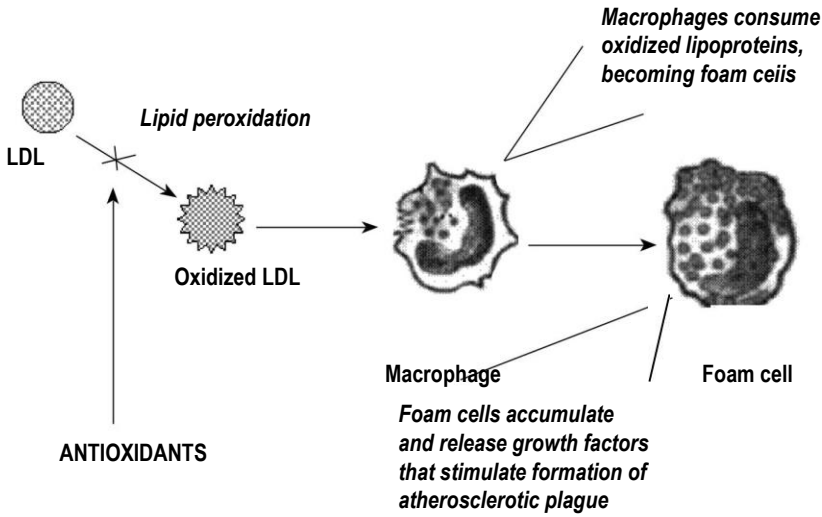


Fig. 20.5. Mechanism of antioxidants action in atherosclerosis.

Direct-acting antioxidants
- Tocopherol acetate
- Ascorbic acid
- Rutin
- Probucol

Indirect-acting antioxidants
- Glutaminic acid
- Methionine
- Cysteine.

Mechanism of antihyperlipoproteinemic action

Direct- acting antioxidants inhibit oxidation of cholesterol resulting in 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 detoxication processes in the liver). In this process, the glutaminic acid takes out the carbon chain, methyonine is a donator of methyl group, cysteine is a donator of the SH-group.

Indications

Antioxidants are used for the treatment of atherosclerosis accompanied by enhanced lipids peroxidation. Their effectiveness is increased if antioxidant prepara-tions are used in a combination.

Peculiarities of preparations

Tocopherol acetate is a fat-soluble vitamin; is taken orally to treat athero-sclerosis; is the most active low-weight antioxidant in the organism; is located in 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 blood serum.

Detail description of antioxidants is represented in chapter 27.

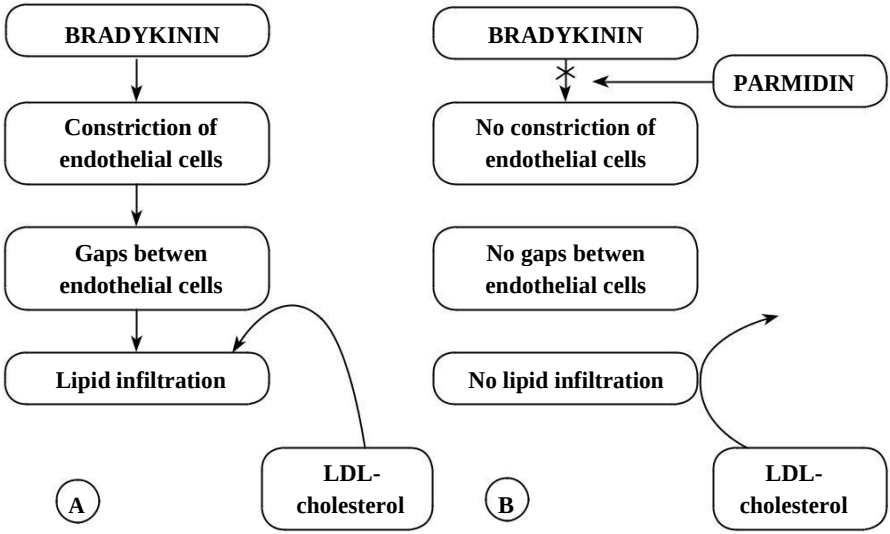


Fig. 20.6. Mechanism of parmidin's action:
A – without parmidin; **B** – under the influence of parmidin.

ANTI-PLATELET DRUGS

Aspirin and low doses of ***heparin*** (IM or by inhalation) are used for the treatment of atherosclerosis accompanied by hypercoagulation of blood.

Pharmacological properties of anti-platelets are described in detail in chapter 22.

ENDOTHELIUM-TROPIC 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 anti-platelet 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, trophic ulcer of the lower extremities

may cause headache, dyspepsia, skin rash.

•

TESTS FOR SELF-CONTROL

№1. Cholestyramine lowers the level of cholesterol by:

Sequestering bile acids in the intestine
The prevention of bile acids reabsorption
An increase of VLDL excretion
The inhibition of lipids peroxidation
The activation of lipoprotein lipase.

№2. The following statements concerning antioxidants are correct, except:

They inhibit free-radical lipids peroxidation
They inhibit the oxidation of cholesterol and its uptake by macrophages
They slow the development of atherosclerosis
They inhibit the synthesis of cholesterol at the stage of the mevalonic acid
Direct acting antioxidants are natural and synthetic substances.

№3. The drugs inhibiting de novo cholesterol synthesis are:

Lovastatin
Parmidin
Fenofibrate
Polysponinum
Tocopherol acetate.

№4. Fibrates decrease the lipoprotein level in blood serum by:

The activation of lipoprotein lipase
Lowering of circulating triglycerids
The prevention of cholesterol absorption from the gut
The alteration of LDL composition
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 blood plasma. Due to this anti-atherosclerotic 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?

Nicotinic acid
Ascorbic acid
Lovastatin
Fenofibrate
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 the production of blood cells from undifferentiated stem cells. It is located in the bone marrow and divided into erythropoiesis and leukopoiesis.

Erythropoiesis is the 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 blood disorder characterized by a 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 hemo-globin concentration caused by the pathological proliferation of erythroid cells in the bone marrow.

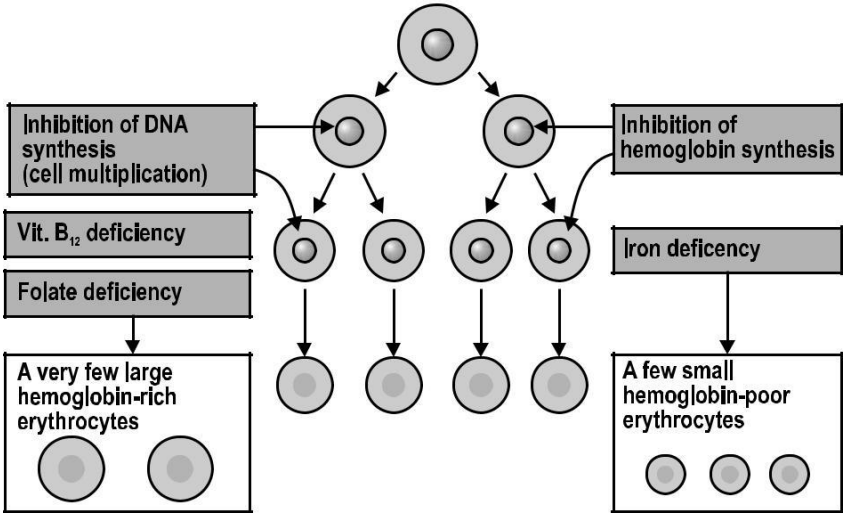


Fig. 21.1. Pathology of erythropoiesis *(by H. Lüllmann, 2000)*.

Leukopoiesis is the production of lymphocytes and granulocytes. ***Pathology of leukopoiesis*** is manifested as leukopenia or leukemia. ***Leukopenia*** is a decrease in the amount of leukocytes in blood resulting from the inhibition of their forming in the bone marrow.

Leukemia (leukosis) is cancer of blood characterized by malignant proliferation of white blood cells precursors in the bone marrow resulting in the increase of the leukocytes amount.

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 rep-resented in each group.

DRUGS ACTING ON ERYTHROPOIESIS

CLASSIFICATION

A. *Erythropoiesis stimulants*

1. Drugs used in hypochromic iron-deficiency anemia
   iron preparations
   – Ferrous sulfate
   – Tardyferon
   – Ferrum-lek
   cobalt preparations
   – Coamid
   combined preparations
   – Ferovenum
   – Ferroplex
   – Hemostimulinum
   adjuvant hematinics
   – Erythropoetin (Epoetin α)
   – Recormon (Epoetin β)
   Drugs used in hyperchromic megaloblastic anemia
   – Cyanocobalamin
   – Folic acid

– Sodium phosphate containing P_{32}
– Imiphos.

DRUGS USED IN HYPOCHROMIC IRON-DEFICIENCY ANEMIA

FERROUS SULFATE

The drug contains 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, chloramphenicol
Fe^{++} binds to transferrin in blood serum and is transported in this complex concentrates in the bone marrow and depo tissues (liver, spleen)

is excreted with urine, feces, epithelial cells, and menstrual blood in women.

Mechanism of action

is used to form hemoglobin in erythrocytes
is used to form myoglobin in muscles
is used to form enzymes (cytochrome oxidase and others).

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 ethiology (anemia from an acute and chronic blood loss, alimentary iron deficiency, pregnancy, etc.).
Depot-preparation of ferrous sulfate (dragee or coated tablets) is used under the name ***Tardyferon***.

Side-effects

1. Dyspepsia
2. Constipation (resulting from 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:

— The lavage of the stomach with 1% solution of sodium bicarbonate

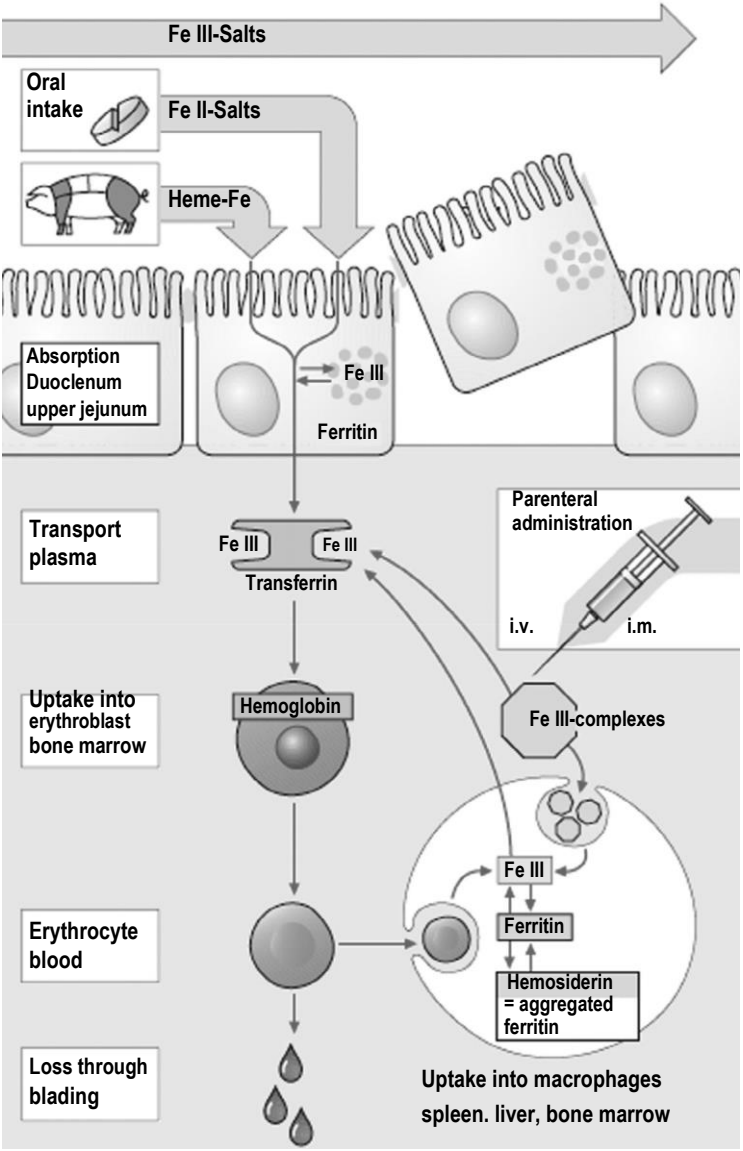


Fig. 21.2. Pharmacokinetics of iron *(by H. Lüllmann, 2000)*.

— 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, hypotension (rarely).

Coamid contains cobalt; is administered IM, IV; accumulates 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, cobalt gluconate, and carbonhydrates; 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 fer-rous sulfate and vitamin C.

Hemostimulinum 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 CNS.

Epoetin β is glycoprotein, natural factor stimulating mitosis and proliferation of erythroid cells; is administered SC or IV; has 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 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, 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, trimethoprim). It leads to the development of ***megalo-blastic anemia*** (also known as malignant, pernicious, Addison-Birmer's anemia). Megaloblastic anemia is characterized by the presence of megaloblasts in 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, co-factor 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, normal-izes the blood film (the amount and qualities of erythrocytes, leukocytes, and thrombocytes);

takes part in the synthesis of myelin and acetylcholine, decreases neurologi-cal disturbances connected with megaloblastic anemia

takes part in the function of the epithelium and decreases disturbances in tongue mucosa (Hunter's glossitis)

is indicated in hypercromic megaloblastic anemia, hypoplastic anemia, radiation sickness, neurological diseases, liver diseases, dystrophy in chil-dren, glossitis

may cause allergy, hypercoagulation, tachycardia, pain in the heart, worsen in angina pectoris.

is contraindicated to patients with hypersensitivity, thrombosis, throm-boembolism.

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 the additional remedy in the treatment of hyperchomic megaloblastic anemia; is used together with cyanocobalamin; is also indicated in chronic gastro-enteritis, sprue, in pregnancy for the prophylaxis of neurological pathology of the fetus and newborn.

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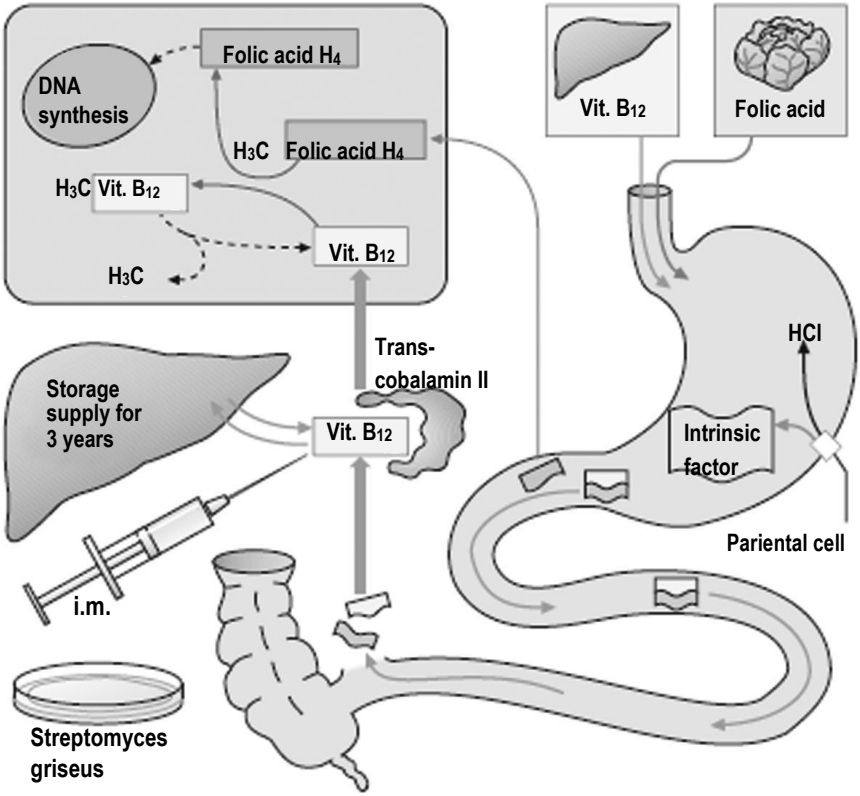

Fig. 21.3. Absorption and storage of folates and cyanocobalamin *(by H. Lüllmann, 2000)*.

ERHYTHROPOIESIS INHIBITORS

Sodium phosphate with radioactive phosphor is administered IV in a 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 blood, improves the condition of patient suffering from polycytemia.

Imiphos is an anti-cancer 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*

Nucleic acid derivatives
– Sodium nucleinate
Pyrimidine derivatives
– Methyluracil
– Pentoxilum
Colony stimulating factors
– Filgrastim
– Molgrastim
– Lenograstim

Alkylating agents
– Mechlorethamide (Embichin)
– Cyclophosphamide
– Dopan
– Myelosan
– Chlorbutin (Leukeran)
– Sarcolysine
Antimetabolites
– Methotrexate
– Mercaptopurine
– Phtoruracil
Anti-cancer antibiotics

– Actinomycin (Dactinomycin)
– Rubomycin

Alkaloids
– Vinblastine
– Vincristine
– Demecolcine (Colchamine)
– Paclitaxel

Enzymes
– L-asparaginase

Steroid hormones
– Prednisolone
– Gonadal hormones and their antagonists (Fosfestrol, Tamoxifen, etc).

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 the 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 leucopenia, wounds and bone fractures with poor regeneration, ulcers, burns, gastric ulcer, chronic inflammations with slow recovering, radiation sickness, suppressed immunity, paradontitis

may cause dyspepsia, allergy

is contraindicated in severe disturbances of leukopoiesis, aplastic anemia, leukemia, cancer.

PECULIARITIES OF OTHER PREPARATIONS

Pentoxylum acts similar to methyluracilum, 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 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 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 chemotherapeutic anti-tumor agents, bone marrow transplantation, or aplastic dis-eases 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 ANTI-CANCER 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 also 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-mercaptopurin) are structural analogs 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.

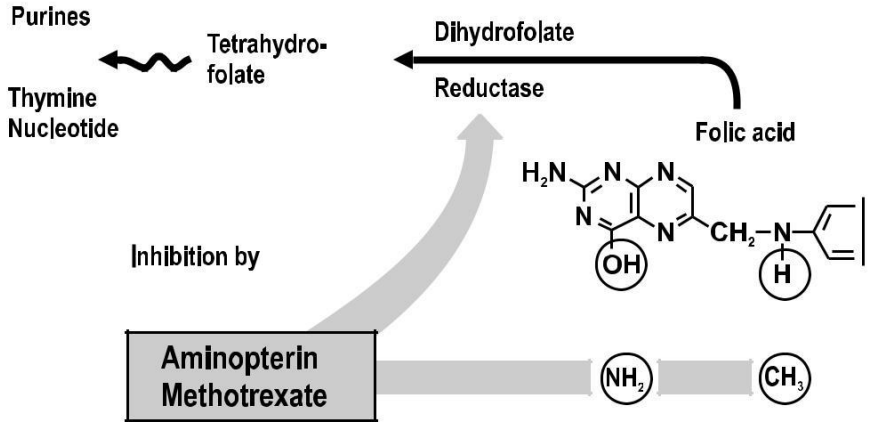

Fig. 21.4. Mechanism of action of methotrexate *(by H. Lüllmann, 2000)*.

Alkylating agents (Chlorbutinum, Dopanum, Myelosanum etc.) are biotrans-formated in anions interacting with nucleophylic centers of DNA (fig. 21.5). As a result, they 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 hy-drolyzes 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 myto-sis 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. Vinblastine is used in the combined treatment of lymphomas and metastatic testicular carcinoma.

Steroid hormones. Glucocorticoids (prednisolone) inhibit the proliferation of lymphoid tissue. They are used in patients with acute lymphocytic leukemia and

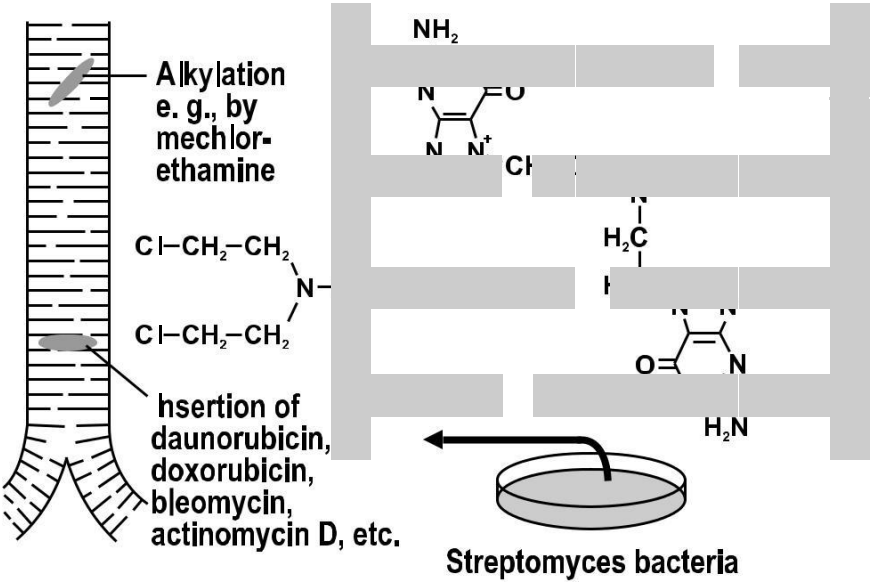

Fig. 21.5. Mechanism of action of alkylating agents and anti-tumor antibiotics *(by H. Lüllmann, 2000)*.

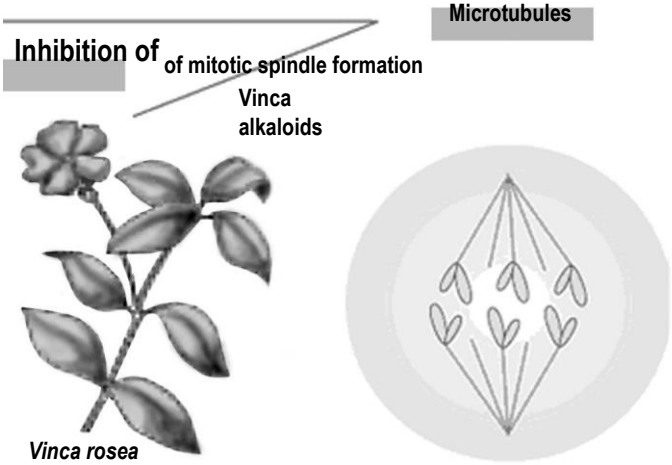

Fig. 21.6. Mechanism of action of alkaloids *(by H. Lüllmann, 2000)*.

lymphomas. Sex hormones and their antagonists are used in the treatment of hormone-dependent cancer of 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

The suppression of hemopoiesis, leukopenia, anemia, thrombocytopenia
The suppression of immunity
A toxic action on CNS (headache, vertigo, nausea, vomiting)
A toxic action on the GI tract (a loss of appetite, dyspepsia)
Necrotic lesions in the skin and mucous membranes including necrotic stomatitis
Alopecia.

All the listed side-effects are reversible, but some of them are dangerous for the patient and must be treated.

TESTS FOR SELF-CONTROL

№1. Only one drug inhibits leukopoiesis:
Fercovenim
Ferroplex
Pentoxilum
6-Mercaptopurine
Methyluracilum.

№2. All the listed is correct, except:
Coamid is an additional drug for the treatment of hypochromic anemia
Ferroplex is combined preparation containing the iron and the ascorbic acid
Folic acid inhibits DNA reduplication in erythrocytes precusors
Pentoxilum is used for the treatment of leukopenia
Inhibitors of leukopoiesis are cytostatics and immunity depressants.

№3. The main effects of cyanocobalamin include:
The transformation of megaloblastic erythropoiesis into normoblastic one
The improvement of leukocytes forming
An increase in the amount of thrombocytes
An anti-platelet action
Reducing of the neurological symptoms of megaloblastic anemia.

№4. Inhibitors of leukopoiesis are used to treat:
Acute leukemia
Cancer
Aplastic anemia
Psoriasis and some collagen diseases
Leukopenia.

№5. A patient has the pale skin and mucous membranes, weakness, tachycardia. The total amount of red blood cells is $3{,}5\times10_{12}$/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 the basic preparation for the therapy.
Iron-deficient anemia, ferrum-lek
Hemolytic anemia, prednisolone
Anemia due to chronic renal failure, epoetin
Hemochromatosis, desferal
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 (pro-fibrinolysin) 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, syndrome of disseminated intravasal blood coagulation.

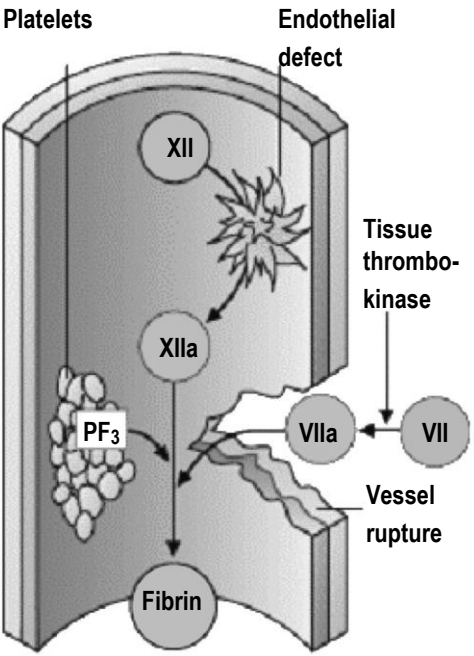

Fig. 22.1. Initial stage of blood coagulation *(by H.Lüllmann, 2000)*.

DRUGS AFFECTING BLOOD COAGULATION AND FIBRINOLYSIS

Drugs affecting blood coagulation and fibrinolysis include coagulants, anticoagulants, anti-platelet drugs, fibrinolytic drugs, inhibitors of fibrinolysis (fig. 22.2).

COAGULANTS

Coagulants are preparations increasing blood coagulation.

CLASSIFICATION

Direct-acting (are active in vivo, as well as in vitro)
- Thrombin
- Spongia haemostatica
- Fibrinogen

– Eptacog alfa (NovoSeven)
– Calcium chloride
– Calcium gluconate

Indirect- acting (are active only in vivo)
– Vitamin K (Phytomenadion)
– Vikasolum.

Drugs of other mechanism of action
– Etamsylate (Dicynone).

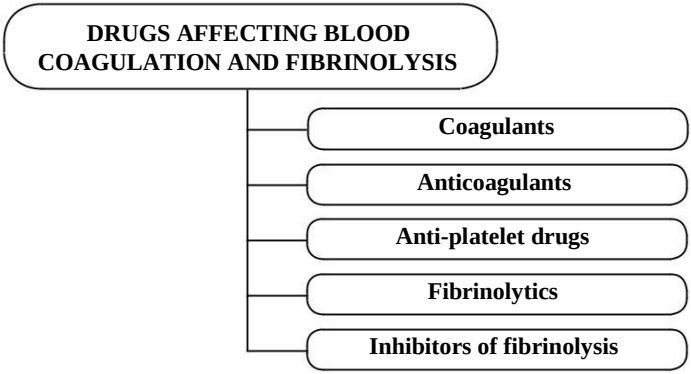

Fig. 22.2. Groups of drugs acting on blood coagulation and fibrinolysis.

DIRECT-ACTING COAGULANTS

Thrombin is an active compound of the blood coagulation system, is used for the bleeding from capillaryl vessels, is applied only topically (IV administration may cause disseminated thrombosis).

Fibrinogen is a non-active compound of the blood coagulation system, is used by IV infusion for the bleeding from bigger vessels, hypofiibrinogenemia, dissemi-nated 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 localized to the site of vascular injury; is approved for use as an intravenous hemostatic agent in patients with congenital hemophilia, for acquired hemophilia, factor VII deficiency, and Glanzmann thrombasthenia; is not immuno-genic 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

VIKASOLUM

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, overdose of indirect-acting anticoagulants
is contraindicated to patients with hypercoagulation, thrombosis, thromboembolism.

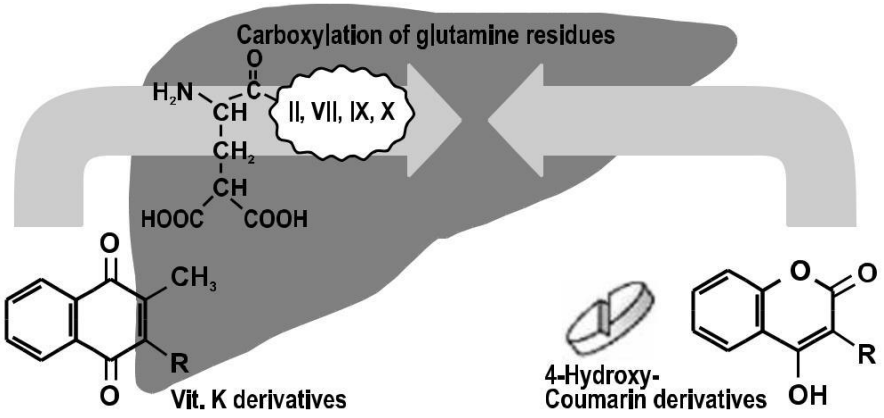

Fig. 22.3. Mechanism of action of vitamin K derivatives (Vikasolum) and their antagonists (coumarin derivatives) *(by H.Lüllmann, 2000)*.

HEMOSTATIC DRUGS OF OTHER MECHANISM OF ACTION

ETAMSYLATE

promotes angioprotective and proaggregant action, stimulates thrombopoie-sis and their release from bone marrow

has hemostatic action which is due to activation of thromboplastin formation on damaged sites of small blood vessels and a decrease of PgI2 (prostacyclin) synthesis; stimulation of platelet aggregation and adhesion stabilises capillaries, reinforcing capillary membranes by polymerising hyaluronic acid; reduces oedema

is used for prophylaxis and control of capillary bleeding of different etiology (menorrhagia and metrorrhagia without organic pathology, trans-urethral 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

Direct-acting (are active in vivo, as well as in vitro)
- – Heparin
- – Fraxiparine
- – Enoxaparin
- – Fondaparinux
- – Rivaroxaban

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 the intestine. It belongs to acidic

mucopolysaccharides (fig. 22.4). A disaccharide component of heparin shows nega-tive charges due to the carboxyl and sulfate groups.

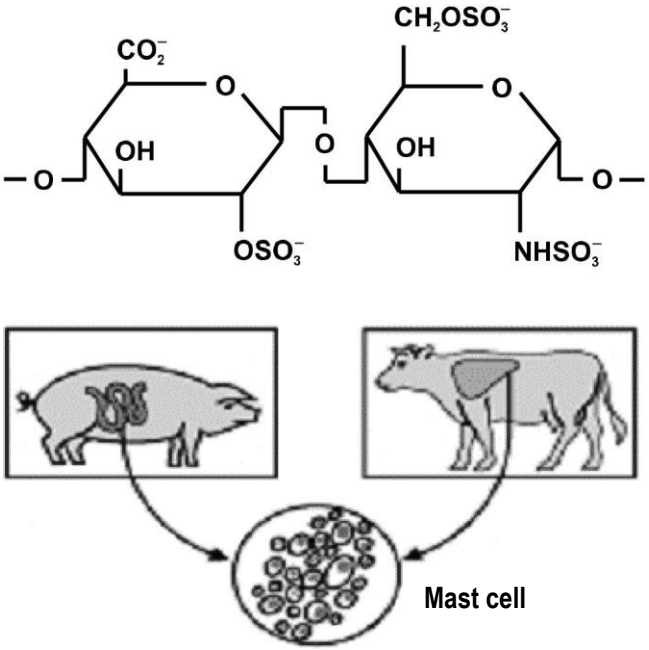

Fig. 22.4. Chemical structure of heparin (A) and its sources (B) *(by H.Lüllmann, 2000)*.

Pharmacokinetics

is administered IV, IM, SC, topically
begins to act immediately after IV administration and acts during 4-6 hrs
begins to act in 15-30 min after IM administration and acts during 6-8 hrs
begins to act in 30-60 min after 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 anti-thrombin 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).
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 endothelial cells.

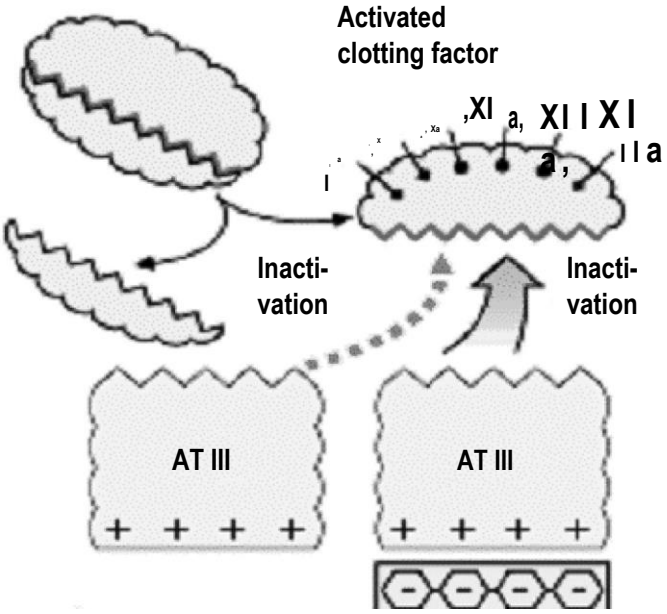

Fig. 22.5. Mechanism of action of heparin *(by H.Lüllmann, 2000)*.

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 blood serum
a decrease in inflammation
a decrease in 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 blood serum (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	**Contraindications**
1. Bleeding	1. Hemorrhages
2. Hematomes	2. Hemorrhagic diathesis
3. Micro- and macrohematuria	3. Leukemia
4. Thrombocytopenia	4. Anemia
5. Allergy	5. Malignant diseases
6. Osteoporosis	6. Gastric ulcer
7. Silvering of the hair.	7. Hypertension
	8. Severe diseases of the liver and kidney.

In overdose – induce of Protamine sulfate!

PECULIARITIES OF OTHER PREPARATIONS

Fraxiparine is 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-Prauers factor more than thrombin; is used for treatment of thromboflebitis, prevention of thrombus formation after surgeries.

Enoxaparin is 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 orthopedic 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 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 caue 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).

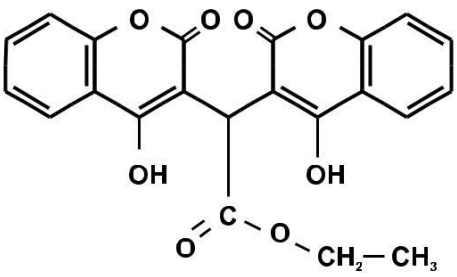

Fig. 22.6. Chemical structure of Neodicumarinum.

Pharmacokinetics

is administered orally
is absorbed in the GI tract

binds to proteins in blood plasma
is metabolized in the liver
begins to act in 2-3 hrs after the administration
develops a 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 Neodicumarinum, 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 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	**Contraindications**
1. Bleeding	1. Hemorrhages
2. Forming of hematomes	2. Hemorrhagic diathesis
3. Hematuria	3. Gastric ulcer
4. Dyspepsia	4. Malignant diseases
5. Suppression of the liver function	5. Diseases of the liver and kidney
6. Allergy.	6. Pregnancy.

For the treatment of overdose – Vikasolum!

PECULIARITIES OF OTHER PREPARATIONS

Warfarin decreases blood coagulation by inhibiting vitamin K epoxide reduc-tase, an enzyme that recycles oxidized vitamin K1 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 indirect-acting anticoagulant; indandione derivative has the same mechanism of action as Neodicumarinum; starts to act slower, has longer duration of action; may cause pink discoloration of urine resulting from excretion of drug and its metabolites.

ANTI-PLATELET DRUGS

Anti-platelets are preparations which inhibit platelet aggregation in blood.

CLASSIFICATION

COX-inhibitors
- Acetylsalicylic acid (Aspirin)

Inhibitors of phosphodiesterase
- Dipyridamole
- Pentoxifylline

Inhibitors of ADP-mediated aggregation
- Ticlopidine (Ticlide).
- Clopidogrel

Anti-platelet action of aspirin

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 methylated xanthine derivative, a competitive nonselective PDE inhibitor which raises intracellular cAMP, reduces inflammation and innate im-munity; 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.

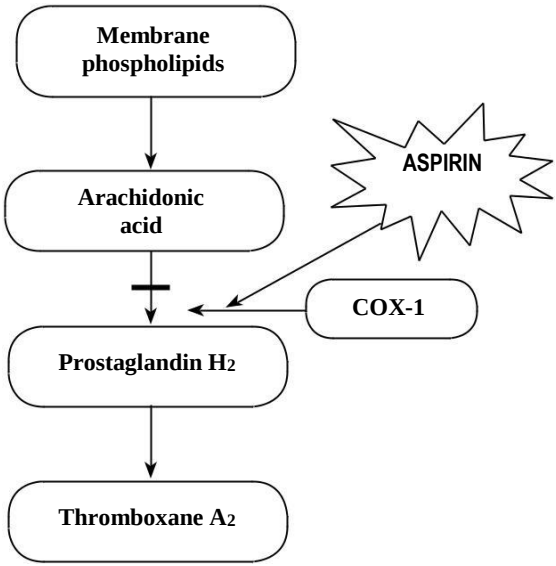

Fig. 22.7. Mechanism of anti-platelet action of aspirin.

Anti-platelet action of dipyridamole

Dypiridamole inhibits adenosine desaminase and phosphodiesterase in 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.

Anti-platelet action of ticlopidine

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 activation of platelets. Patients 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.

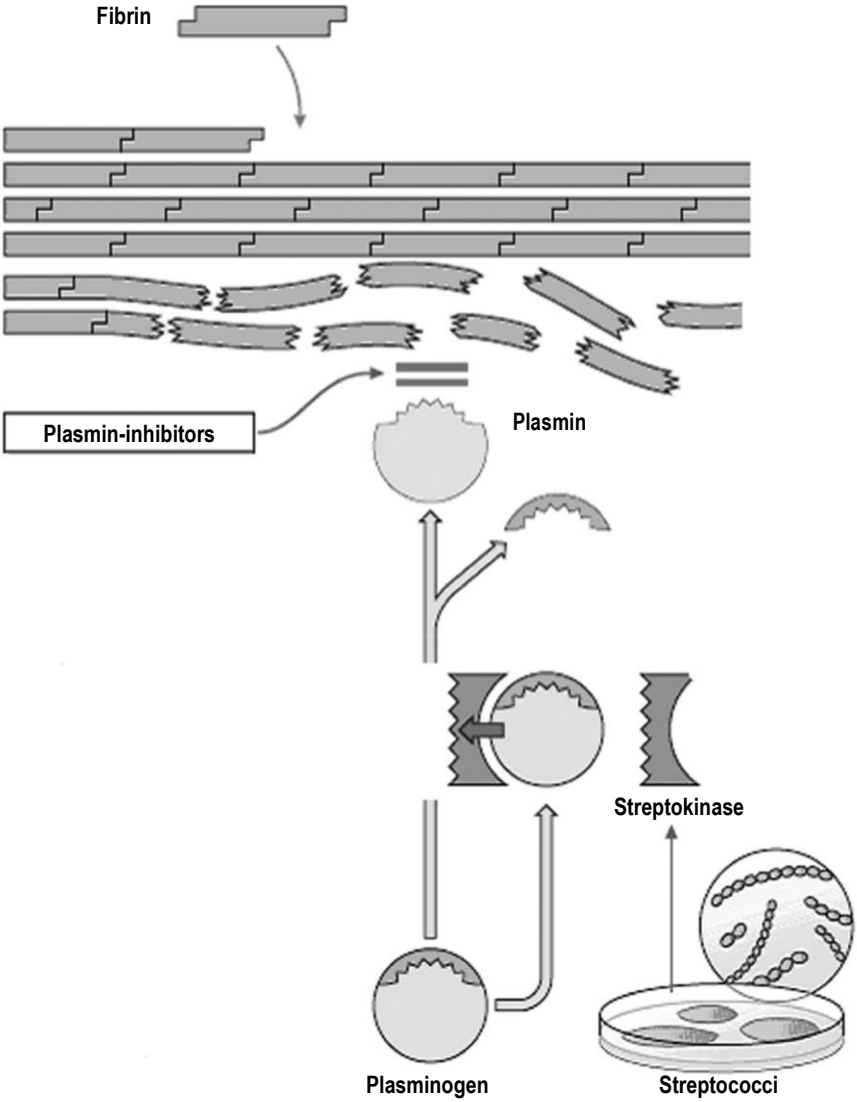

Fig. 22.8. Mechanism of action of streptokinase and plasmin inhibitors *(by H.Lüllmann, 2000)*.

Common indications to anti-platelets usage

Indications to anti-platelets 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*
Direct-acting
– Fibrinolysin
Indirect-acting (activators of pro-fibrinolysin)
non-selective
– Streptokinase
selective (tissue plasminogen activators, t-PA)
– Alteplase
– Tenecteplase ***B.***
Inhibitors of fibrinolysis
Direct-acting
– Contrykal
Indirect-acting
– Aminocaproic acid.

FIBRINOLYTICS

Fibrinolytics are drugs producing the lysis of the blood clot.

FIBRINOILYSIN

is the 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, hypotension
is contraindicated in bleeding, a cerebral vascular accident, recent trauma of the brain, surgery, uncontrolled hypertension.

STEPTOKINASE

is the 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 fi-brinogen resulting in the dissolving of thrombus (fig. 22.8)
has a plasma half-life of 23 min; is administered by IV infusion (intracoro-nary infusion in myocardial infarction)
is more potent than fibrinolysin
does not cause arrhythmia.

TISSUE PLASMINOGEN ACTIVATORS

Alteplase (Actilise) is tissue plasminogen activator (t-PA), product of biotech-nology; 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.

Tenecteplase is an enzyme used as a thrombolytic drug; a tissue plasminogen activator produced by recombinant DNA technology; binds to the fibrin component of the thrombus and selectively converts thrombus-bound plasminogen to plasmin, which degrades 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.

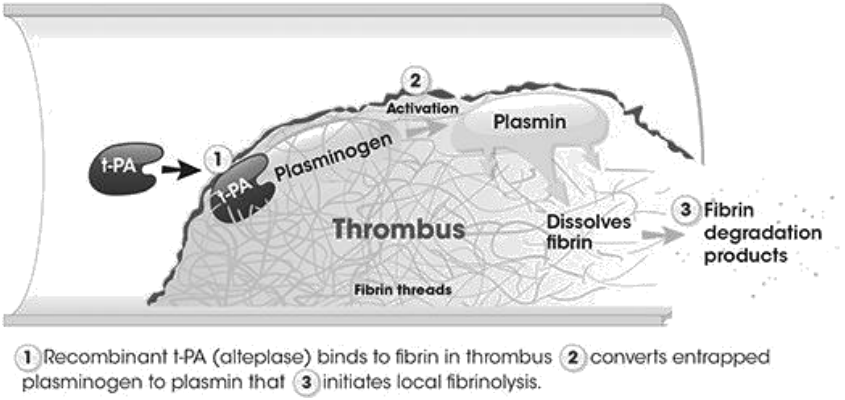

Fig. 22.9. Mechanism of action of tissue plasminogen activators

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 fibrinoly-sis; 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, the thyroid gland, the bigger salivary glands, and lungs
may cause allergy, nausea, vomiting, hypotension, tachycardia.

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, hypoplastic anemia
may cause side-effects, such as dizziness, hypotension, bradycardia, arrhythmia, skin rash, vomiting, nausea.

PHLEBOTONICS

Phlebotonics are a heterogenous class of drugs consisting of plant extracts (i.e. diosmin ***(detralex), aescusan)*** and synthetic compounds (i.e. ***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 haemorrhoids.

TESTS FOR SELF-CONTROL

№1. Drug for the prevention of bleeding is only:
Heparin
Vikasolum
Thrombin
Streptokinase
Contrykal.

№2. Aminocapoic acid is:
Direct-acting anticoagulant
Indirect-acting anticoagulant
Fibrinolytic
Activator of fibrinolysis
Inhibitor of fibrinolysis.

№3. Therapeutic uses of anti-platelet drugs include:
The prevention of secondary thrombosis
Acute thrombosis
Use of prosthetic heart valves
Arteriovenous shunt for hemodialysis
Thrombophlebitis.

№4. Heparin is an anticoagulant which:
Is effective orally
Is effective in vivo, as well as in vitro
Is the antagonist of vitamin K
Is bound with antithrombin and inactivates clotting factors
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?
To cause the lysis of thrombus directly
To transform plasminogen into plasmin
To prevent further thrombosis
To prevent platelets activation
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 the RESPIRATORY SYSTEM

THE 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 temperature regulation.

Many drugs in 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 passages against the entrance of 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 productive one. ***Bronchial asthma*** is a recurrent episodic short-

ness 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 re-sponds poorly to therapy. The following respiratory disorders have a chronic airway obstruction as a dominant feature.

DRUGS ACTING ON 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 oxi-dative 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

Direct-acting
– Etimizol
Reflexly-acting
– Lobeline
– Solution of ammonia
Mixed-acting
– Nikethamide (Cordiaminum)
– 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 overdose of general anesthetics, asphyxia, bronchial asthma, and asphyxia of newbons.

Camphor is an analeptic with a mixed mode of action and expectorant proper-ties 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, cardiac insufficiency.

Lobeline stimulates N -cholinoreceptors located in 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 reflex in the case of dizziness.

ANTITUSSIVES

Antitussives are drugs suppressing cough which are used in the case of dry cough.

CLASSIFICATION

A. *Drugs of central action*

Opioids
- Codeine phosphate
- Ethylmorphine hydrochloride

Non-opioid drugs
- Glaucine hydrochloride
- Oxeladin

- Prenoxdiazin hydrochloride (Libexinum)
- Falimint.

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 by their analgesic activity and are highly effective in the suppression of the tussive center;

may cause tolerance and drug dependence. Codeine is described in chapter 12 as a narcotic analgesic.

Glaucine hydrochloride is an alkaloid; inhibits the medulla center of 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.

Prenoxdiazin hydropchloride (Libexinum) has a broncholytic and local anesthetic effect, realizes its action in bronchi; is administered orally; is used for dry cough; may produce the sensation of local anesthesia in the oral cavity.

Falimint has antitussive and antimicrobial effects.

EXPECTORANTS

Expectorants are drugs which transform non-productive cough into productive one. Some of these drugs are described in Chapter 4. They are devided into bronchosec- retor drugs which assist liquid mucus expelling and mucolytics which melt mucus.

CLASSIFICATION

A. *Drugs of central action*

Opioids
- Codeine phosphate
- Codterpine
- Ethylmorphine hydrochloride

Non-opioid drugs
- Glaucine hydrochloride
- Butamirate citrate

B. *Drugs of peripheral action*
- Prenoxdiazin hydrochloride (Libexinum)

Peculiarities of preparations

Codeine, ethylmorpine are alkaloids of opium and have all 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 tussive center; may cause tolerance and drug dependence. Codeine is described in the Chapter 12 as narcotic analgesic.

Codterpine is a combined preparation containing codeine, sodium bicarbonate and terpinhydrate. Codeine is opioid receptor agonist that reduces the excitability 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 lungs and respiratory pathways.

Glaucine hydrochloride is an alkaloid; inhibits medulla center of cough with-out tolerance and drug dependence; is taken by mouth to treat diseases of lungs and bronchi accompanied by dry cough; may cause hypotension.

Butamirate citrate is 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, allergic reactions.

Prenoxdiazin hydropchloride (Libexinum) has broncholytic and local anesthetic effect, realizes its action in bronchi; is administered orally; is used for dry cough; may produce the sensation of local anesthesia in oral cavity.

EXPECTORANTS

Expectorants are drugs which transform non-productive cough into 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

Bronchosecretor drugs

Reflexly acting

– Infusion from the herb of *Thermopsis*

– Decoction from the root of *Althea*

– Mucaltinum

Directly acting

– Potassium iodide

– Sodium bicarbonate

Mucolytics

Synthetic

– Acetylcysteine

– Ambroxol

– Bromhexine

Enzymes
– Trypsin
– Chymotrypsin
– Ribonuclease.

AMBROXOL

Ambroxol is a bromine-containing compound (fig. 23.1).

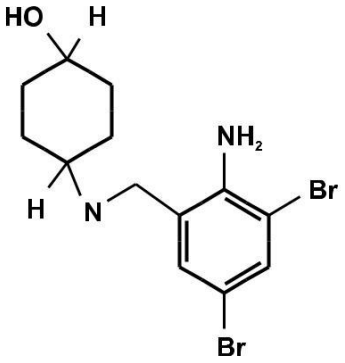

Fig. 23.1. Chemical structure of ambroxol.

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 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 Clarck's cells.

It stimulates production of surfactant in the lungs and activates the transport function of ciliated cells.

Pharmacodynamics

an expectorant action
a mucolytic action.

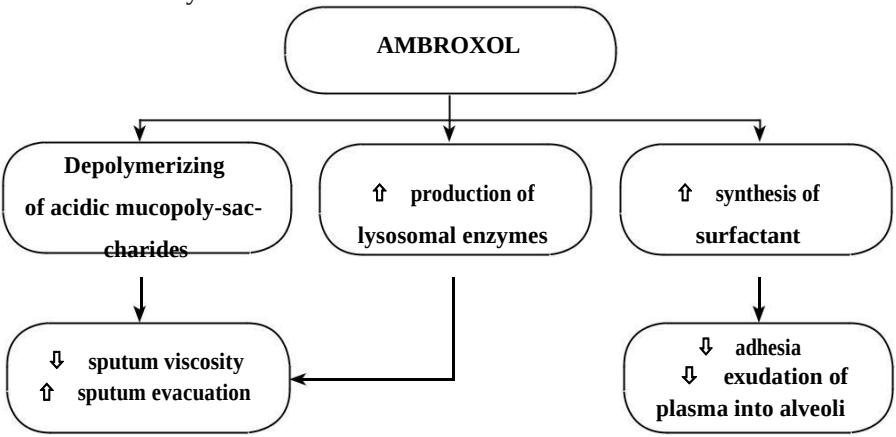

Fig. 23.2. Ambroxol's mechanism of action.

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 stomach
2. Seizures
3. Pregnancy
4. Hypersensitivity.

ACETYLCYSTEINE

It is an amino acid derivative, contains SH- group (fig. 23.3).

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 blood plasma
is distributed in the liver, kidney, lungs, and bronchial mucus
penetrates placenta
developes maximal concentration in 1 hr after the administration
has plasma half-life of 2 hrs
is excreted with urine and nursing mother's milk.

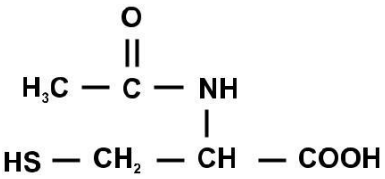

Fig. 23.3. Chemical structure of acetylcysteine.

Mechanism of action

SH-group of acetylcysteine tears disulfide connections in acidic mucopoly-saccharides 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 bronchi)
3. Nasal bleeding, hypotension, palpitation.
4. The retention of sputum if it is used together with antitussives.

Contraindications

1. Ulcer of stomach
2. Lungs bleeding
3. Hypersensitivity to preparation
4. Age till 5.

PECULIARITIES OF OTHER PREPARATIONS

Infusion from the herb of Thermopsis, decoction from the root of Althea, and Mucaltinum 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 excretes through 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 bronchi, the 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 shortness of breath and makes 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:

avoidance of asthma triggers
treatment of allergic inflammation
dilatation of bronchi (fig. 23.4).

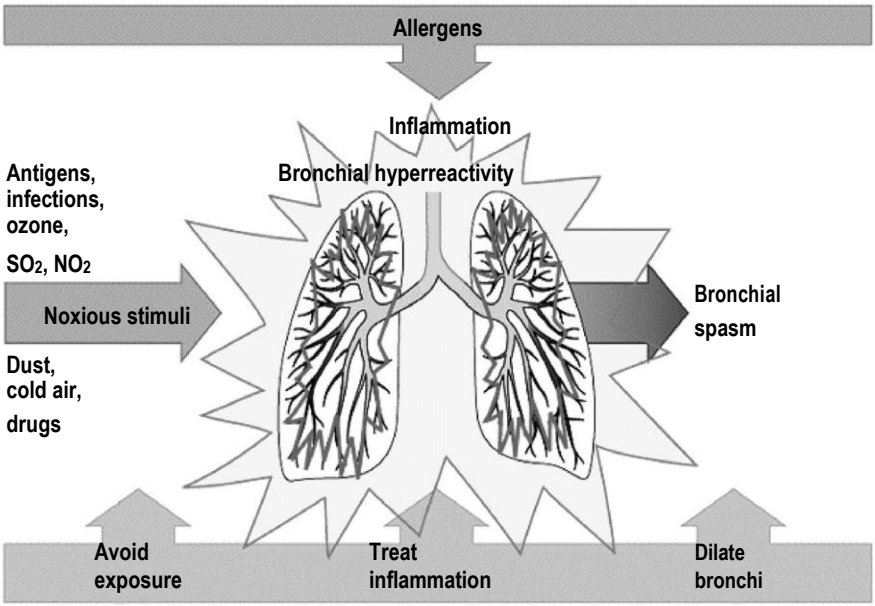

Fig. 23.4. Bronchial asthma and its management *(by H.Lüllmann, 2000)*.

THEOPHYLLINE

Theophylline (Euphyllinum) is 1,3-dimetylxantine (fig. 23.5).

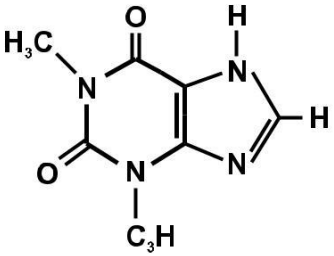

Fig. 23.5. Chemical structure of theophylline.

Pharmacokinetics

is administered orally, IV, by IV infusion
begins to act in 5-15 min after 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 of 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 blood by oxygen
a decrease in intracranial pressure and edema of the brain tissue
an anti-platelet 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 bronchi of different origin
Chronic obstructive bronchitis
Status asthmaticus
Emphysema of the lungs
Noctural apnea
Apnea of a new born
Lungs hypertension
Disturbances of cerebral blood circulation, liquor hypertension, edema of the brain caused by ischemic stroke.

Side-effects	Contraindications
Restlessness, insomnia	Hypersensitivity
Headache, tremor, seizures	Acute heart failure
Tachycardia, arrhythmia, hypotension, an increase in the frequency of angina attacks	Angina pectoris
	Acute myocardial infarction
	Heart arrhythmia
	Hypotension, severe hypertension
Diarrhea, atony of the gut	Prone to seizures
Allergic reactions (skin rash, itch).	Hyperthyroidism
	Pregnancy, lactation
	Hepatic and renal failure
	Children till 14 (for IV administration).

PECULIARITIES OF OTHER BRONCHODILATORS

Adrenergic agents with β-activity are the drugs of choice for mild intermitted asthma. These potent bronchodilators relax airway smooth muscle 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 (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, Methacinum*** are used as bronchodilators. They increase the cGMP concentration, decrease Ca^{++} concentration that leads to smooth muscle 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 bronchocon-striction. Not all the patients respond to a 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 anti-exudative effect, interferes with the development of bronchospasm, displays the antagonism with mediators of inflammation and allergy: serotonin, histamine (at the level of H1-histamine receptors), bradykinin; has 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, 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.

Combained 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 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:

Drugs decreasing hydrostatic pressure in lung vessels:

– *Sodium nitroprusside* and organic nitrates *(nitroglycerine, isosorbide dinitrate)*

– Ganglioblockers *(Pentamine, Benzohexonium, Hygronium)*

Broncholytics *(Euphyllinum)*

Drugs with α-blocking properties *(chlorpromazine)*

Opioid analgesics *(morphine hydrochloride)*

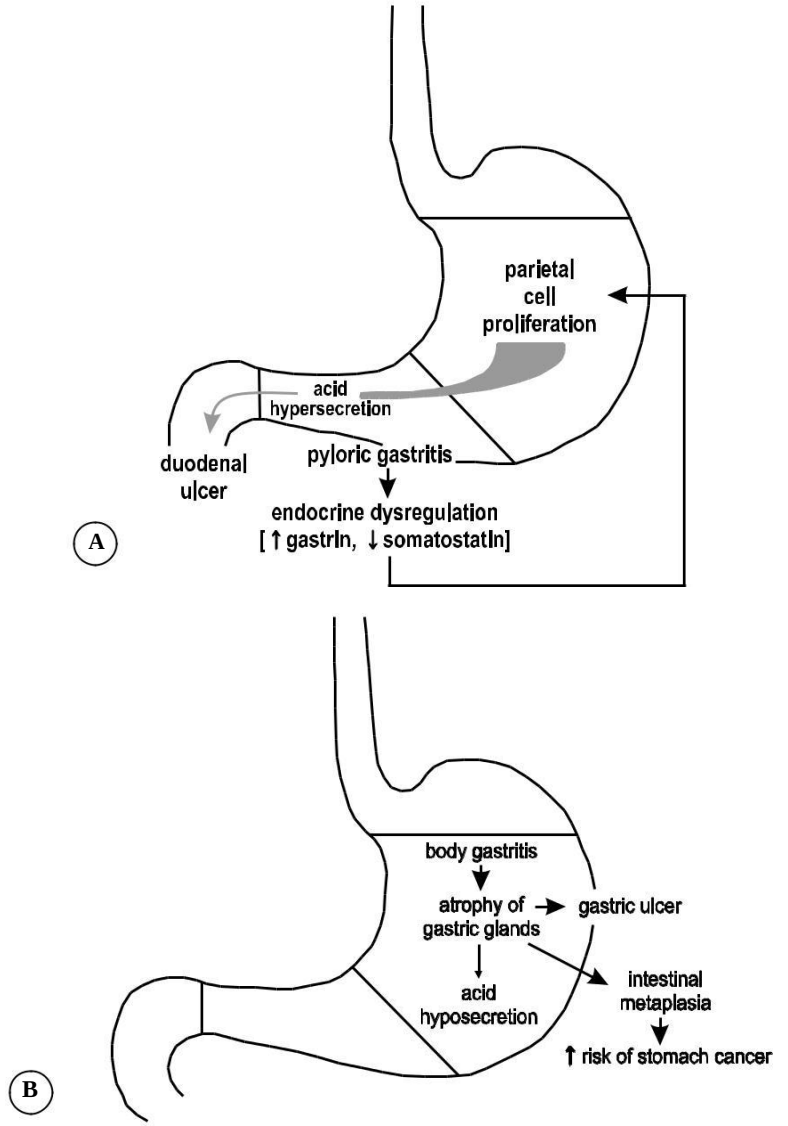

Fig. 24.2. Pathogenesis of peptic ulcer disease and gastritis:
A – duodenal ulcer and hyperacidic gastritis; B – gastric ulcer and hypoacidic gastritis *(http://www.picsearch.com)*.

Corticosteroids *(prednisolone, dexamethasone*)
Drugs improving heart contractility:
– Cardiac glycosides *(Corglycon, digoxin, strophanthin)*
– Non-glycoside inotropics *(dobutamine)*
Drugs decreasing circulating blood volume:
– Loop diuretics (*furosemide, torasemide)*
– Osmotic diuretics in the conditions of tolerance *to furosemide (mannitol, Urea pura)*
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:
It is non-opiod antitussive
It has a central action
It suppresses cough
It decreases BP
It stimulates respiratory center.

№2. Long-acting β-adrenergic agonist for treatment of bronchial asthma is:
Adrenaline
Salbutamol
Fenoterol
Salmeterol
Isoprenaline.

№3. Theophylline is:
Contraindicated in tachyarrhythmia
Synthetic catecholamine
Bronchodilator
PDE inhibitor
Expectorant.

№4. Ambroxol produces:
The stimulation of surfactant synthesis
An expectorant action
The dilatation of bronchi

An anti-allergic action
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 (Isadrinum). The doctor advices him to use salbutamol. What is the mechanism of salbutamol's action?
The stimulation of β_1-adrenoceptors
The stimulation of β_2-adrenoceptors
The stimulation of α_1-adrenoceptors
The stimulation of α_2-adrenoceptors
The inhibition of M-chlolinoreceptors.

Answers

№ 1 – E; № 2 – D; № 3 – A, C, D; № 4 – A, B; № 5 –B.

Chapter 24 GASTROINTESINAL DRUGS

FUNCTIONS OF THE GI TRACT AND THE MAIN GASTOINTESTINAL DISEASES

The main GI tract functions are digestion and absorption of food. It also plays the role of one of the major endocrine systems in the body. Gastric exocrine cells secrete pepsinogen, the 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, 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).

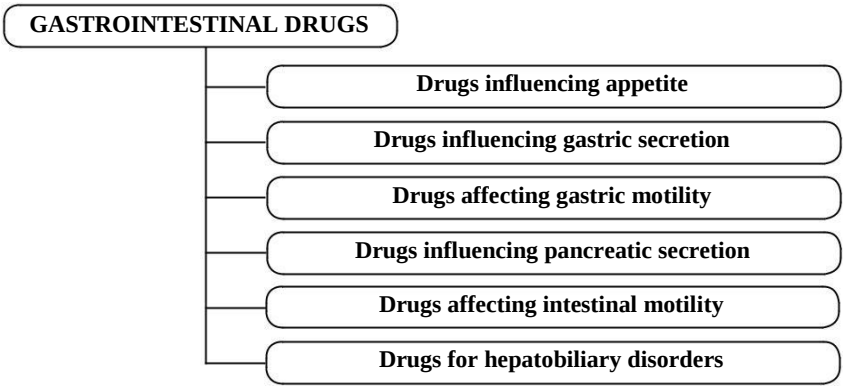

Fig. 24.1. Groups of gastrointestinal drugs.

Among them, there are agents influencing appetite, drugs used in disturbances of the gastric secretory function, drugs affecting gastric motility, agents used in disturbances of pancreatic secretion, drugs 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)*

Bitters

– Tincture of *Absintium*

Hormonal preparations

– Insulin

– Retabolil

B*. Suppressors of appetite (Anorexigens) and drugs for the treatment of obesity*

Adrenergic
– Amfepranone (Phepranonum)
– Chlorpheniramine (Desopimon)
– Mazindol
Serotoninerghic
– Fenfluramine.
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 character-ized in Chapter 15.

Orlistat is the 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 (H. pylori).* Infection caused by *H. pylori* produces chronic ***gastritis*** which is the inflammation of the stomach lining.

Peptic ulcer disease takes two very different courses, depending on the predomi-nant 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.

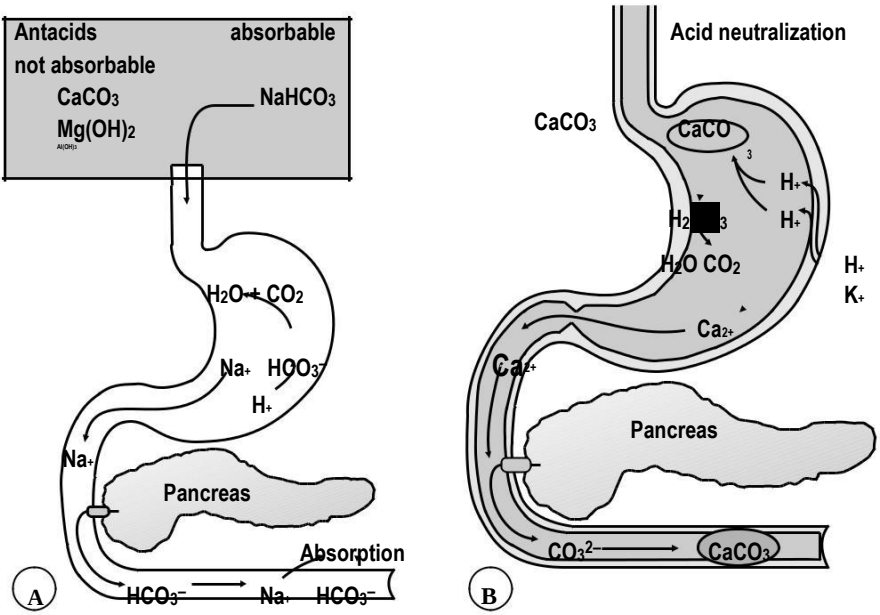

Fig. 24.6. Mechanism of action of absorbable (A) and non-absorbable antacids (B) *(by. H. Lüllmann, 2000)*.

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).

H.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:

Eradication of *H. 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

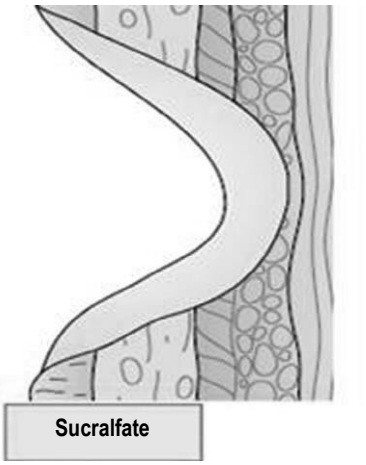

Fig. 24.7. Sucralfate's mechanism of action *(by H.Lüllmann, 2000)*.

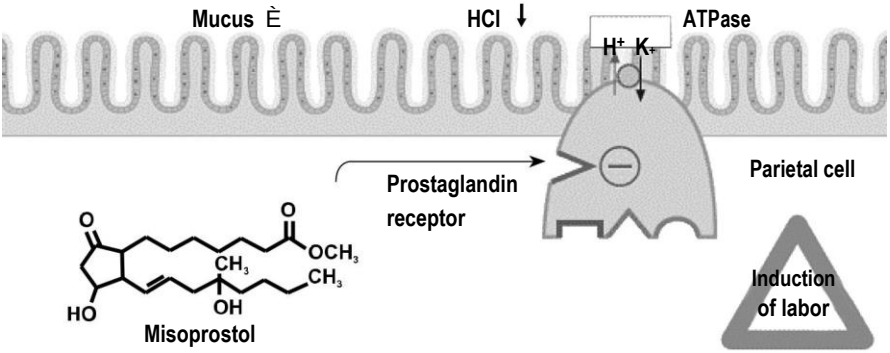

Fig. 24.8. Chemical structure and mechanism of action of misoprostol *(by H. Lüllmann, 2000)*.

DISEASE AND GASTRITIS

CLASSIFICATION

A. *Stimulants of gastric secretion*

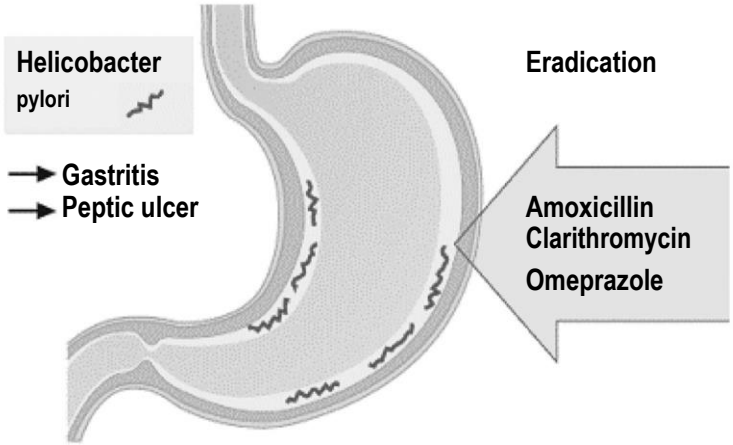

Fig. 24.9. Antimicrobial agents for eradication of *H. Pylori (by. H.Lüllmann, 2000)*.

– Pentagastrin
– Bitters

– Pepsin
– Hydrochloric acid (diluted)

C*. Suppressors of gastric secretion*

M-cholinoblockers
– Atropine
– Pirezepine

H_2 - histamine receptor blockers
– Ranitidine
– Famotidine

Inhibitors of proton pump
– Omeprazole
– Pantoprazole
– Lansoprazole

Gastroprotectors (mucosal protector agents)

Coverings
– Colloidal bithmus subcitrate (De-nol)
– Sucralfate

Ulcer healing drugs

– Misoprostol
– Carbenoxolone

D. *Antacids*
– Sodium bicarbonate
– Calcium carbonate
– Magnesium hydroxide
– Aluminium hydroxide
– Combined preparstions (Almagel, Maalox)

E. *Antimicrobial drugs for 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. Pentagastrin is also used as a stimulation test to elevate of several hormones in carcinoid syndrome. 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 side-effect.

Diluted hydrochloric acid, when taken before meals, reduces the pH in the stomach to 1.5-2, 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 s possible.

OMEPRAZOLE

Omeprazole is a benzimidazole derivative (fig. 24.3).

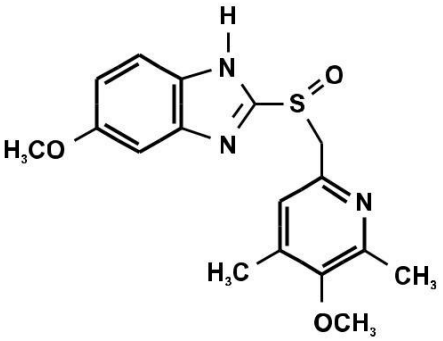

Fig. 24.3. Chemical structure of omeprazole.

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
binds to plasma proteins (90-95%)
is metabolized in the liver with the formation of hydroxiomeprazole
has a half-life of 40-60 min
is excreted with urine (80%) and feces.

Mechanism of action

It inhibits H^+/K^+-ATPase (proton pump) which is necessary for the transport of H^+ from parietal cells of the gastric mucous membrane to the lumen of the stomach (fig. 24.4).

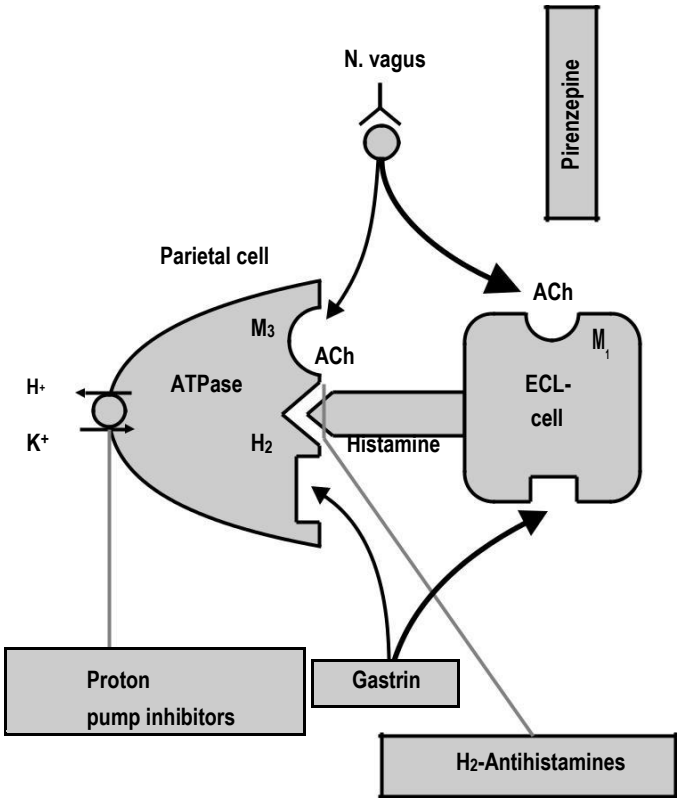

Fig. 24.4. Mechanism of action of proton pump inhibitors, H_2-antihistamines, and selective M-cholinoblockers *(by H.Lüllmann, 2000)*.

Pharmacodynamics

the inhibition of the final stage of basal and stimulating acid secretion.

Indications

Peptic ulcer disease
Gasatroesophagal 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.

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, significantly less interacts with the cytochrome P-450 system. Reception of antacids, like food, does not affect the pharmacokinetics of the drug.

RANITIDINE

Ranitidine is H_2-antihistamine, an etylendiamine derivative (fig. 24.5).

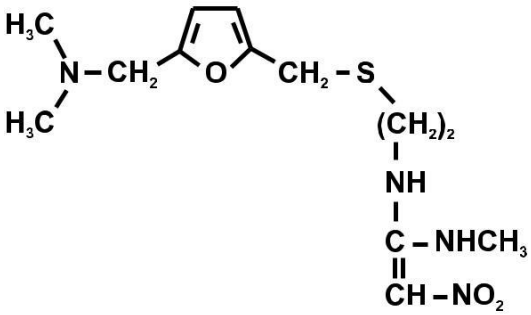

Fig. 24.5. Chemical structure of ranitidine.

Pharmacokinetics

is administered orally, IM, IV

is well absorbed in the GI tract: absorption is not disturbed by meals 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 surgery under 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 H2-histamine receptor blockers

Famotidine (Quamatel) is histamine H2 receptor antagonist that inhibits stom-ach acid production. Unlike cimetidine, the first H2 antagonist, it has no effect on the cytochrome P450 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 treatment for 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 bed-time).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).

Protective drugs are represented by coverings and ulcer healing drugs. ***Sucralfate*** contains aluminium hydroxide residues. It is a suspension for oral admin-istration 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 bicarbo-nates, 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, functional dyspepsia. The drug has no significant side-effects (it causes black discoloration of feces, rarely nausea, vomiting, diarrhea, rash).

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 *H.pylor*i (fig.24.9). The properties of these antimicrobial agents are described in Chapters 31, 33. They are applied in the combination with omeprazole.

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

C. *Anti-emetics*

Cholinergic antagonists
- Scopolamine (hyoscine)

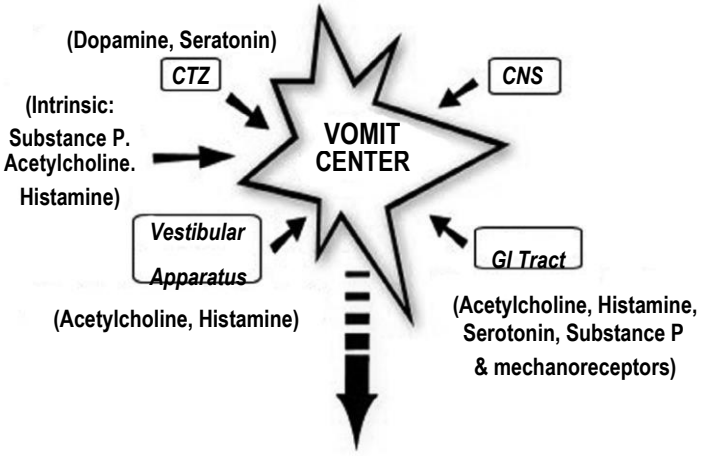

Fig. 24.10. Neurotransmitters participating in a vomit reflex (http://www.picsearch.com).

H$_1$-antihistamines
– Promethazine
– Diphenhydramine

Neuroleptics
– Chlorpromazine

D_2-dopamine receptor antagonists
– Metoclopramide
– Domperidone

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 IV injection and in 10-15 min after IM admin-istration
penetrates CNS and placenta
has a duration of a prokinetic effect of 3 hrs, of anti-emetic action – 12 hrs
is excreted with urine in an unchanged state (85% of a dose).

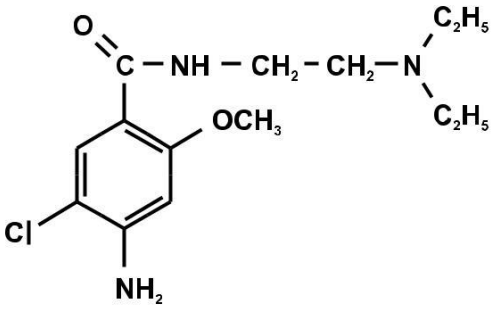

Fig. 24.11. Chemical structure of metoclopramide.

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.

Pharmacokinetics

a decrease in vomiting and nausea
an increase in the tone of the stomach and intestine
the promotion of gastric evacuation
the prevention of a 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, gastro-duodenitis, 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, extrapy-ramidal 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. Pheochromacytoma
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 prepara-tions are described in Chapter 4.

Domperidone (Motilium) is a peripherally selective dopamine D2 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 D2 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-HT3 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 a well-tolerated. Side effects are constipation, diarrhea, dizziness, headache, ototoxicity (if injected too quickly), and prolongation of the QT interval resulting dangerous heart rhythm disturbances.

Scopolamine is a 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 a H_1-histamine receptor antagonist (see Chapter 8) is used as an antiemetic to prevent kinetosis, cytotoxic drug-induced, or posoperative 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 move-ments (***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 also leads to an increase in the tone and the motility of the intestine.

Abnormalities of intestinal motility can manifest by ***constipation***, ***diarrhea***, and a ***spasm*** of smooth muscles (spastic colitis, colic).

The pharmacological management of disturbances of 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.

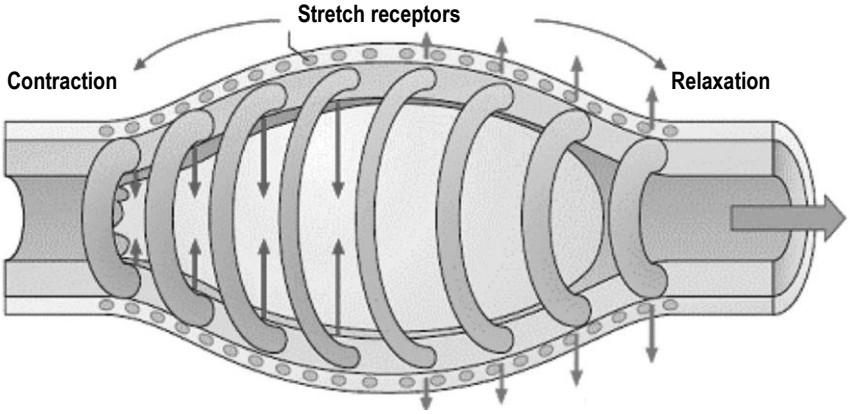

Fig. 24.12. Intestinal peristalsis as a target for drugs regulating motility of the gut *(by H.Lüllmann, 2000)*.

CLASSIFICATION

A. *Agents increasing intestinal motility (Laxatives and purgatives)* 1. Bulk laxatives

Osmotic purgatives

– Magnesium sulfate
– Sodium sulfate
– Lactulose

Bulk-forming agents
– Laminaria saccharina
– Methylcellulose

2. Irritant laxatives (purgatives cathartics)
Small intestine irritant purgative
– Castor oil
Large bowel irritant purgatives
– anthraquinone derivatives (preparations from *Senna, Frangula, Rheum*)
– synthetic preparations (Bisacodyl, Sodium picasulfate (Guttalax))
Lubricant laxatives
– Liquid parafin

B*. Agents decreasing intestinal motility (Spasmolytics and antidiarrheals)*
Cholinoblockers
– Atropine
– Plathyphylline
– Hexamethonium
A myotropic spasmolytics
– Papaverine
– Drotaverine
An 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 a 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 administration. ***Synthetic preparations*** also act after a 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, lipoid pneumonia (after the aspiration into the bonchial tract).

Antidiarreals. Loperamide is an opioid antidiarrheal of 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, disturbances of defecation. Loperamide must not be applied in 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 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

   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 anti-toxic 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 detoxication and bile secretion. Liver lesions are manifested as ***acute hepatitis, chronic hepatitis, and cirrhosis***.

Cholecystitis and ***cholelythiasis*** are also widely spread diseases of 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

Agents stimulating bile secretion (choleretics)
- Osalmid (Oxaphenamidum
- Cholenzym
- Allochol

Agents promoting bile release (cholekinetics)
- Atropine
- Papaverine
- Drotaverine
- Magnesium sulfate

Gall stone dissolving drugs
- Chenodeoxycholic acid
- Ursodeoxycholic acid

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, 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 stimu-lates secretion and motility in the gut, normalized 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 prepara-tions 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 aggres-sive factors. They are divided into plant preparations and drugs containing essential phospholipids, amino acid derivatives etc.

Ademetionine (Heptral) is hepatoprotector with antidepressant activity described in the Chapter.15.

Thioctic acid (α-lipoic acid, Dialipin) is an antioxidant. It participates in the oxidative decarboxylation of pyruvic acid and alpha-keto acids, helps to reduce blood glucose and increase glycogen 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 pres-sure, 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 hepatoprotec-tive effect due to its antioxidant, antihypoxic and membrane stabilizing properties. In alcoholic intoxication the drug stimulates the utilization of alcohol, displays anti-toxic and effervescent effects. 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 morpholinium salt of thiazole acid. The pharmacological effect is due to anti-ischemic, membrane-stabilizing, antioxidant and immunomodulatory proper-ties. 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

Fig. 24.13. *Silybum mariarum* containing hepatoprotective flavonoids.

fund. The presence in the structure of thiol and tertiary nitrogen causes the activation of the antioxidant system. Influence of thiazole acid leads to 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, side effects of some other drugs.

Essentiale is a combined preparation containing essential phospholipids (phosphotidilcholine) and vitamins (pyridoxine, cyanocobalamin, nicotinic acid, pantothe-nate).

It is administered orally or by IV infusion. The drug improves lipid metabolism, protein synthesis, and oxidative phosphorilation, inhibits lipids peroxidation, stabilizes cell membranes. In such a way, it protects liver tissue against hepatotoxic poisons, inhibits hepatic necrosis, promotes the restoration of a 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.

DRUGS FOR THE 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 contain-ing the bacteria in freeze-dried form are also available: ***hylak forte (Antidiarrheal microorganisms), lactobacterin (Lactobacillus acidophilus), bifidumbacterin (Bifidobacterium bifidum), linex (Lactic acid producing microorganisms combination)*** etc. 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:

Histamine
Pentagastrin
Acetylcholine
NSAIDs
None of the listed.

№2. The preparation which prevents the activation of proteolytic enzymes in the pancreas is:

A. Pancreatin

Festal
Aprotinin
Omeprazole
Atropine.

№3. An ulcer-healing effect of bismuth subcitrate is based on:
Acid neutralization
An increase in prostaglandin synthesis
The irradication of *H.pylori*
The inhibition of proton pump
The inhibition of M-cholinoreceptors.

№4. The true statements concerning laxatives and antidiarrheals are:
Osmotic laxatives are used to remove the poison from intestine
Castor oil is applied for the elimination of lipophilic toxins
Antraquinone derivatives act in 6-8 hrs after the administration
Loperamide is an antidiarrheal drug of the first choice
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:
Pirenzepine
Omeprazole
Ranitidine
Bisacodyl
Metoclopramide.

Answers:

№ 1 – A; № 2 – C; № 3 – B, C; № 4 – A, C, D; № 5 – B.

Chapter 25

DIURETICS. ANTI-GOAT 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 dehydrohynase. 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 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:

Increase of glomerular filtration

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).

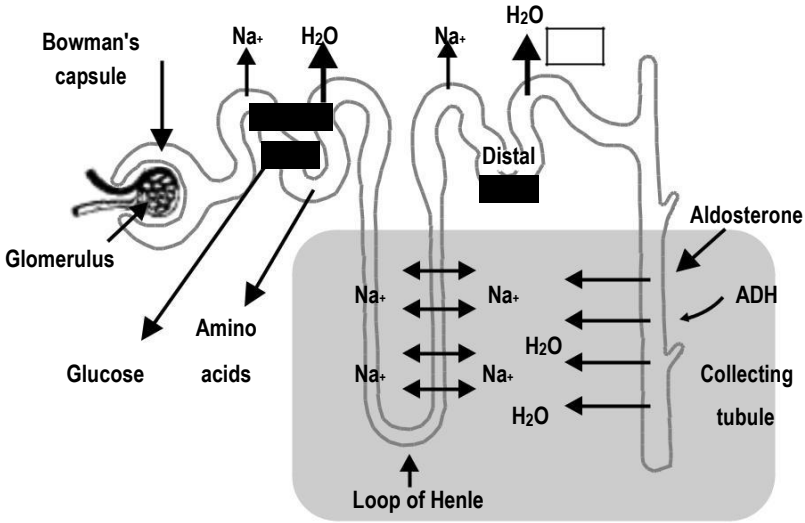

Fig. 25.1. Structure and function of nephron (http://www.picsearch.com).

DIURETICS

Diuretics are drugs which increase water and salts excretion from the body by a direct action on kidney functions.

CLASSIFICATION

Thiazides
- Hydrochlorothiazide (Dichlothiazide)
- Indapamide

Loop diuretics
- Furosemide (Lasix)
- Ethacrynic acid
- Torasemide

Carbonic anhydrase inhibitors
- Acetazolamide (Diacarbum)

Potassium-sparing diuretics
- Spironolactone
- Triamterene

Osmotic diuretics
- Mannitol
- Urea.

HYDROCHLOROTHIAZIDE

It is a thiazide diuretic (fig. 25.2).

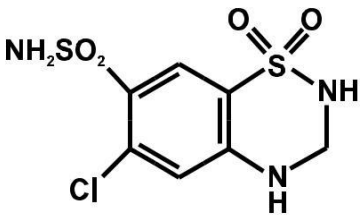

Fig. 25.2. Chemical structure of hydrochlorothiazide.

Pharmacokinetics

is administered orally
is quickly absorbed in the gut (60-80% of the dose)
develops effect in 2 hrs after 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 tubule, it blocks K_+/Na_+-ATP-ase and succinate dehydrohynase and inhibits energetic metabolism (fig. 25.3).
Inhibition of energy production blocks Na_+, a Cl_- symporter that is associated with the luminal (basal) membrane.
A decrease in an active transport of Na_+ to the blood leads to the elevation of Na_+ concentration in the cell and inhibition of a 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.

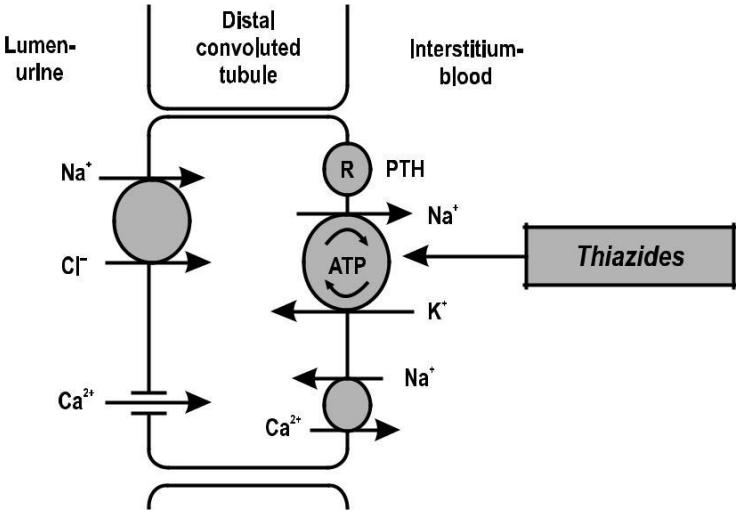

Fig. 25.3. Mechanism of action of hydrochlorothiazide.

Pharmacodynamics

an enhance in Na_+, 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, enhance in the excretion of Mg_{++}
an increase of diuresis and a decrease in 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 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

Increased plasma levels of LDL-cholesterol, and triglycerides
Sexual dysfunction (impotence)
Heart arrhythmias due to hypokalemia
Worsening of renal and hepatic insufficiency
A variety of drug interactions: a decrease in the efficacy of anticoagulants and uricosurics; an increase in the toxicity of cardiac glycosides and anti-arrhythmic drugs.

Contraindications

1. Anuria
2. Goat
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 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 T½ = 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^+, a Cl^- symporter. Because of the large absorptive capacity and the 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 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, 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, leu-copenia, 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 erhythema-tosus, first half of pregnancy, 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 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 by furosemide, is effective in the treatment of bromides accumulation in the body

has no significant influence on the electrolytes balance in blood , but is tolerated worse than furosemide, especially in patients with renal insufficiency.

TORASEMIDE

is 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 diu-retic effect than equipotent doses of furosemide and relatively decreased potassium loss; does noti induce ototoxicity .

INDAPAMIDE

is a thiazide-like diuretic
is used in hypertension and edema due to CHF
side effects are 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 tubule 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 lumen 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 a 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

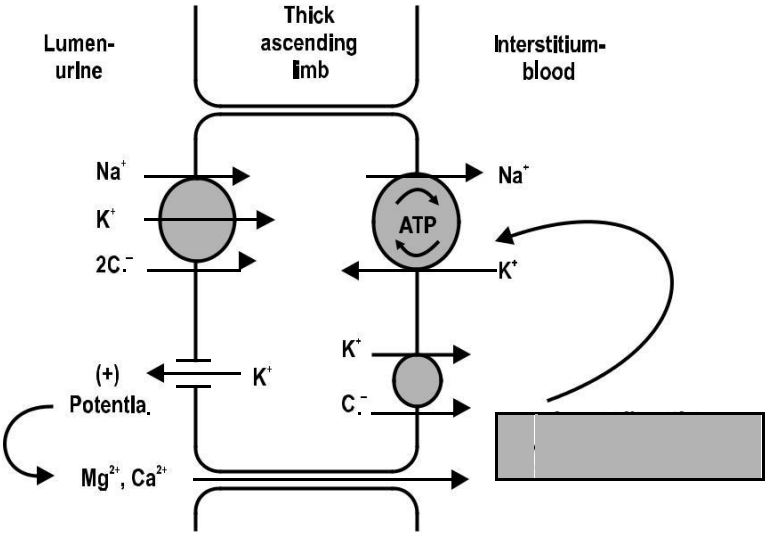

Fig. 25.4. Mechanism of action of furosemide.

may cause side-effects, such as metabolic acidosis, sedation, and paresthe-sia; because of the structural similarity to sulfonamides, acetazolamide can cause bone marrow depression and allergic reactions.

SPIRONOLACTONE

is a potassium-sparring diuretic

is taken orally; is metabolized to canrenone which is the 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 hyperaldo-steronism, CHF refractory to cardiac glycosides, myastenia

may cause hyperkalemia, GI disturbances, diarrhea, somnolence, disturbances in the menstrual function in women, ginecomastia and impotence in men (due to anti-androgenic activity).

TRIAMTERENE

is 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 cells in collecting tubules (is a Na_+ channel in-hibitor); 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, dizziness.

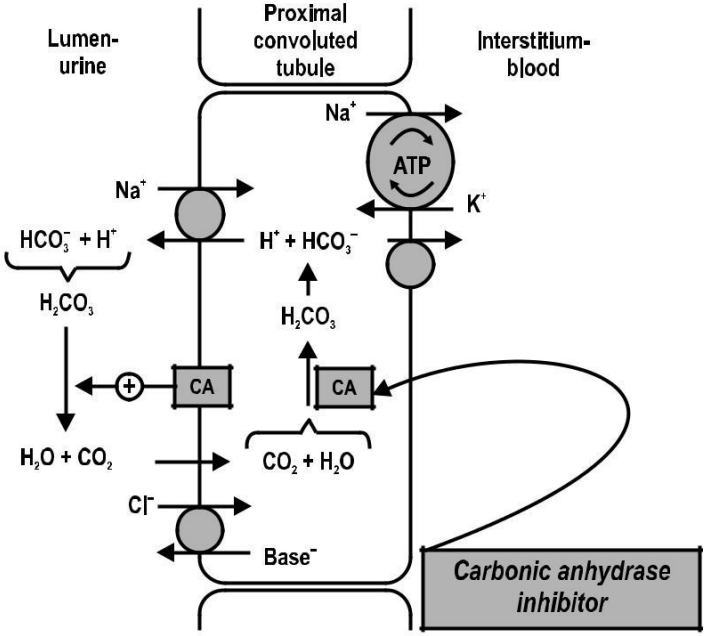

Fig. 25.5. Mechanism of action of acetazolamide: CA – carbonic anhydrase.

OSMOTIC DIURETICS

are represented by ***mannitol and urea***
are administered by IV infusion
have the mechanism of action connected with an increase of the osmolar-ity 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

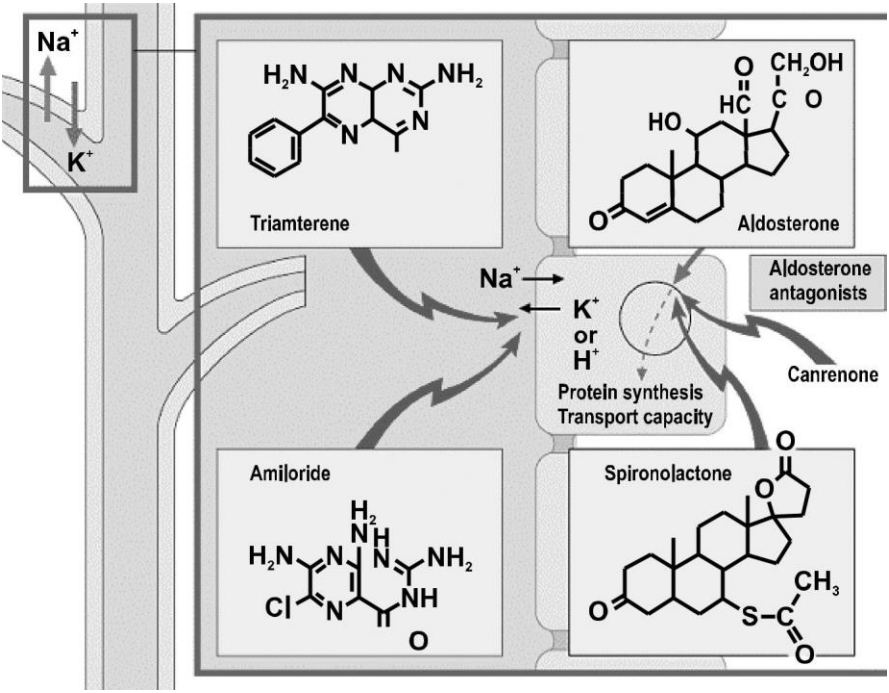

Fig. 25.6. Chemical structure and mechanism of action of potassium-sparring diuretics *(by H. Lüllmann, 2000)*.

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, hemolytic transfusion reactions

may cause headache, nausea, vomiting, chest pain, an increase in blood volume resulting in heart decompensation, 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.

DRUGS USED IN 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, glucocorticoids

prophylaxis of gout attacks with the diet low in purines, uricostatics, uricosurics.

CLASSIFICATION

A. *Uricostatics (They decrease urate production)*
– Allopurinol
B. *Uricosurics (They promote renal excretion of uric acid)*
Drugs inhibiting reabsorption of ureic acid
– Probenecid
– Etebenecid
Drugs increasing the solubility of urates
– Urodanum
Drugs decreasing forming of urate concrements
– Urolesanum.

ALLOPURINOL

is hypoxantine (purine) on chemical structure
is taken orally; is transformed into the active metabolite alloxantine (oxypurinol)

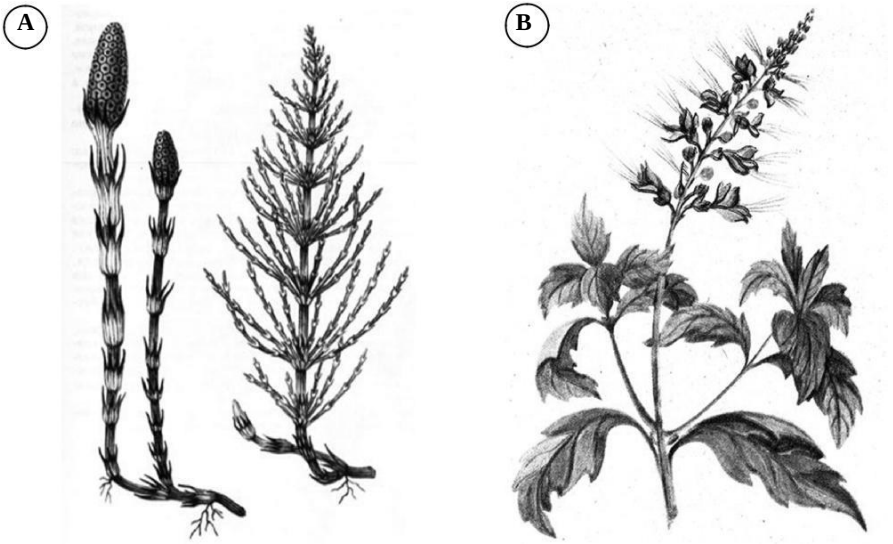

Fig. 25.7. Medicinal plants with diuretic action:
A – *Equisetum*; B – *Orthosiphonum*.

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 urolythiasis
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 reabsorbion; 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.

Urodanum is a combined preparation in granules for the oral administration; contains substances binding to urates and increasing their solubility.

Urolesanum is a combined preparation with plant ingredients; decreases form-ing 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 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 labor.

DRUGS ACTING ON UTERUS CONTRACTILITY

CLASSIFICATION

A. *Drugs stimulating myometrium*

Stimulants of rhythmic contractions a) prostaglandins
- – Dinopros
- – Dinoprostone

hormones
- – Oxytocin
- – Estron
- – Estradiol dipropionate

other preparations
- – Neostigmine
- – Castor oil
- – Calcium chloride

Stimulants of uterine tone

ergot alkaloids
- – Ergometrine maleate

agonists of oxytocin receptors
- – Carbetocin (Pabal)

Uterine relaxants (Tokolytics)

β-adenomimetcs
- – Partusisten
- – Hexaprenaline (Gynipral)

Antagonists of oxytocin receptors
- – Atosiban (Tractocile)

Other preparations
- – Magnesium sulfate
- – Nifedipine
- – Aspirin
- – Progesterone,
- – Tocopherol acetate

C. *Drugs decreasing uterine cervix tone*
- – Atropine sulfate

– Magnesium sulfate
– Drotaverine
– Lydasum.

OXYTOCIN

is octapeptide, hormone of posterior pituitary (fig. 25.8)
is administered IM, IV, into the wall of uterus, intranasally; starts to act in ½ – 1 min after 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

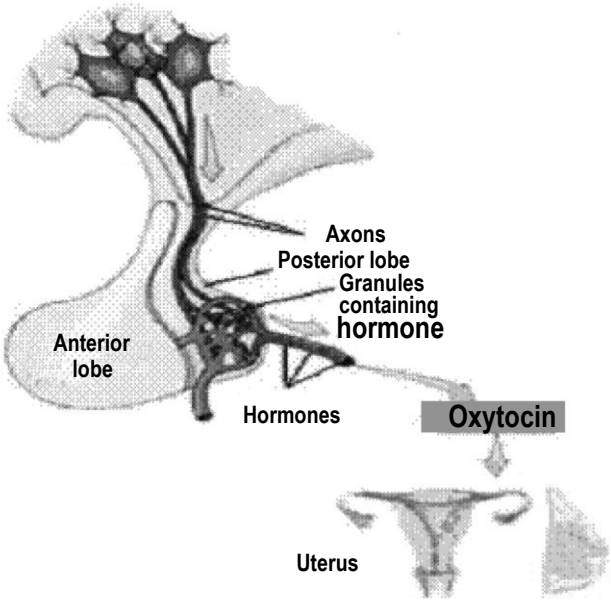

Fig. 25.8. Oxytocin as hormone of posterior pituitary (http://www.picsearch.com).

may cause nausea, vomiting, heart arrhythmia in the fetus, urine retention, the elevation of BP, a thetanic contraction of myometrium, the hyperstimulation of labor activity resulting in the fetus hypoxia and a rupture of the uterus is contraindicated in danger of a uterus rupture, hypoxia of the fetus, abnormal position of the fetus.

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, a spasm of bronchi, an increase in BP and an elevation of intraocular pressure; is contraindicated in patients with scars of the uterus, severe diseases of the cardio-vascular system, liver, and kidney; bronchial asthma, 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.

Carbetocin (Pabal) is an eight amino acid long analogueue of oxytocin and has a similar mechanism of action. It can be administered intravenously or intramuscularly. 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 myopepithelial cells.

Fig. 25.9. Ergot ***(Secale cornutum) containing ergometrine.***

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 is a competitive antagonist of oxytocin receptors. It is used as an IV medication as labor 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 improving the pregnancy outcome of in vitro fertilization-embryo transfer in patients with repeated implantation failure.

Hexoprenaline (Gynipral) is selective β2-adrenergic receptor agonist used in the treatment of asthma and as 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, hypocalcemia at the beginning of therapy. In newborns the drug may cause hypoglycemia and acidosis, bronchospasm, 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 guanylyl 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 dysfynction 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 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 miust 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 forced diuresis in acute poisoning is:
- Hydrochlorothiazide
- Spironolactone
- Ergometrine maleate
- Furosemide
- Triamterene.

№2. All the concerning dinopost and dinoprostone is true, except:
- They are prostaglandins
- They stimulate uterus contractions
- They are effective only at the end of pregnancy
- They relax the uterine cervix
- They are used for the stimulation of labor and induction of abortion.

№3. Osmotic diuretics:
- Are administered by IV infusion
- Cause dehydratation of body tissues

Block carbonic anhydrase in the proximal tubules
Reduce Na^+ reabsorption in the proximal tubules
Has a weak diuretic action.

№4. The correct statements concerning treatment of gout are:
Colchicine is used to treat a gout attack
Allopurinol is a uricosuric agent
Allopurinol is the inhibitor of xantine oxidase
Probenecid is uricostatic
Uricostatics are used for the prevention of a gout attack.

№5. A patient has chronic cardiac insufficiency and essential hypertension. The 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?
Furosemide
Amiloride
Spironolactone
Mannitol
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 endocrinal glands into blood which achieve humoral regulation of body functions.

Hormonal preparations are medicinal forms of hormones used for treatment of diseases.

Anti-hormones are drugs which decrease effects of hormones by the inhibition of their secretion or binding to hormonal receptors.

Hormonal drugs are divided into several groups by their origin and clinical properties (fig. 26.1). They may be classified according to the mode of action and chemical structure.

Classification of hormones according to the mode of action

A. *Kinetic hormones* (oxytocin, vasopressin)

B. *Morphogenous hormones* (somatotropin, thyroid hormones)

Metabolic hormones

Anabolic (androgens, insulin)

Catabolic (epinephrine, glucocorticoids).

Classification of hormones according to the chemical structure

Amino acids derivatives (e.g., epinephrine, L-thyroxine, Triiodthyronine hydro-chloride)

Peptides (e.g., Corticotropin, Somatotropin, Menopaustic gonadotropin, Chorionic gonadotropin, Oxytocin, Adiurecrin, Calcitonin, Parathyroidin, Insulin)

Steroids

Glucocorticoides (e.g., Hydrocortisone acetate, Prednisolone, Dexamethasone, Triamcinolone, Flumetasone pivalate)

Mineralcorticoides (e.g., Desoxycorticosterone acetate (DOCSA)

Estrogens (e.g., Estron, Estradiol benzoate, Ethinylestradiol)

Progestins (e.g., Progesterone)

Androgens (e.g., Testosterone propionate)

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, corticotro-pin, 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 inositol-phospate / 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, mineral- corticoids, 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).

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 hypofunc-tion of the endocrinal 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 Viadrilum for IV anesthesia)

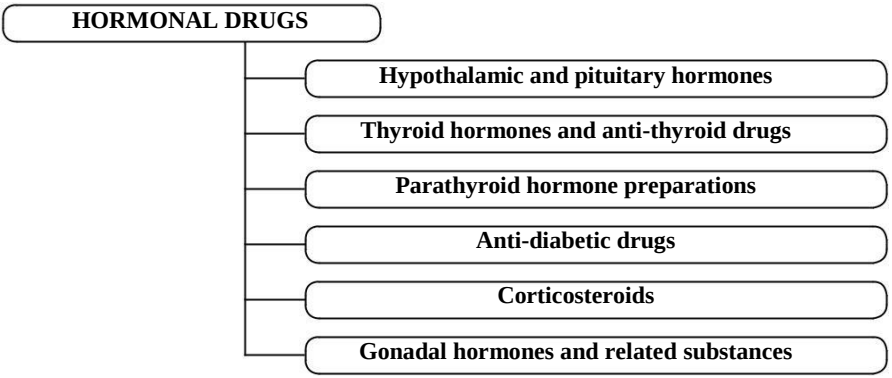

Fig. 26.1. Main groups of hormonal preparations.

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 anti-hormones (e.g. methimazole for hyperthyroidism).

Principles of hormonal therapy

An individual selection of the dose for each patient (e.g. 1IU of insulin for utilization of 3-5g of sugar excreted with urine per day)
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
Stimulation therapy at the end of treatment (e.g. corticotropin before the abolishing of glucocorticoids (fig. 26.2).

HYPOTHALAMIC HORMONES

CLASSIFICATION

Gonadorelin analogues
– Buserelin
– Triptorelin
Prothyrelin analogues
– Prothyrelin

Somatostatin analogues
– Ocreotide
– Lanreotide.

PECULIARITIES OF PREPARATIONS

Buserelin is a synthetic analogue of gonadotropin-releasing hormone ago-nist (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 anovulation in women. The drug in is used in the treatment of hormone-responsive

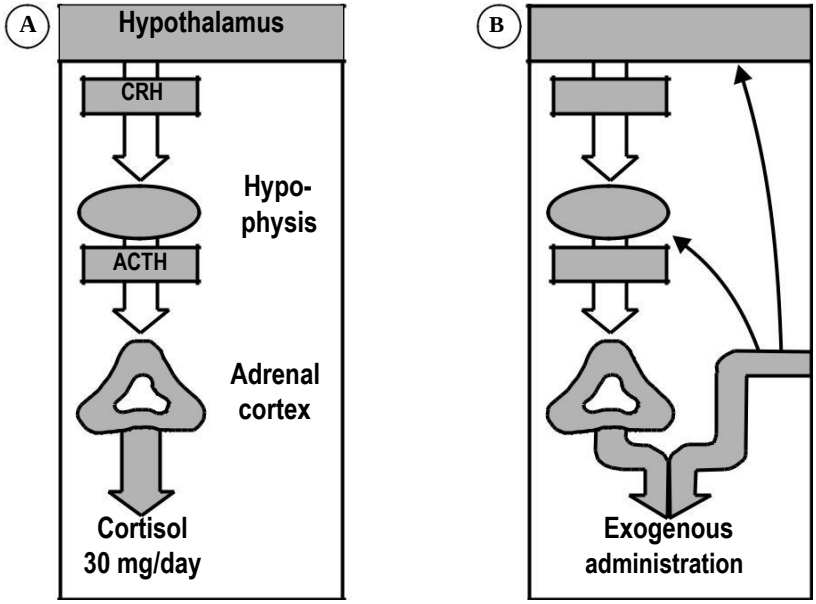

Fig. 26.2. Back-cross regulation of cortisol production:
A – cortisol production under normal condition; B – a decrease in cortisol production with a cortisol dose < daily production *(adapted by H. Lüllmann, 2000)*.

cancers (prostate cancer and premenopausal breast cancer), endometriosis, uterine fibroids, precocious puberty, as a component of transgender hormone therapy, and in 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. T1/2 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, allergic reactions.

Octreotide (Sandostatin) is an octapeptide that mimics natural somatostatin. It is administered SC and IV and has half-life 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 GI motility and inhibits contraction of the gallbladder, inhibits the action of certain anterior pituitary hormones, causes vasoconstriction, and reduces portal vessel pressures in bleeding varices. The drug is more potent inhibitor of growth hormone, glucagon, and insu-lin 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 tumours. The most frequent side effects are headache, hypothyroidism, cardiac conduction changes, GI 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 GI 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

Posterior pituitary hormones and related substances
- Oxytocin
- Desaminoxytocyn
- Vasopressin
- Desmopressin
- Terlipressin

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 follicle-stimulating hormone (FSH) and luteinizing hormone (LH), causes ovarian follicular growth and maturation. hCG is a placental hormone and LH agonist promoting ovulation. In men treatment with hCG causes external sexual maturation, and 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.

Folitropin 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. and 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 anti-gonadotropic 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 recep-tors 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 management of menorrhagia, fibrocystic breast disease, immune thrombocytopenic purpura, pre-menstrual syndrome, breast pain, and hereditary angioedema. The use of danazol is limited by masculinizing side effects.

Oxytocin stimulates uterus contractions and promotes contractions of myoepithe-lial cells in 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.

Demoxytocin (Desaminooxytocin) 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 lver, and other tissues to regulate the vascular tone, the tone of smooth muscles,

and blood coagulation; is used in diabetes insipidus, shock, hemorrhage, hemophylia, atony of the gut; may cause water intoxication, hyponatremia, enhanced BP, a spasm of bronchi, headache, 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 V2 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, 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 contrac-tion, necrosis at the site of IM injection.

THYROID HORMONES AND ANTI-THYROID DRUGS

CLASSIFICATION

Thyroid hormones
- Levothyroxine (L-thyroxine)
- α-Triiodthyronine hydrochloride
- Thyreocomb

Anti-thyroid drugs
- Methimazole (Thiamazole, Mercazolil)

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 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 growth and mental development in children.	Hypothyroidism (myxedema, cretinism) Diffuse non-toxic goiter Thyroiditis.

ANTITHYROID DRUGS

Anti-thyroid drugs are preparations for the treatment of hyperthyroidism (thy-rotoxicosis, 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, leucopenia, skin rash, fever, joint pain, the depigmentation of the hair, paradontitis, 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 back-cross decreasing of thyroid secretion, the decreasing of size and vascularity of gland).

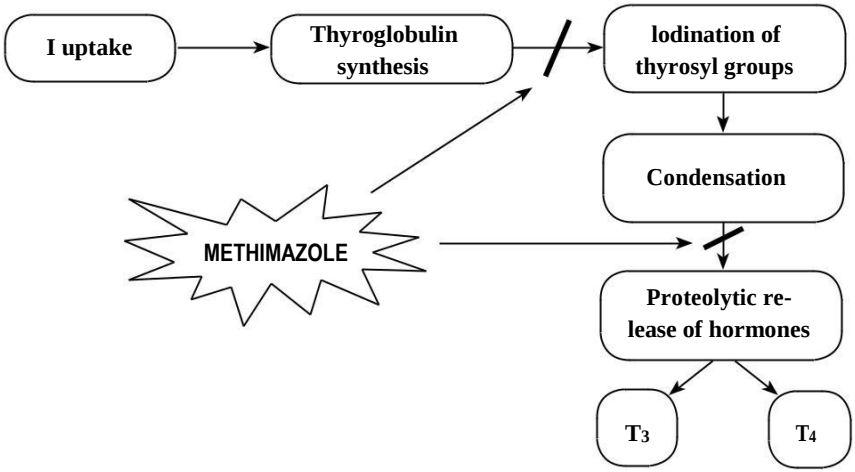

Fig. 26.3. Mechanism of action of methimazole.

HORMONES REGULATING METABOLISM OF CALCIUM AND PHOSPHATE

CALCITONIN (CALCITRINUM)

Calcitonin is produced by C-cells of thyroid gland (fig. 26.4). It is a protein, that's why it is not administered orally. ***Calcitrin and miacalcic*** are calcitonin's preparations. Calcitrin is a substance obtaining from the thyroid gland of pigs and is administered IM or SC. ***Miacalcic*** contains salmon calcitoin 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
Oppression of bones decalcification	Osteoporosis
An increase in the activity of osteo-	Padget's disease
blasts	Bone fractures
A decrease in the activity of osteo-	Bone pain in neoplastic malignant diseases
clasts Inhibition of bone resorption	Hypercalcemia
A decrease in the calcium level in	Caries, severe paradontitis
blood serum.	Hypercalcemia
Inhibition of gastric and exocrine	Nephrocalcinosis
pancreatic secretion	Combined therapy of acute pancreatitis.

PARATHYROIDIN

Parathyroidin is an antagonist of calcitonin (fig. 26.4). It is a polypeptide pro-duced by parathyroid glands. It is only administered parenterally.

Pharmacodynamics	Indications
An increase in calcium absorption in the intestine	Hypoparathyroidism
An increase in calcium reabsorption in the kidney	(teta-nus, spasmophylia)
A decrease in phosphate reabsorption in the kidney	Allergic diseases.
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.	

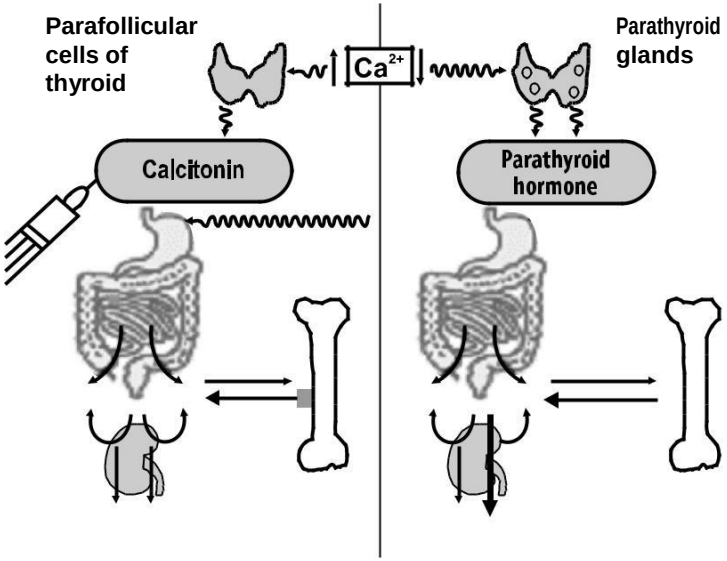

Fig. 26.4. Action of calcitonin and parathyroidin on calcium metabolism *(by H. Lüllmann, 2000)*.

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 intermit-tent 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 a hyperglycemia caused by relative or absolute deficiency of insulin. The classic symptoms of diabetes mellitus are polydipsia, polyphagia, 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 treat-ment of diabetes mellitus.

CLASSIFICATION

A. *Insulin preparations*

Fast-acting (begin to work within 5-15 min and are active for 3-4 hrs)
- Aspart
- Lispro
- Glulisine

Short-acting (begin working within 30 min and is active about 5-8 hrs)
- Regular insulin
- Actrapid
- Humulin R

Intermediate-acting (begin working in 1-3 hrs and is active 16-24 hrs)
- Protaphane
- Monotard

Long-acting (begin working within 1-2 hrs and continue to be active, without major peaks or dips, for about 24 hrs)
- Glargine

Ultra-long acting (begin working within 30–90 min and continues to be active for greater than 24 hrs)
- Degludec

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*

Sulfonylureas

– Glibenclamide
– Glycvidone
– Glycolide

Biguanides
– Metformin

α-glucosidase inhibitors
– Acarbose

Glinides (Prandial glusose regulators)
– Repaglinide

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 *E. 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.

Pharmacodynamics

An increase in glucose entry into 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 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 1, type 2) Diabetic (hyperglycemic) coma Gestational diabetes
Cachexia
Furunculosis
Liver diseases
Insulin-comatous therapy of schizo-phrenia
For better availability of glucose du- ring IV infusion.

Side-effects

Hypoglycemia (tachycardia, confusion, vertigo, sweating, hypoglycemic coma)

Lypodystrophy in the site of administration

Low blood potassium

4. Allergy.

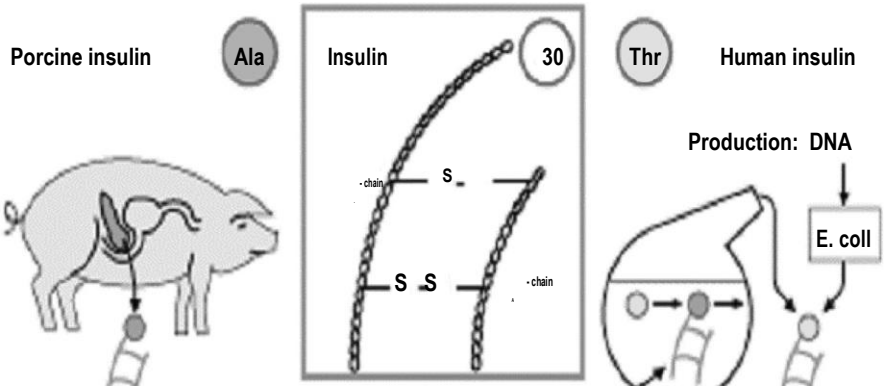

Fig. 26.5. Sources of insulin *(by H. Lüllmann, 2000)*.

INSULIN PREPARATIONS OF PROLONGED ACTION

Protaphane is 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 intermediate-acting insulin preparation containing biosynthetic human zinc-insulin as suspension of amorphous and crystalline particles; is admin-istered 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 micro-precipitates, 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 multihex-amers (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 breathing air and urine, hyperglycemia and ketoacidosis.

Emergency help:

– regular insulin (IV)

– 0,9% solution of sodium chloride for a decrease in hyperosmolarity of blood (IV infusion)

– 4% solution of sodium bicarbonate for the decrease in acidosis (IV infusion)

– thiamine as synergist of insulin (bigger dose).

Insulin (hypoglycemic) coma

Signs:

This coma results from a low blood sugar level caused by an overdose of insu-lin. It is characterized by slow development, the pre-coma period, unconsciousness, 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 blood. Preparations from each group are characterized by a common mechanism of action and pharmacological properties.

Mechanism of action

Sulfonylurea derivatives (Glibenclamide, Glycvidone, Glycolide):

an increase of insulin release from the pancreas
reduction of serum glucagon concentration
the potentiation of insulin action on target cells.

Biguanides (Metformin)

an increase of glycolysis in tissues
the inhibition of hepatic gluconeogenesis
a decrease in glucose reabsorption 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.

α-glucosidase inhibitors (Acarbose)

a competitive inhibition of a-glucosidase
a decrease of monosaccharide absorption
a decrease in the blood sugar level

Prandial glucose regulators (Repaglinide)

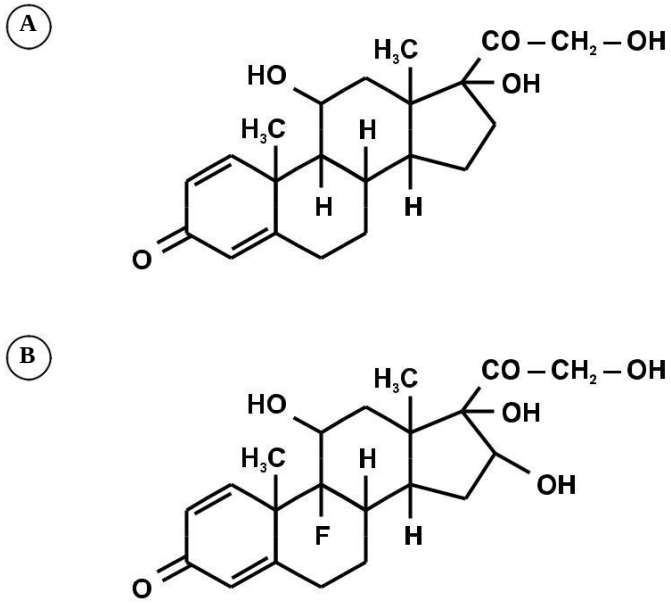

Fig. 26.6. Chemical structure of some adrenal steroids:
A – hydrocortisone; B – triamcinolone.

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

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

Hypoglycemia
GI disturbances
Itch
Anemia
Hyponatremia, hypotension, disulfiram-like reaction (after the administra-tion of some drugs).

GLUCAGON

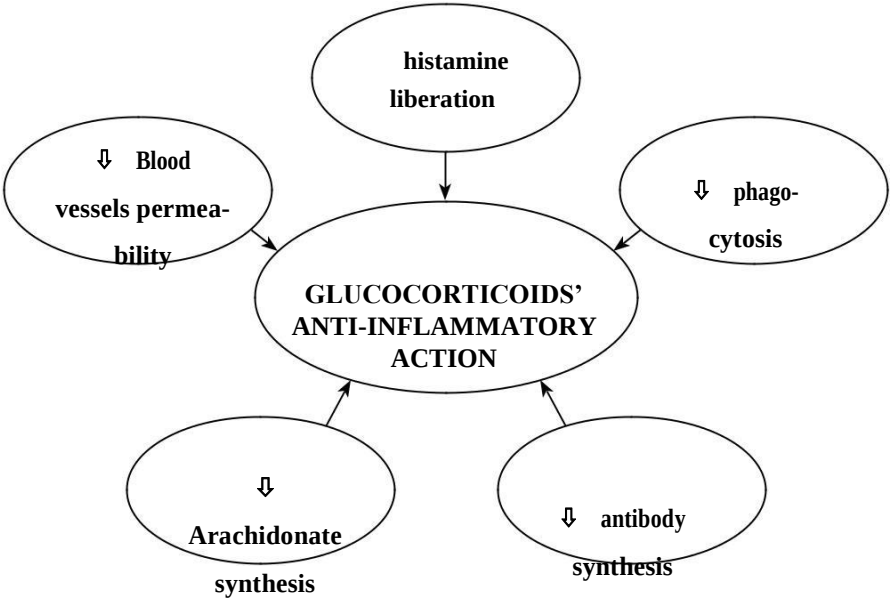

Fig. 26.7. Components of glucocorticoids anti-inflammatory action.

is a peptide hormone, produced by α-cells of the pancreas
is given IV, IM, or SC
binds to the glucagon receptor, a G protein-coupled 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 analogs (fig. 26.6).

CLASSIFICATION

A. *Glucocorticoids*

Short-acting (8-12 hours)
– Hydrocortisone acetate
Intermediate-acting glucocorticoids (18-36 hours)
– Prednisolone
– Methylprednisolone
– Triamcinolone
Long-acting glucocorticoids (1-3 days)
– Dexamethasone
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 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 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 blood film (eosinopenia, lymphopenia)	Adrenal insufficiency (natural hormones are preferable)
The inhibition of lymphoid tissue proliferation	
An increase in 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 hyaluroni-dase 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.

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 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
    Psychic disorders (depression, insomnia, somno-lence, “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 eye surgeries (not earlier than 7 days after the operation); is also applied in allergic skin diseases and administered in arthritis, arthrosis (into 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 T½ 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 pharmacodynamic 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 T½ of 3-4,5 hrs; is characterized by 72 hrs duration of an anti-inflammation effect after the oral administration.

Triamcinilone (Kenalog) contains fluorine; has a prolonged action; has T½= 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, rheumatism; is injected in the site of lesion in psoriasis, neurodermitis, lupus erythematoidis; 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 a 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 erythematoidis; should not be used for a 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, 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.

Ketokonazole 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

Male gonadal hormones and related substances

Androgens
- Testosterone propionate
- Methyltestosterone

Anti-androgens
- Flutamide
- Finasteride
- Cyproterone acetate

Anabolic steroids
- Methandienone (Methandrostenolone)
- Nandrolone phenylpropionate (Phenobolin)
- Nandrolone deconoate (Retabolil)

Female gonadal hormones and related substances

Estrogens
- Estron
- Estradiol benzoate
- Estriol
- Ethinylestradiol
- Synoestrol
- Diethylstilbestrol

Combined preparations
- Klimonorm

Anti-estrogens
- Clomiphene citrate
- Tamoxifen citrate

Progestins

Progesterone

– Hydroxyprogesterone caproate
– Allilestrnol
– Dydrogesterone
– Norethisterone

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 caue side-effects, such as masculinization in women, an altered bone development in children, the inhibition of gonadotropin release and reduc-tion of spermatogenesis; gynecomastia in men, hepatitis, 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, a 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 a 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 flashes, sexual dysfunction, infertility, and osteoporosis. In women, antiandrogens can cause low estrogen levels and associated symptoms like hot flashes, 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 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

Edema
An increase in body weight
Liver disturbances
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 less active in 100 times 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 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, stimulation of labor (together with oxytocin)

may cause side-effects, such as nausea, vomiting, edema, headache, hyper-tension, breast tenderness.

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 in 3-5 days; has the indications similar to the indications of estrone.

Estriol is 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 interven-tions by vaginal access, climacteric syndrome; infertility caused by cervical factor; dryness of the vagina, 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, vertigo.

Synoestrol is a synthetic compound – a stilben derivative; has not a steroid 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 endo-metrial 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 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.

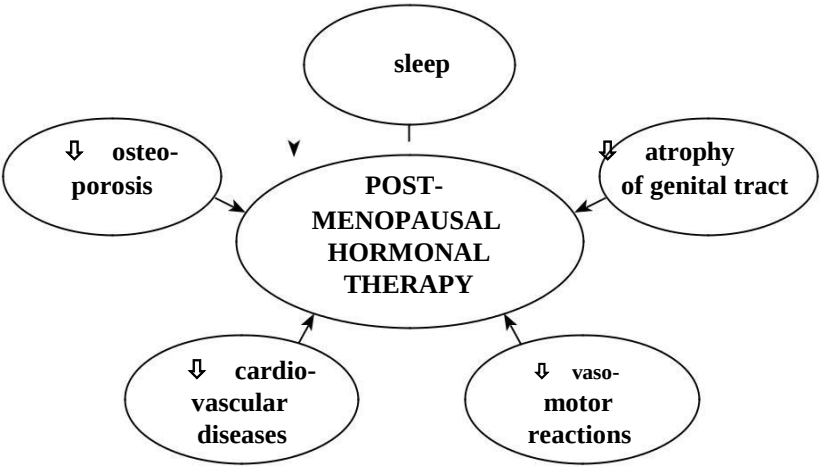

Fig. 26.8. Main effects of postmenopausal hormonal therapy by estrogens.

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 analogueues also have antiestrogen effect.

Antiestrogens are mainly used as estrogen deprivation therapy in the treatment of estrogen-positive breast cancer, for infertility, male hypogonadism, and gyneco-mastia and as a component of hormone replacement therapy for transgender men.

Clomiphene interacts with estrogen receptors; by a feed-back 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 native progestine

is given IM, orally (as a micronized form), intravaginally (vaginal cream)

takes part in the development of sexual 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 carbohydrate metabolism and stimulates fat deposition

is used for the prevention of spontaneous abortion, dysfunctional uterine bleeding, dysmenorrhea, endometriosis, suppression of postpartum lactation, endometrial carcinoma

may cause side-effects, such as uterine bleeding, dyspepsia, edema, depres-sion, an increase in the cholesterol level, an increase in blood coagulation, acne, hirsutism, 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 insufficiency, 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 alon or in cominatio with estrogen, is applied in birth control pills, menopausal hormone therapy, and for the treatment of gynecological disorders. Side effects are typical to progesrins 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.

Mefipristone 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. 23.9).

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 prepara-tion is ***Anteovin***, Triphasic preparations are ***Tri-regol, Triquilar, Trisiston***.

Progestin pills contain a 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).

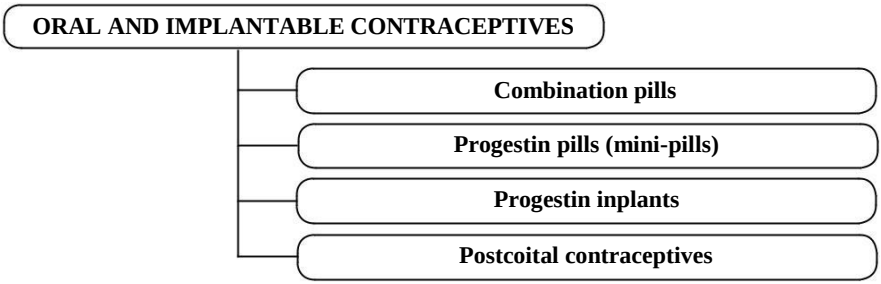

Fig. 26.9. Classes of oral contraceptives.

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 lipo-protein profile, cholestatic jundice, skin pigmentation, acne, hirsutism, amenorrhea, uterine bleeding.

TESTS FOR SELF-CONTROL

№1. The hormonal preparation with mineralcorticoid activity is:
Prednisolone
Dexamthasone
Testosterone propionate
Desoxycorticostrone acetate
Estradiol caproate.

№2. Glucocorticoids may cause all the following side-effects, except:
Hypertension
Bronchospasm
Thromboembolism

Hypokalemia
Osteoporosis.

№3. Regular insulin:
Is produced by genetically modified *E.coli*
Is administered SC, IV
Is used for replacement therapy of I type diabetes mellitus
Is taken orally in II type diabetes mellitus
May cause hyperglycemia.

№4. Anabolic steroids:
Have high androgenic activity
Have high anabolic activity
May cause feminization in men
May cause masculinization in women
Are contraindicated to sportsmen.

5. The patient suffering from the hypofunction of the thyroid gland was treated by hormonal preparation. Overdose of this preparation causes restlessness, insomnia, fever, headache, tachycardia, pain in the heart, palpitation, tremor. What drug was used by this patient?
Insulin
Methimazole
L-thyroxine
Triamcinolone
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 membrane-tropic and enzyme-tropic vitamins

Division of vitamins into groups is based on their biochemical properties and participation in biological processes. Some common characteristics make it possible to speak about membrane-tropic and enzyme-tropic vitamins (table 27.1).

Table 27.1. **Distinguishes between groups of vitamins**

Membrane-tropic vitamins	Enzyme-tropic vitamins
1. Are fat and water-soluble substances	1. Are only water-soluble substances
2. Have a requirement of 100 mg per day	2. Have a requirement of 1-10 mg per day
3. Are components of cell membranes	3. Are components of enzymes (co-enzymes)
4. Are not phosphorilized	4. Are phosphorilized
5. Take part in the forming and protection of cells membranes	5. Take part in biochemical reactions
6. May cause hypervitaminosis	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 hypovitaminosis is caused by factors inside the organism and is divided into physiological and pathological.

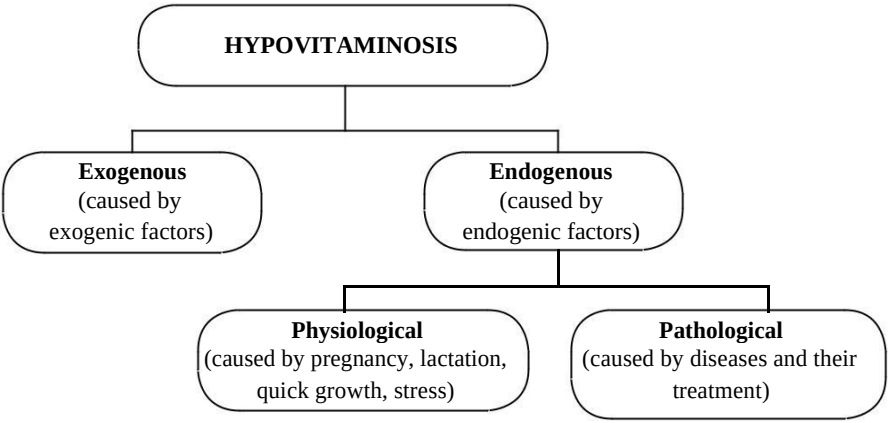

Fig. 27.1. Types of hypovitaminosis.

Antivitamins

Antivitamins are substances which decrease a vitamins action.

There are three groups of antivitamins:

antimetabolites which are chemical analogues of vitamins (e.g. Neodicumarinum 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, ascorbinase)
substances which increase the utilization of vitamin (e.g. anti-atherosclerotic drug Linaetholum increases the utilization of vitamin E).

Hypervitaminosis

Hypervitaminosis is the overdose of a vitamin preparation.

Most of vitamins are comparatively safe, but vitamins A and D can cause seri-ous toxic effects. Hypervitaminosis may be acute and chronic.

Vitamins therapy

Vitamins therapy is the 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, tocopherol acetate, and multivitamins preparations in healthy persons under the conditions of stress or physical overstrain).

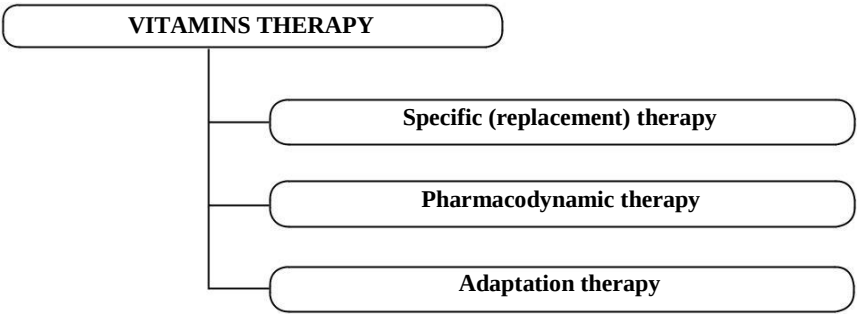

Fig. 27.2. The types of vitamins therapy.

CLASSIFICATION

According to the solubility

1. Water-soluble
   - Thiamine chloride (B_1)
   - Riboflavin (B_2)
   - Nicotinic acid (B_3 or PP)
   - Calcium pantothenate (B_5)
   - Pyridoxine hydrochloride (B_6)
   - Cyanocobalamin (B_{12})
   - Folic acid (B_c)
   - Calcium pangamate (B_{15})
   - Ascorbic acid (C)
   - Rutin (P)
2. Fat-soluble
   - Retinol acetate (A) and related substances
   - Ergocalciferol (D) and related substances
   - α-Tocopherol acetate (E)
   - Naphthoquinon (K)

According to the biological activity

1. Membrane-tropic
   - Vitamin A
   - Vitamin E
   - Vitamin D
   - Vitamin K
   - Vitamin C
   - Vitamin P
2. Enzyme-tropic (co-enzymic)
   - Vitamin B_1
   - Vitamin B_2
   - Vitamin PP
   - Vitamin B_5
   - Vitamin B_6
   - Vitamin B_{12}
   - Vitamin B_C

MEMBRANE-TROPIC VITAMINS PREPARATIONS

RETINOL ACETATE

Retinol has a polyenic structure (fig. 27.3). It is a fat-soluble vitamin.

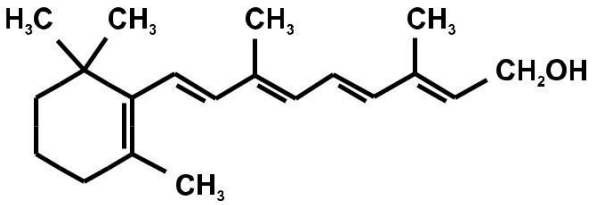

Fig. 27.3. Chemical structure of retinol.

Pharmacokinetics

is taken orally, rarely IM, is applied topically
is absorbed in the intestine in the presence of bile acids
binds to proteins in blood serum that protects retinol from renal excretion

concentrtes 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, lysosome enzymes.
It activates glycogen deposit in the muscles, heart, and liver.
Retinol activates release of STH, 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, the 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

***Acute hypervitaminosis*:** fatigue, headache, sleepiness, nausea, vomiting, pho-tophobia, convulsions (resulting from an increase in intracranial pressure).

***Chronic hypervitaminosis*:** weakness, fatigue, sleepiness, nausea, skin pigmen-tation, hyperkeratosis, bone pains, the liver and spleen enlargement.

Contraindications

Acute diseases of the liver and kidney
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: 1st generation (tretinoin (retinoic acid), isotretinoin, and alitretinoin); 2nd generation (etretinate and its me-tabolite acitretin); 3rd generation (adapalene, bexarotene, and tazarotene).

are used in the treatment of many dermatological conditions such as inflam-matory skin disorders, skin cancers, psoriasis, acne, 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 anti-rachitic 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 ul-traviolet rays (fig. 27.4).

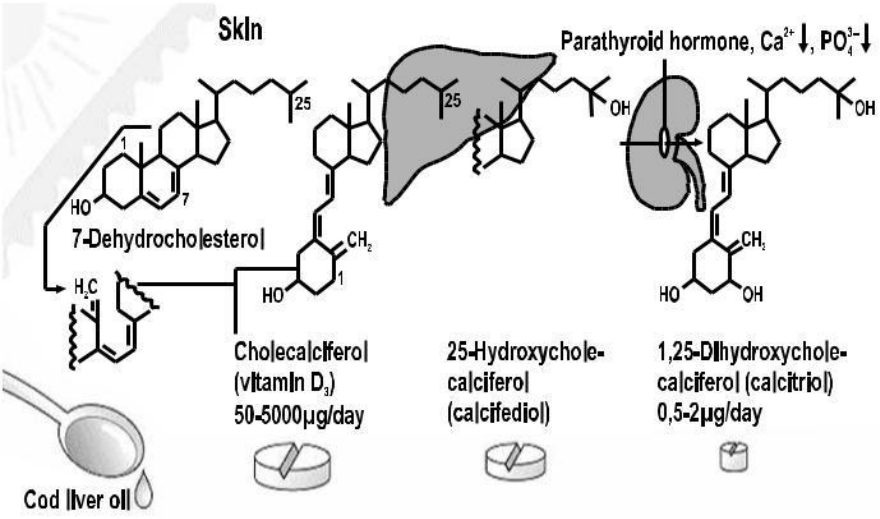

Fig. 27.4. Vitamin D and its active forms *(by H. Lüllmann, 2000)*.

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 blood plasma
is transformed into calcidiol in the liver and into calcitriol in 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
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 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.

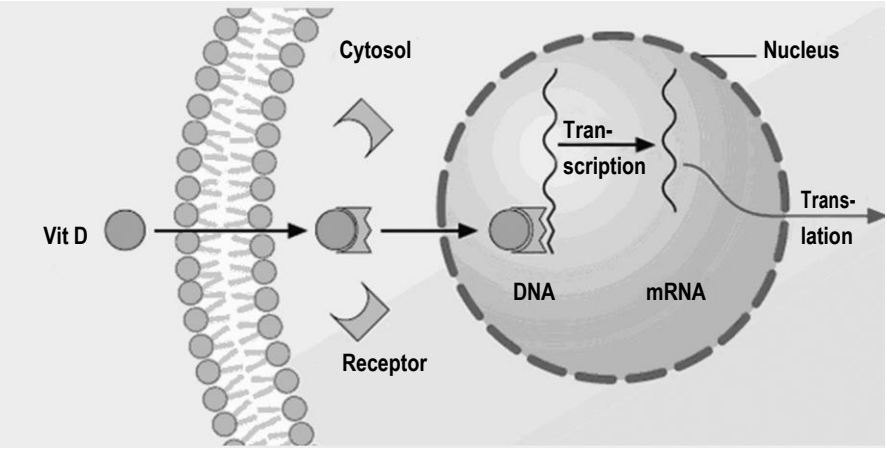

Fig. 27.5. Vitamin's D mechanism of action *(by H. Lüllmann, 2000)*.

Pharmacodynamics

Main task of vitamin D is to regulate calcium-phosphor homeostasis and to support calcium level in 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 blood serum
an increase in fixation of calcium in bone tissue under the conditions of the normal calcium level in blood serum, but stimulation of calcium mobiliza-tion from bones if the serum calcium level is low
an increase in the calcium influx into 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 prophylaxis 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%

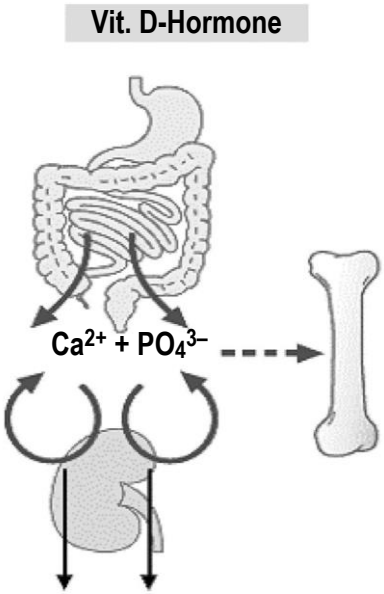

Fig. 27.6. Vitamin D and regulation of calcium homeostasis in the body *(by H. Lüllmann, 2000).*

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
Skin diseases
Tuberculosis.

Side-effects

***Acute hypervitaminosis*:** weakness, sleepiness, nausea, vomiting, dyspepsia, hypotension, arrhythmia, an increase in body temperature, an increase in the calcium concentration in blood serum, changes in urine (protein, cylinders, calcium salts, erythrocytes, and leukocytes).

***Chronic hypervitaminosis*:** bone demineralization, calcium deposit in blood vessels, the kidney, and other organs (calcinosis), CNS damage, heart insufficiency, an increase in BP, an increase in the calcium level in blood serum and in urine.

Treatment of D hypervitaminosis

— Abolishing of drug
— Antioxidants (vitamins E, C, A)
— Glucocorticoides
— 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

Severe atherosclerosis
Elderly age.

α-TOCOPHEROL ACETATE

It belongs to quinons (fig. 27.7), is fat soluble.

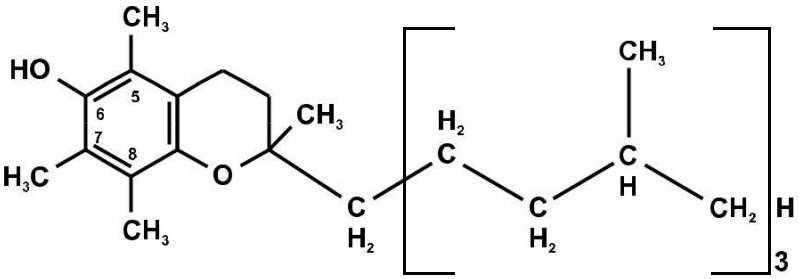

Fig. 27.7. Chemical structure of tocopherol.

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 adrenal glands and fat tissue
is excreted in an non-transformed status with feces (more than 80% of drug).

Mechanism of action

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
Tocopherol increases the secretion of gonadotropines and sexual 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 spermato-genesis in males)
the improvement of skeletal muscles trophy
a cardio-protective action
an increase in stability to hypoxia

the stimulation of erythropoiesis
an improvement of reological properties of blood
an anti-atherosclerotic action
a stress-protective action
a hepatoprotective action
the stimulation of regeneration.

Indications

Spontaneous abortions, sexual glands function impairment, climax
Myodystrophy
Angina pectoris, a omplex 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, an increase in BP (in bigger doses).

PHYTOMENADIONE

is known as vitamin K1 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, pan-creatic and intestinal enzymes.
is used in hemorrhagic syndrome associated with a deficiency of vitamin K1 or violation of its absorption in the gut; an overdose of anticoagulants of indirect action (coumarin and indanedione derivatives), salicylates, sulfona-mides, 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, 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.

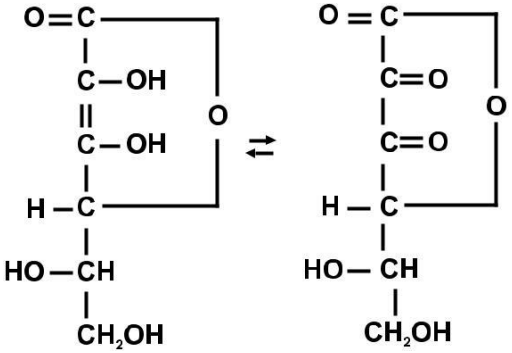

Fig. 27.8. Chemical structure of ascorbic acid.

Pharmacokinetics

is administered orally, IM, IV
is well absorbed in the intestine
vitamin C concentration in erythrocytes and leukocytes is more than that in blood serum
concentrates in gland tissue, especially in adrenal glands
is excreted with urine if the depo is complete.

Mechanism of action

The 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
stimulation of regeneration
participation in the transformation of the 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, activation of sympathetic nervous system
improvement of immunity and phagocytosis
a decrease in the permeability of blood vessels
participation in cholesterol metabolism and the inhibition of the development of atherosclerosis
detoxication of xenobiotics in the liver
an increase in 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:

A decrease in the secretion of insulin
Renal concrements
An increase in BP
A decrease in permeability of blood-tissue barriers
Hypercoagulation of blood.

RUTIN

is a water-soluble membrane-tropic vitamin, a flavonoid
is taken orally
is an antioxidant; protects the ascorbic acid and epinephrine from oxidation, participates in 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, paradontitis.

CALCIUM PANGAMATE

is a water-soluble membrane-tropic vitamin, a derivative of gluconic acid and dimethylglycine
is taken orally
has the mechanism of action connected with the ability to be a donator of active methyl groups
improves lipids metabolism; enhances oxygen utilization in tissues; increases the concentration of creatin phosphate and glycogen in skeletal muscles and the liver; decreases hypoxia; has neuroprotective, cardioprotective, antihy-poxic, antidystrophic, 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, skin diseases; may be applied to improve the tolerance to sulfa drugs and adrenal steroids
may cause allergy, abdominal pain.

CO-ENZYMIC VITANINS PREPARATIONS

Co-enzymic 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 co-enzymic vitanins are:

Thiamine deficiency – beri-beri (polyneuritis, CHF, psychic disturbances; in babies – heart failure, tachycardia, seizures, vomiting, anorexia, nervous excitement)

Riboflavin deficiency – ariboflavinosis (cheilosis, angular stomatitis, perio-ral dermatitis, photophobia, conjunctivitis)

Nicotinic acid deficiency – pellagra (dermatitis, diarrhea, dementia, dys-trophy)

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, ataxia).

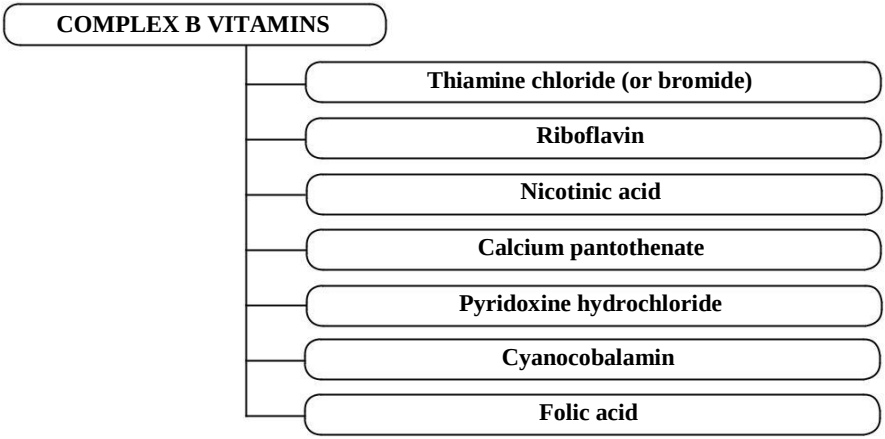

Fig. 27.9. Vitamins preparations of B complex.

THIAMINE CHLORIDE

It is co-enzymic water-soluble vitamin from 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 co-enzyme 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 co-enzyme of transketolase and takes part in a pentosophosphaste way of glucose metabolism.
B_1 stimulates synthesis of acetylcholine.

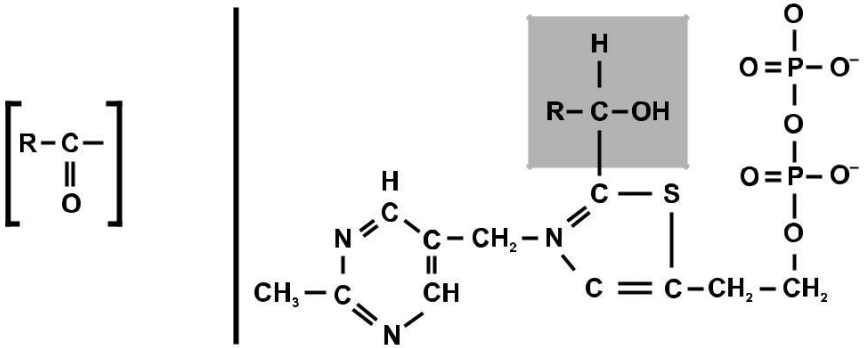

Fig. 27.10. Active form of thiamine is for oxidative decarboxilation of α-ketoacids: acid residue is shown on the left *(by J. Musil et all, 1980)*.

Pharmacodynamics

Neurotropic effect: it improves impulses conduction in nervous fibers, decreases pain, has ganglia blocking action, decreases the action of depolarized myorelaxants
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.

Indications

Hypovitaminosis (beriberi)
Polyneuritis, radiculitis, neuralgia
Chronic heart failure, arrhythmia
Diabetes mellitus
Ulcer of the stomach and duodenum
Skin diseases.

Side-effects

Allergic reactions, anaphylactic shock
Lethargy, ataxia, nausea, hypotension (in overdose).

Contraindications

Should not be used in allergy to 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, diseases of CNS.

RIBOFLAVIN

It is a co-enzymic 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, in the 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-monucleotide). They are co-enzymes of flavin enzymes which take part in the H^+ transport chain in tissue respiration (fig. 27.11).

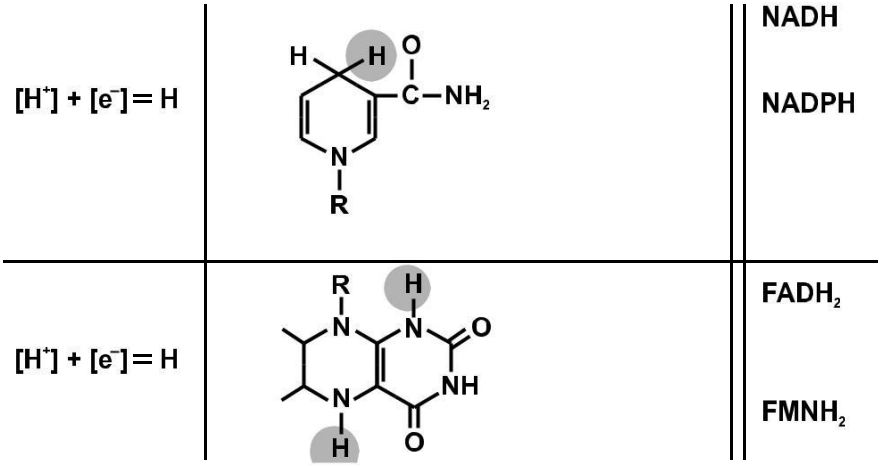

Fig. 27.11. Active forms of vitamins B_2 and PP participated in tissue H^+ and e- transport *(by J. Musil et all, 1980)*.

Pharmacodynamics	**Indications**
The improvement of trophy of the eye and function of vision	Hypovitaminosis (heilosis, glossitis, photophobia)
The stimulation of the regeneration of epithelium	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 co-enzymic 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 tissue respiration (fig. 27.11), are acceptors of H_+

Vitamin PP active forms participate in the synthesis of amino acids, neurotrans-mitters, 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 anti-epileptic properties	Hypovitaminosis (pellagra)
Cardiotrophic effect	Diseases of the skin and mucous membrane
The improvement of the skin trophy	Liver diseases
The improvement of the liver function	Atherosclerosis
Hypolipidemic action: it decreases triglycerids, cholesterol, and LDL level in blood (in a bigger dose)	Spasms of blood vessels
Vasodilatation (in a bigger dose)	Gastritis, gastric ulcer
Activation of fibrinolysis and an anti-platelet action (in a bigger dose)	Radiation sickness.
Stimulation of the gut's activity.	

Side-effects

Skin hyperemia, itch, hypotension (flush-syndrome)
A loss of appetite, nausea, vomiting
Lipid liver infiltration.

CALCIUM PANTOTHENATE

is administered orally, parenteraly and applied topically
takes part in the formation of co-enzyme A and acyl carrier protein. In such a way it participates in the synthesis of acetylcholine, 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 intestine, toxicosis of pregnancy
has minimal side-effects (nausea, vomiting).

PYRIDOXINE HYDROCHLORIDE

It is a co-enzymic water-soluble vitamin from B complex.

Pharmacokinetics

is administered orally, SC, IM
is absorbed in a connective status, is liberated from this status under the influence of digestive juices and absorbed again
is phosphorilized in the tissues
is oxidized and excreted with urine.

Mechanism of action

Vitamin B_6 exists in three forms: pyridoxine, pyridoxamine, pyridoxal.
Pyridoxalphosphate is the 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, amino-levulinic acid, serotonin, GABA, glutaminic acid.
It promotes the transition of linoleic acid into arachidonic acid.

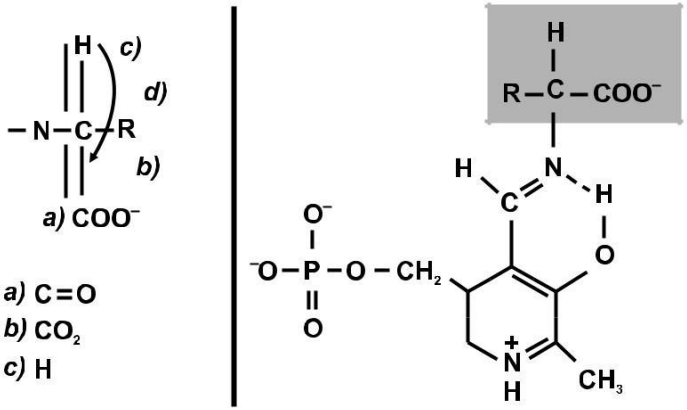

Fig. 27.12. Active form of pyridoxine and groups which are transported by it (at left) *(by J. Musil et all, 1980)*.

Pharmacodynamics	**Indications**
Neurotropic effect: increases synbthesis of neurotransmitters in CNS, improves func-tions of the brain, decreases epileptic activ-ity, 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 desintoxication in the liver	Hypovitaminosis (normochromic microcytes anemia) Neuritis, radiculitis Chorea, Parkinson's disease, epilepsy Myocardiodystrophy, chronic heart failure Liver diseases Chronic alcoholism Gestational toxicosis Anemia, leukopenia, aplastic anemia Radiation sickness
Stimulation of hemopoiesis: it activates the synthesis of hem and forming of leukocytes.	Prophylaxis and the treatment of side-effects of antimycobacterial drugs, hormonal contraceptives and some other drugs.

Side-effects

Allergy
A reduce of prolactin secretion.
Damage of sensor nerves and the liver.

CYANOCOBALAMIN

It is a water-soluble co-enzymic 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 biotransformated to deoxyadenosylcobalamine and methylcobalamine.

Mechanism of action

Active form of cyanocobalamin is a co-factor of the folic acid reductase (fig. 27.13).

It takes part in the synthesis of purine and pyrimidine nucleotides and transforms megaloblastic hemopoiesis into 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 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 normoblastic one; the improvement of the formation of erythrocytes, leukocytes, and throm-bocytes	Hypovitaminosis (megaloblastic anemia, glossitis, myelosis)
The regulation of the epithelium forming The improvement of the neurotrans-mission and functions of nervous system	Radiation sickness
The stimulation of regeneration and growth	Neuritis, neuralgia, radiculitis, neurologi-cal diseases of the spinal cord and the brain
	Liver diseases
	Hypotrophy in children
	Glossitis, stomatitis.

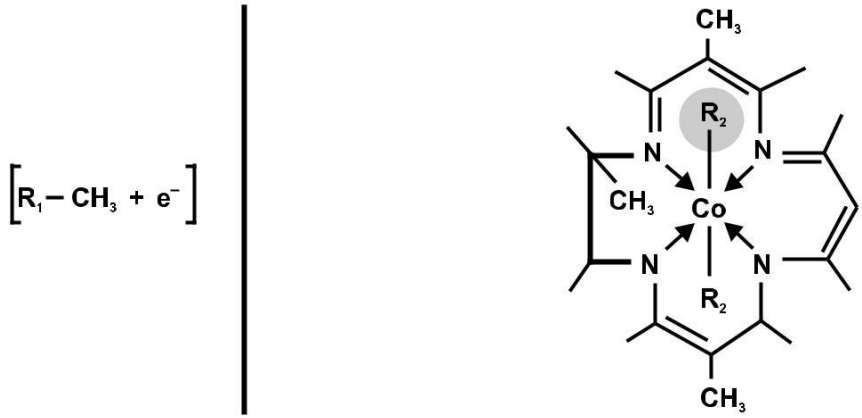

Fig. 27.13. Active form of cyanocobalamin and methyl group transported by it (on the left) *(by J. Musil et all, 1980)*.

Side-effects

Allergy
Hypercoagulation
Tachycardia, pain in the heart, 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.

FOLIC ACID

is 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 gastro-enteritis, 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 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 the nicotinic acid take part in tissue respiration
C. Thiamine chloride regulates calcium homeostasis
D. Cyancobalamin and the folic acid transform megaloblastic hemopoiesis into normoblastic one
E. Calcium panthotenate improves regeneration and skin trophy.

2. Rutin is:
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:
Stimulates calcium absorption in the GI tract
Stimulates calcium reabsorption in the kidney
Stimulates resorption of bones
Inhibits bones resorption
Supplies 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 bone tissue.

5. A patient has disturbances of vision (hemeralopia), xerophthalmia, xeros-tomia, dry skin, and hypochromic anemia. Point a correct diagnosis and basic preparation for the therapy.
Rickets and ergocalciferol
Megaloblastic anemia and cyanocobalamin
Malaria and chloroquine
Hyperthyroidism and methimazole
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 neces-sary 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, 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: the coagulation necrosis of the skin or mucous membrane, acute pain in the mouth, gullet, the stomach, vomiting with admixtures of blood, acidosis, shock.

Emergency help:

— lavage of the stomach with cold water
— neutralization of the acid and the protection of the gastric mucosa (magne-sium oxide, egg albumin, milk)

— neutralization of the acid by weak solution of alkali on the surface of the skin or mucous membrane
— IV administration of sodium bicarbonate
— narcotic analgesics.

ALKALIS (BASES)

Bases are electrolytes dissociated the with 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
decreases the acidity of gastric juice (after the oral administration), decreases acidosis, has expectorant, anti-arrhythmic 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.

A solution of ammonia is an antiseptic. It is used for the processing of the surgeon's hands. It is an irritable 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: a 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:

— the avage of the stomach with cold water
— coverings (egg albumin, milk) —
narcotic analgesics
— neutralization by a weak solution of the acid on the surface of the skin or mucous membrane.

SALTS OF ALKALINE AND ALKALINE-EARTH METALS

Salts are electrolytes which dissociate into the ions of metal and acid (fig.28.1).

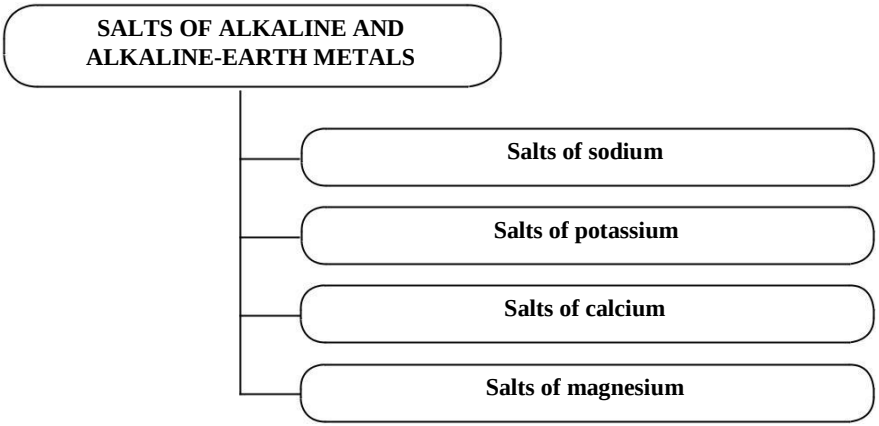

Fig. 28.1. Main groups of salts used in a clinic.

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 polarization and depolarization of cell membranes, participates in the neu-rotransmission, 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, intoxica-tions, hemorrhages, for forced diuresis; is used to dissolve other drugs and to irrigate wounds, cavities, 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 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 poison-ing with cardiac glycosides; to prevent hypokalemia caused by some drugs (cardiac glycosides, glucocorticoids, 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 the functions of CNS and autonomic nervous system, stimulate sympathetic activity, participate in 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, in-flammations, bleedings and their prophylaxis, vasculitis, acute intoxications with fluorides, oxalates, magnesium salts
may cause the necrosis of 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 min-eralization of bones and teeth, has an anabolic action, is used orally for the treatment of bone fractures, osteoporosis.

MAGNESIUM SULFATE

is administered IV, IM, orally
is an antagonist of calcium ions in the cell
after parenteral administration, has sedative, hypnotic and narcosis actions; inhibition of the vasomotor center; an anti-seizure action; the dilation of blood vessels and a decrease in BP; an anti-arrhythmic action; the dehydratation- of tissues; a diuretic action; a decrease in intracranial pressure; a spasmolytic action; an antidote effect in acute poisoning with compounds of calcium
after the oral the administration, acts as a laxative

is used for hypertensive emergency, chronic hypertension, a seizures attack, edema of the brain, tachyarrhythmia, myocardial infarction, toxicosis of pregnancy overdose of calcium preparations, acute constipation
may cause side-effects, such as pain and infiltrate in the site of administration (IM); suppression of respiration (IV). If suppression of respiration occurs, calcium chloride (IV) and carbogenum (inhalation) should be used.

DRUGS FOR TREATMENT OF OSTEOPOROSIS

Osteoporosis is a condition of skeletal fragility due to progressive loss of bone mass. It is characterized by frequent bone fractures, which are a major cause of dis-ability among the elderly, especially among postmenopausal women.

New options in 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 analogs of pyrophosphate, They decrease osteoclastic bone resorption via 1) inhibition of the osteoclastic proton pump necessary for dissolution of hydroxyapatite, 2) decrease in osteoclastic formation/activation, 3) increase in osteoclastic apoptosis, 4) 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 treatment of bone metastases and hypercalcemia of malignancy. Side-effects include diarrhea, abdominal pain, 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 effec-tive 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 dissolution of bone, but when it is given SC once daily, bone formation is the predominant effect. The safety and efficacy of this agent have not been evaluated beyond 2 years. Teriparatide is an alternative prepara-tion for patients who cannot tolerate other osteoporosis therapies.

ENZYMES AND INHIBITORS OF ENZYMES

ENZYMES

Enzymes are preparations which play the 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 a clinic.

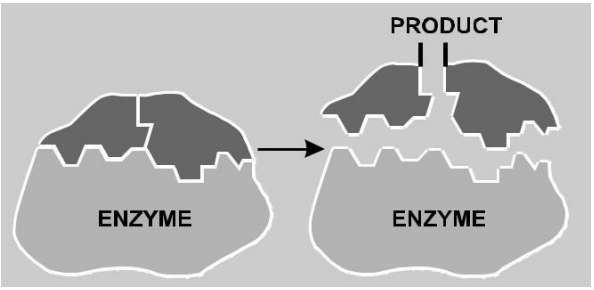

Fig. 28.2. Restriction of substrate by enzyme (http://www.picsearch.com).

Classification

Peptidases and proteases
- Pepsin
- Trypsin
- Chymotrypsin

Nucleases
- Ribonuclease
- Desoxyribonuclease

Preparations of hyaluronidase
- Lidase
- Ronidase

Fibrinolytic enzymes
- Fibrinolysin
- Streptolyase

Enzymes of another action
- L-asparaginase
- Penicillinase

Combined polyenzyme preparations
- Pancreatin
- Creon
- Festal
- Wobenzym.

Peculiarities of preparations

Pepsin is a normal constituent of gastric juice; is active in an 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, 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 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 connected tissue, increases tissues permeability and the penetration of other drugs; is used to treat contractures of joints, scars after burns and surgeries, hematomas, chronic inflammation; may cause allergy.

Ronidase is hyaluronidase preparation; its pharmacological properties are close to lidase, 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, 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. Pancreatine is prescribed for chronic pancreatitis, cystic fibrosis, chronic inflammatory-dystrophic diseases of the stomach, intestine, liver, gall bladder. The drug can be used in people with normal function of the GI tract in case of errors in nutrition.

Creon is 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 creone, 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 patho-physiological processes. It contains pancreatin, papain, bromelain, lipase, amylase, trypsin, and chymotrypsin. After oral administration, 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 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 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 pan-creas, 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 + 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.

GLUCOSE

is administered IV,SC, orally

isotonic 5% solution of glucose is used for an increase of fluids volume, as a energetic source, as a solvent for other drugs

hypertonic 40% solution increases osmotic pressure, improves antitoxic liver function, and contractility of myocardium, decreases permeability of

blood vessels; is used to treat hypoglycemia, hypotension, asthenia, liver diseases, heart failure, 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

Low weight solutions
- 0,9% solution of sodium chloride
- 4% solution of sodium bicarbonate
- 5% solution of glucose
- Ringer-Lock solution
- Trisol
- Trasamine

Plasma substitutes and hemodynamic solutions
- Albumin
- Rheopolyglukin
- Refortan

Detoxification drugs
- Neohemodez

Drugs for IV nutrition
- Aminosteril
- Lipofundin.

Peculiarities of preparations

Low weight solutions 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, metabolic acidosis with loss of fluid. Indications for the use are shock, col-lapse, 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 trometamol. 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 CO2 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 (shock, massive blood transfu-sion, extracorporeal blood circulation, burns, peritonitis, 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, hyponatremia, hypokalemia, dyspeptic disorders, local reactions in the site of administration (venous spasm, phlebitis).

Plasma substitutes and hemodynamic solutions restore the volume of circulat-ing 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 viola-tions of liver function; condition after organ transplantation. Possible side effects are a decrease in hematocrit and protein level in the blood, liver damage. itch of the skin, pain in the kidney area, and anaphylactic reactions.

Rheopolyglukin 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 enter of water into the blood vessels, reduce the viscosity of the blood, restore blood flow in small capillaries, prevent and eliminate 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. Reopolyglukin is used for the prevention and treatment of shock; thrombosis, thrombophlebitis, 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, anuris, and heart failure.

Detoxification drugs increase tWhe transport of toxic substances from tissues into blood and their excretion, improve microcirculation. They are used to treat sepsis, severe burns, endotoxic reactions, and acute poisonings.

Neohemodez has the effect due to abilityz 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, 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, 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, unconsciousness patients, etc. Aminosteril and lipofundin are preparations of this group.

TESTS FOR SELF-CONTROL

№1. The following statements concerning Lidasum are correct, except:
- It is hyaluronidase
- It is used to promote drug absorption
- It is used for replacement therapy
- It is used for the treatment of joint contractures
- It is used for scar softening.

№2. The salt drug for the treatment of purulent wounds is:
- 0,9% solution of sodium chloride
- 5% solution of glucose
- 25% solution of magnesium sulfate
- 10% solution of calcium chloride
- 10% solution of sodium chloride.

№3. The main indications for the calcium chloride use are:
- Allergic reactions
- Vasculitis
- Thrombosis
- Bleeding
- Overdose of vitamin D.

№4. Aminocaproic acid
- Is proteolytic enzyme
- Is the inhibitor of proteolysis
- Is the inhibitor of fibrinolysis

Has anti-allergic and antitoxic properties
Is used to treat purulent diseases.

№5. A patient has bronchoectasia with purulent dense exudation. The physician prescribes him inhalations of an enzyme preparation. The drug suitable in this case is
Lydasum
Aprotinin
Trypsin
Parathyroidin
Pancreatinum.

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 infection 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.

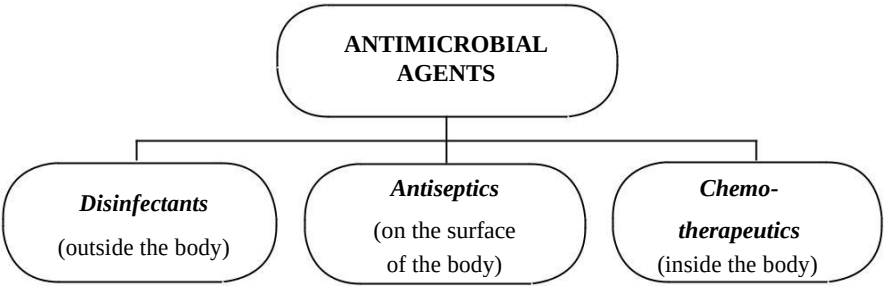

Fig. 29.1. Main classes of antimicrobial agents.

Antimicrobial drugs may have a bactericidal or bacteriostatic type of action (fig. 29.2). Antimicrobial drugs of a ***bactericidal action*** produce death of microbes.

Bacteriostatic drugs stop the growth and replication of bacteria and then the immune system destroys such microbes.

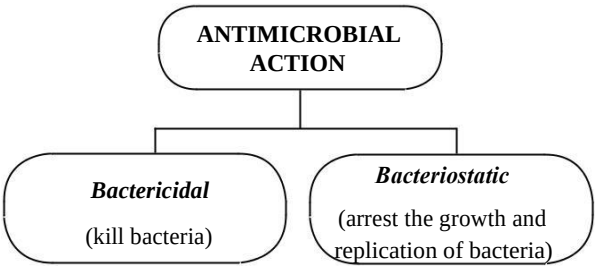

Fig. 29.2. Types of antimicrobial action.

ANTISEPTICS AND DISINFECTANTS

Good antiseptic and disinfectant should meet such demands as:

Bactericidal action
Chemical stability
A 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 irritability.

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	***B. Organic substances***
1. Halogens	1. Aldehydes

- Iodine (5% alcohol solution)
- Povidone- iodine
- Ioddicerin
- Chloramine B
- Chlorhexidine (Hibitane)

2. Oxidizing agents
   - Hydrogen peroxide
   - Potassium permanganate
3. Metallic salts
   - Mercury dichloridum
   - Yellow mercury oxide
   - Silver nitrate
   - Copper sulfate
   - Zinc sulfate
   - Zinc oxide
4. Acids and alkalis
   - Boric acid
   - Salicylic acid
   - Solution of ammonia
   - Formaldehyde (Formalinum)
   - Hexamethylentetraminum (Methenamine)
2. Alcohols
   - Ethyl alcohol (Spiritus aethylicus)
3. Phenol derivatives
   - Phenol (Phenolum purum, Carbolic acid)
   - Resorcinol
4. Dyes
   - Methylene blue (Methylenum coeruleum)
   - Brilliant green (Viride nitens)
   - Etacridine lactate
5. Detergents
   - Etonium
   - Decamethoxine
   - Miramistin
6. Tar, resins, products of petroleum
   - Birch tar (Pix liquida Betulae)
   - Ichthyol
   - Liniment by Vishnevsky

Nitrofuran derivatives
- Nitrofurasone (Furacilinum)

Antiseptics from medicinal plants
- Chlorophylipt
- Novoimanin

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).

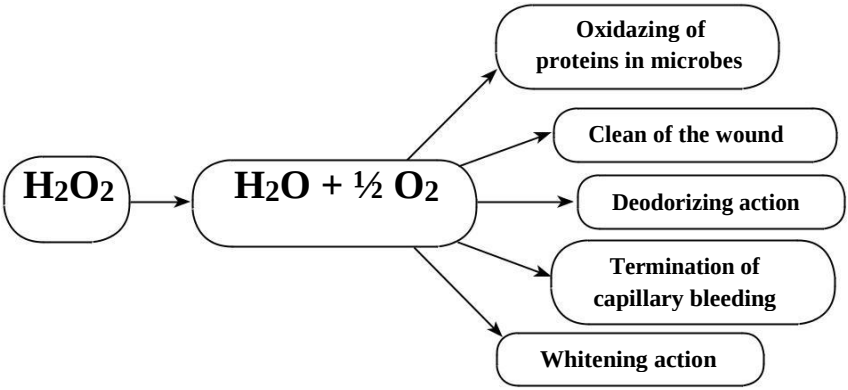

Fig. 29.3. Pharmacological effects of hydrogen peroxide.

Indications:

processing of wounds (3% solution)
processing of impaired skin
gargling and mouthwash in diseases of the throat and oral cavity
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 the 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.

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)
the lavage of the stomach in acute poisoning with morphine, alcohol, alka-loids (0,1% solutions).

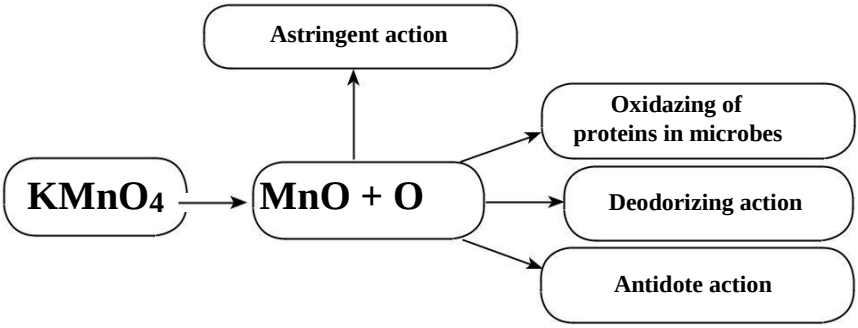

Fig. 29.4. Pharmacological effects of potassium permanganate.

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 bac-tericidal, fungicidal and irritative actions.

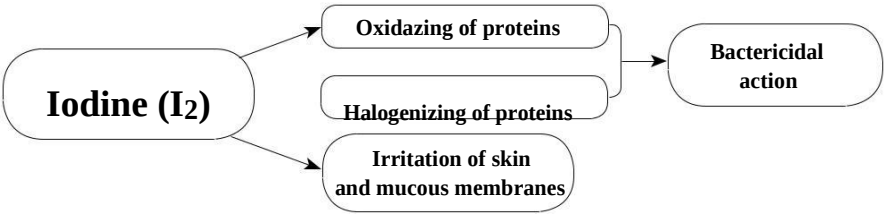

Fig. 29.5. Pharmacological effects of iodine.

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).

Toxity:

Iodine may cause the irritation of the skin, allergy, idiosyncrasy. On the surface of the skin or mucuos membrane it should be neutralized by sodium thiosulphate.

PECULIARITIES OF OTHER HALOGENS

Povidone-iodne is a chemical complex of povidone, hydrogen iodide, and elemental iodine. It works by iodine releasing with 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, Dimexidum, and glycerin; due to Dimexidum, has an increased antiseptic activity and penetration through the skin; is used for the treatment of skin diseases, ulcers, wounds; may be used on the mucous membranes due to less irritation (in otitis, tonsillitis, chronic atrophic rhinitis, paradontosis, 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 (Chlorhexidinum bigluconas) is an organic chlorine containing preparation with detergent properties; has an antimicrobial, antifungal activity, im-proves 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, the 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 a very dilute aqueous solution as eye drops in bacterial conjunctivitis.

Salicylic acid has an antimicrobial action, an anti-inflammatory effect, a kera-tolytic 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 astrin-gent 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, zinc – an astringent action only.

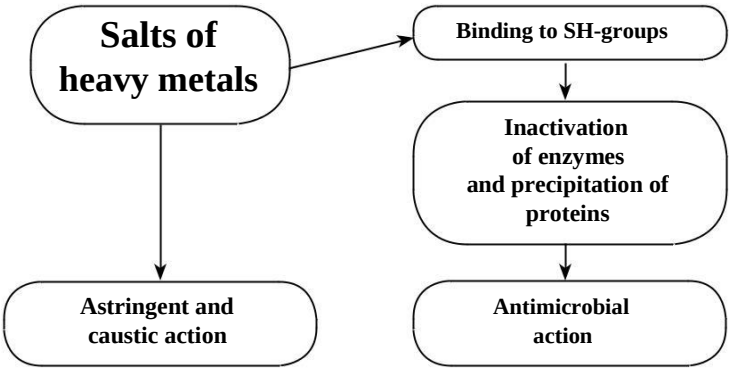

Fig. 29.6. Pharmacological effects of heavy metal salts.

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, non-metallic instruments.

Yellow mercury oxide is not soluble, is used in the form of ointments for the treatment of pyoderma, blepharitis, seborrhea, 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, 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, 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)

ALCOHOL (SPIRITUS AETHYLICUS)

Mechanism of action and effects:

The alcohol's mechanism of action is connected with the inhibition of oxidoreductases, 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 action), dehydrates proteins and tissues (mummifying action), has deodorizing properties (fig.29.7). Standard 40% solution of formaldehide is called Formalinum.

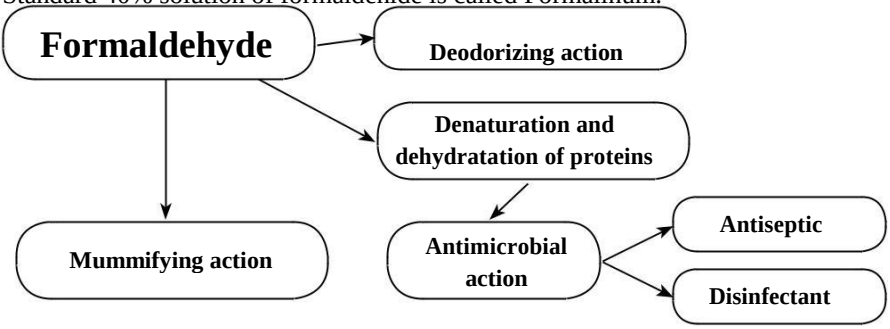

Fig. 29.7. Pharmacological effects of formaldehyde.

Indications:

freet 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.

Toxity:

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 (UROTROPINUM)

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 (ozena)
infections of the oral mucosa and throat (spray).

Toxity:

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, 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 (Pix liquida Betulae) 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 by 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 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 antidote 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).

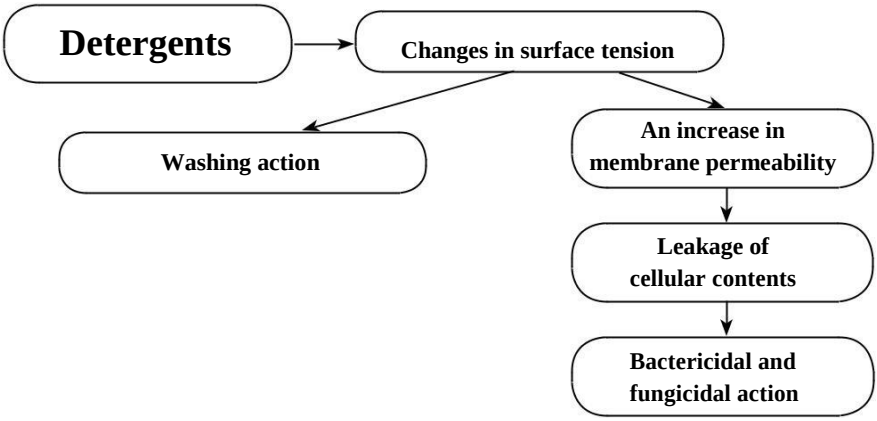

Fig. 29.8. Pharmacological effects of detergents.

Peculiarities of preparations

Etonium is a quaternary ammonium compound, cationic detergent; has an antiseptic action, stimulates regeneration, causes local anesthesia and decreases intoxica-

tion; is used for the treatment of wounds, trophic ulcers, radiation injures (0,02-1% solution), eye diseases (0,1% eye drops), otitis, tonsillitis, burns, dermatitis (ointment).

Decamethoxine is a quaternary ammonium compound, cationic detergent; by its pharmacological activity is similar to Aethonium; may be also used for the process-ing of the surgeon's hands, surgical area, disinfection of surgical instruments and nursing items, for the irrigations of bronchi, and washing of 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 treat-ment of infected wounds and burns, prevention and treatment of postpartum infec-tions; 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 (FURACILINUM)

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, 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, 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* (st. John's wort), acts on Gram (+) cocci, is used topically for treatment of wounds, burns, abscesses, etc.

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 ac-tion for 1 hr on the skin, 3 hr – 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 pharma-cies, children's institutions, food industry enterprises, etc.; can be used in caring for newborns, old people, patients, on travel, 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 group of preparations are most suitable in the cases pointed at fig. 29.10.

TESTS FOR SELF-CONTROL

1. The antiseptic from the oxidizers group is only:

A. Silver nitrate
B. Hydrogen peroxide
C. Aethonium
D. Phenol
E. Iodine solution.

2. For the processing of the surgeon's hands all the drugs are used, except:

Fig. 29.9. Eucalypt as a source of antiseptics.

Alcohol
Mercury dichloride
Chlorhexidine bigluconate
Solution of ammonia
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:
An organic antiseptic
Used for the irrigation of wounds
Protoplasmic poison
A chemotherapeutic agent
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 re-nal failure and the defeat of CNS are appeared. What is the cause of the poisoning? What must antidote therapy include?

Iodine and solution of sodium thiosulfate
Formaldehyde and solution of ammonia chloride
Mercury dichloride and Unithiolum
Strong acid and sodium bicarbonate

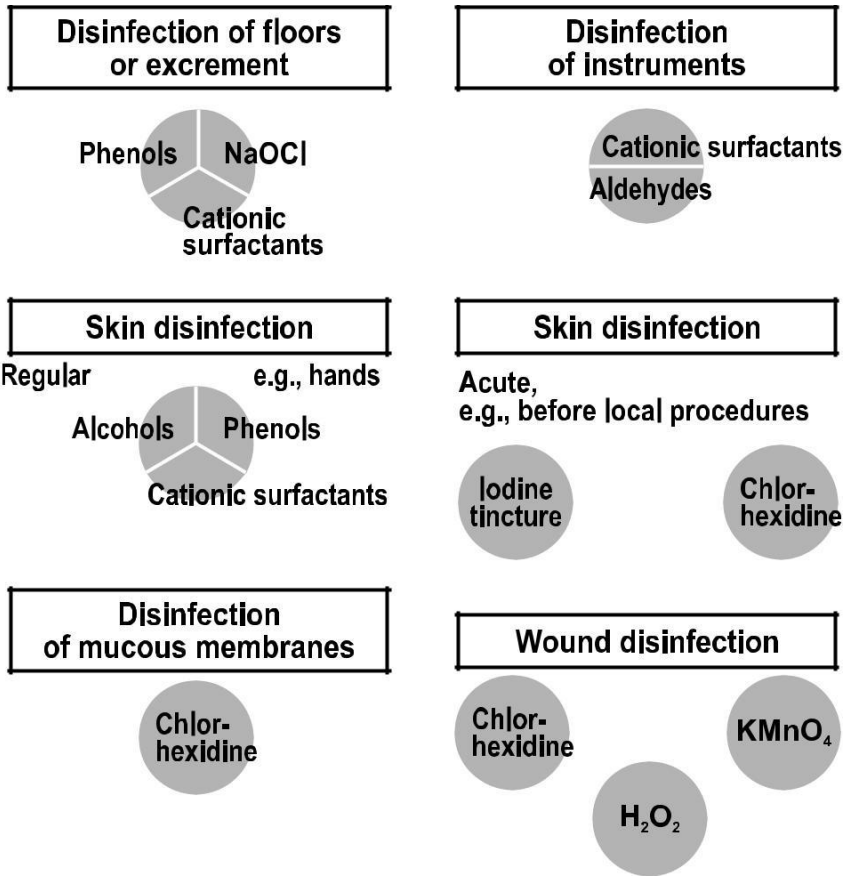

Fig. 29.10. Summary of application of antiseptics and disinfectants *(by. H.Lüllmann, 2000)*.

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, fluorquinolones and antimicrobial drugs of different chemical structure, antifungal drugs, antimycobacterial drugs, antiviral drugs, antiprotozoal drugs, 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.

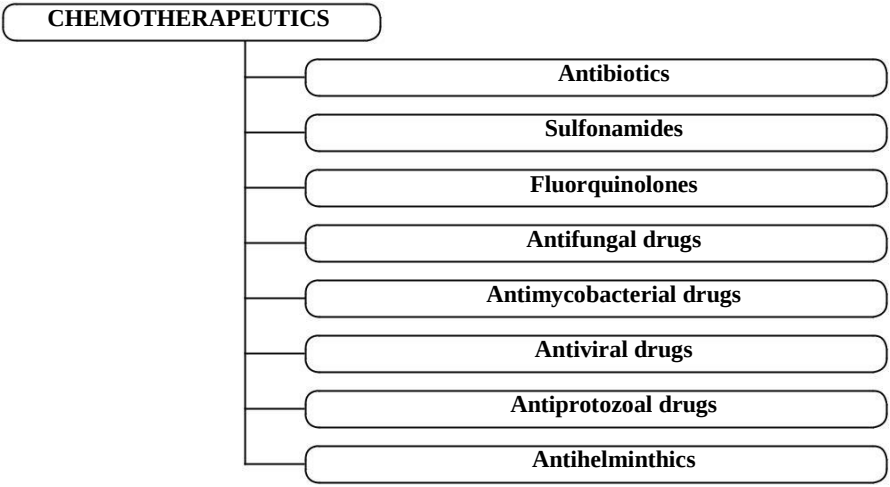

Fig. 30.1. Main classes of chemotherapeutics.

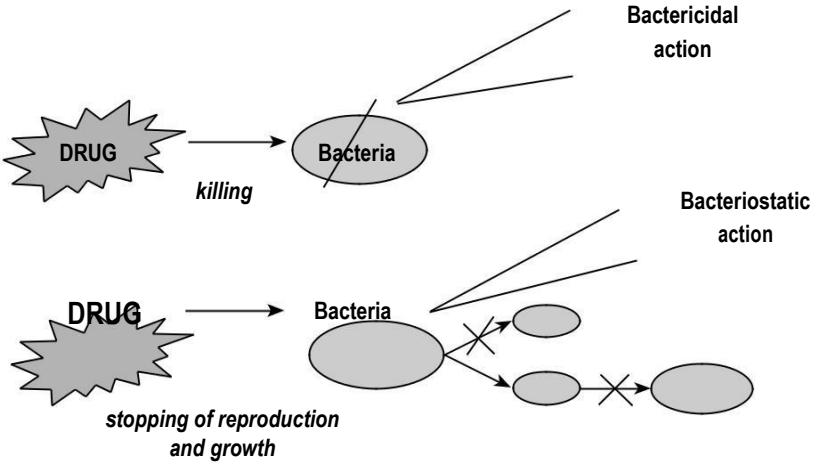

Fig. 30.2. Types of antimicrobial action.

SPECTRUM OF ACTION

The spectrum of action is the list of species of microbes affected by this chemo-therapeutic (fig. 30.3).

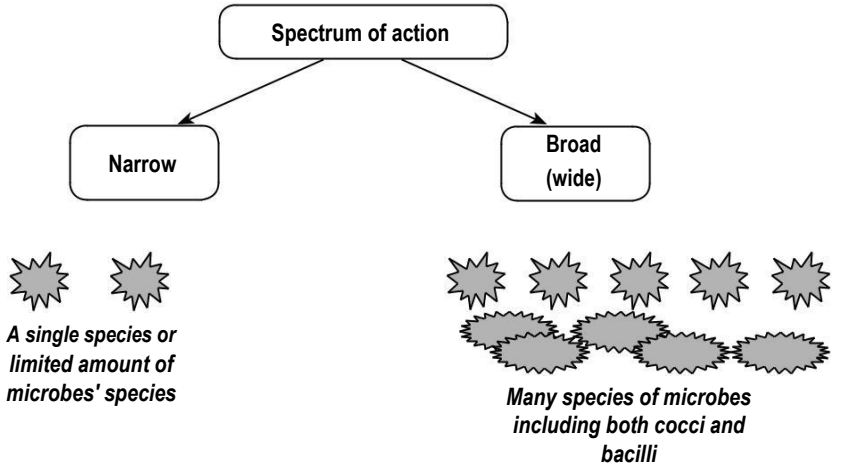

Fig. 30.3. Spectrum of antimicrobial action.

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 drugs (or drugs combination) should be used.

The selection of the optimal route of administration and dose

The maintenance of a constant chemotherapeutic concentration

The discontinuation of chemotherapy during 2-3 days after the normaliza-tion of body temperature

A rational combination of drugs

Taking into account the patient's sensitivity to the drug (an allergic test before the start of treatment)

Taking into account the site of infection, the immune competence, the age, and physiological status

The clinical and laboratory monitoring of a 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 analogs of para-aminobenzoic acid (PABA) (fig. 30.4). All sulfas have common pharmaco-logical properties.

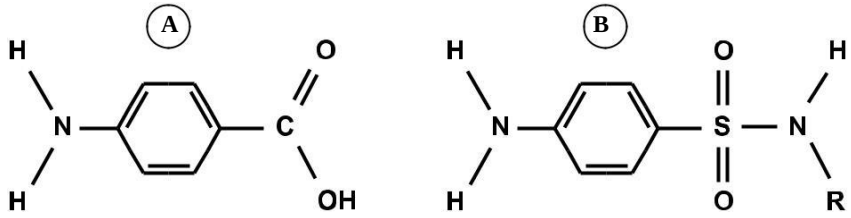

Fig. 30.4. Chemical structure of PABA (A) and sulfonamides (B).

CLASSIFICATION

A. *Highly absorbed sulfonamides*

Short-acting
- Sulfamethazine (Sulfadimezin)
- Aethazolum

Intermediate-acting
- Sulfamethoxazole
- Sulfaphenoxazole

Long-acting
- Sulfamethoxypyridazine (Sulfapyridazinum)
- Sulfadimethoxine

Ultralong-acting
- Sulfamethoxypyrazine (Sulfalenum)

B. *Poorly absorbed sulfonamides*
- Phthalylsulfathiazole (Phthalazolum)

C. *Sulfonamides for a local use*
- Sulfacetamide sodium (Sulfacylum natrium, Albucid)
- Sulfonamide (Streptocidum)

D. *Derivatives of sulfonamide 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 serum albumen
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 renal tubuli
are excreted the 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).

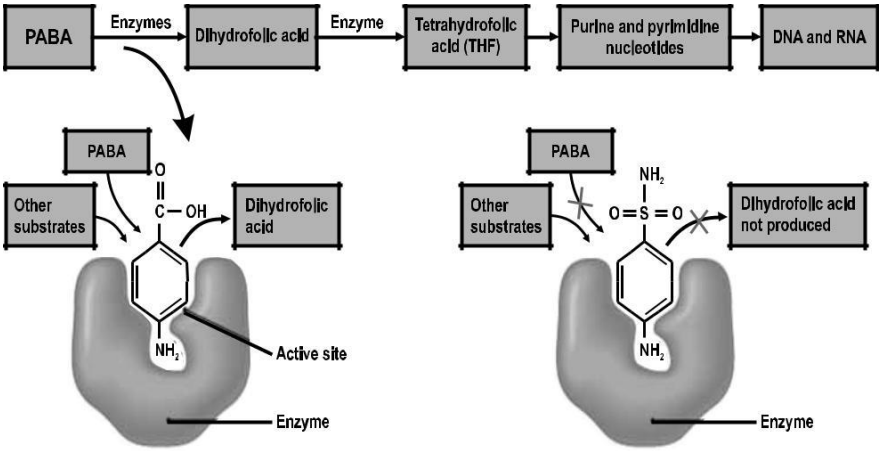

Fig. 30.5. The role of PABA in folate synthesis (at left) and its blockade by sulfonamides (at right) (http://www.picsearch.com).

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 basis and then in the synthesis of nucleic acids.
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 in 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 (*Streptococci, Staphylococci*), Gram (–) cocci (*Neisseria gonorrhoeae*), Gram (-) bacilli *(Haemophilus influenzae, E.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 (2,0) for the 1st administration, then 2 tablets (1,0) 4 times a day, after the normalization of body temperature 1 tablet (0,5) 4 times a day during 3 days. (Total dose is 20-30 g).

For long-acting drugs: 4 tablets (2,0) for the 1st administration, then 2 tablets (1,0) once a day, after the normalization of body temperature 1 tablet (0,5) once a day during 3 days. (Total dose is 8-10 g).

For ultra-long-acting drugs: 5 tablets (1,0) for the 1st administration, then 1 tablet (0,2) once a day (Total dose is 2 g). The total dose may be taken once a week.

Side-effects

Crystalluria
Allergy
Hemopoietic disturbances
Dermatitis and phototoxicity
Stevens-Johnson syndrome
Hepatitis
Kernicterus (in newborns)
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 con-junctivitis, trauma of the eyes, 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.

Aethazolum 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 48hrs due to strong bonds with serum 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 the active form of the folic acid). Trimetoprim inhibits dehydrofolate reductase (stage II of the synthesis of an active form of the folic acid). A result is a bactericidal action. The antimicrobial spectrum of trimethoprim is similar to that of sulfonamide, however the combination is in 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, special adverse reactions in HIV infected persons.

Salazopyridazine and sulfasalazine are the combinations of sulfonamides with the 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
- Nitrofurantoin (Furadoninum)

Quinolones and fluorquinolones

Quinolones
- Nitroxoline (5-NOK)
- Nalidixic acid

Fluorquinolones

the 1st generation
- Ciprofloxacin
- Ofloxacin

the 2nd generation
- Lomefloxacin

the 3rd generation
- Levofloxacin

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 nitrofuran derivative
is taken orally every 6 hr, 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 emergence of drug-resistant strains
is used in diarrhea caused by gram-positive and some gram-negative bacte-ria, 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), 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.

FLUORQUINOLONES

are fluor-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 topoi-somerase 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.
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 gen-eration is active against streptococci. Fourth-generation fluoroquinolones' dual action on DNA gyrase and topoisomerase IV development of resist-ance. Fluoroquinolones can enter cells easily via porins and, therefore, are often used to treat intracellular pathogens (Lgionella 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, 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.

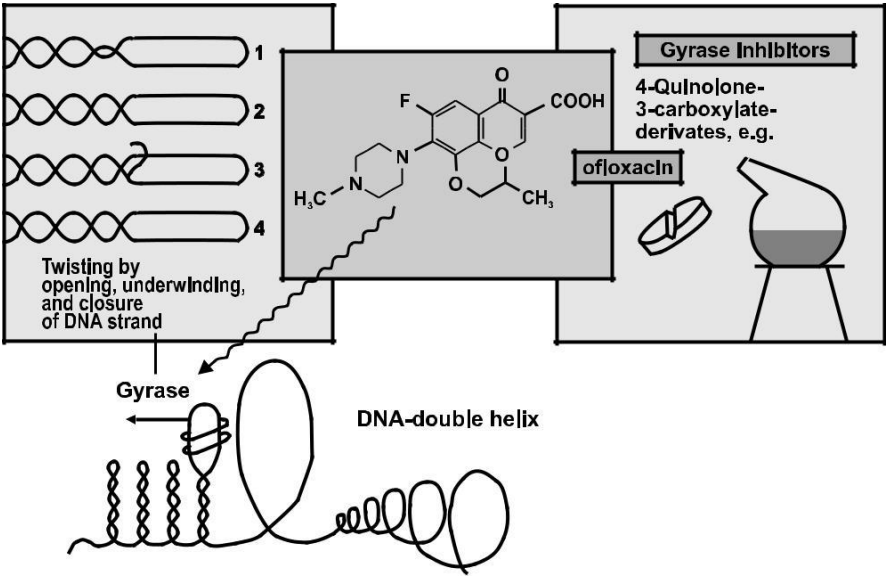

Fig. 30.6. Mechanism of action of fluorquinolones (http://www.picsearch.com)

ANTIFUNGAL DRUGS

Antifungals are the preparations for the treatment of infections caused by pathogenous 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 contain 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

Antibiotics

Polyenes

– Nystatin

– Amphotericin B

Heterocyclic benzofurane

– Griseofulvin

Azoles

Imidazoles

– Clotrimazole

– Miconazole

– Ketokonazole

Triazoles

– Fluconazole

– Itraconazole

Antimetabolites

– Flucirosine

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 depolarization of the membrane and formation of pores that increase permeability to proteins and monovalent and divalent cations, eventually leading to cell death. Amphotericin B may also induce oxidative damage in fungal cells and has been reported to stimulate of host immune cells.

Amphoterricin B has a wide antifungal spectrum of action including *Histoplasma capsulata, Cryptococcus neoforenans, Coccidioides immitis, Blastomyces dermati-tidis, 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.

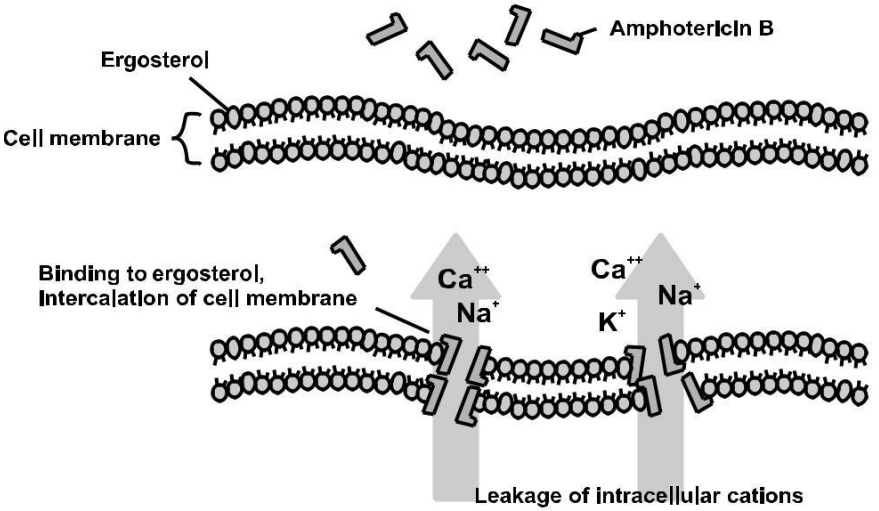

Fig. 30.7. Mechanism of action of polyenes (http://www.picsearch.com).

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, hair), is metabo-lized 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 the 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, rifampim; are widely distributed in body tissues; penetrates into CNS poorly; are metabolized in the liver and inhibit cytochrome P-450

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 intermedi-ate 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.

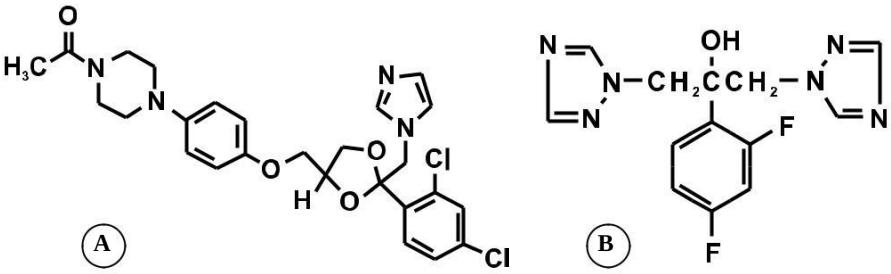

Fig. 30.8. Chemical structure of ketokonazole (A) and fluconazole (B).

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 function 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 into 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 the 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.

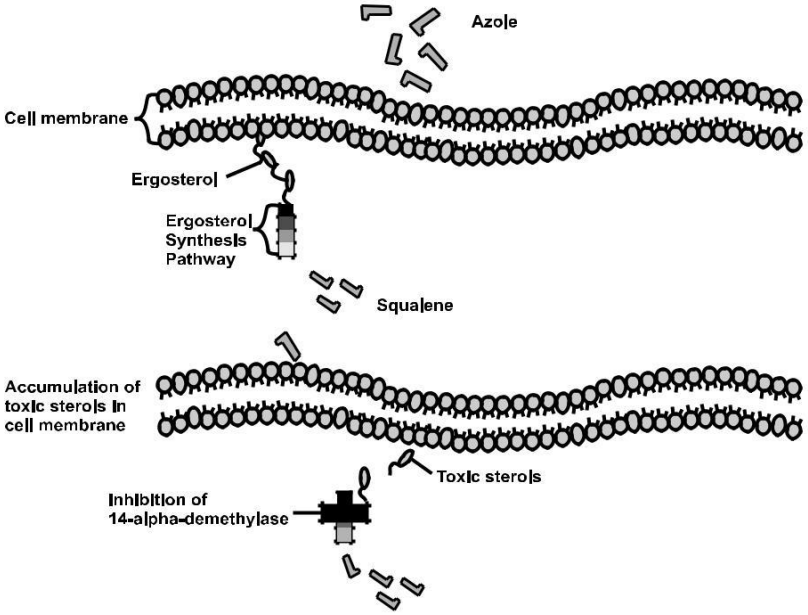

Fig. 30.9. Mechanism of action of azoles (http://www.picsearch.com).

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 anti-cancer 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 fungal cells.

TESTS FOR SELF-CONTROL

№1. The following is the bases for sulfamethoxazole and trimethoprim combination:
The both drugs act at the same stage of folates metabolism
The both drugs are bacteriostatic agents
The combination of these drugs has less side-effects
The combination has a long duration of action
The both drugs have nearly similar plasma half-life.

№2. The mechanism of a sulfonamides' action is:
Competitive antagonism with PABA
The inhibition of the synthesis of microorganisms' membrane
An increase in permeability of microorganisms' membranes
The inhibition of the synthesis of microorganisms' proteins
The blockade of the sulfhydric groups of enzymes.

№3. Drugs with antifungal activity belong to:
Sulfonamides
Polyenes
Imidazoles
Fluorquinolones
Allylamines.

№4. The correct statements concerning antifungals are:

Nystatin has a narrow spectrum of action
Amphotericin B is never used to treat systemic mycoses
Griseofulvin concentrates in the skin, hair, and nails
Itraconazole is antibiotic for the treatment of Candida infection only
Ketoconazole has 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 depression of DNA-gyrase. This drug influences negatively cartilaginous tissue. What drug was prescribed?

Sulfalene
Furozolidone
Ciprofloxacine
Nalidixic acid
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:

According to the type of action

- bactericidal
- bacteriostatic.

According to the spectrum of action

- antibiotics of a wide spectrum (with Gram (+) and Gram (-) coverage including Gram (-) bacilli)
- antibiotics of a narrow spectrum of action (with a limited list of microbes, Gram (+) and Gram (-) coverage without Gram (-) bacilli, only Gram (+), or only Gram (-) coverage).

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 practice according to some common rules concerning both microorganism and macroorganism. These rules (principles) are:

An early beginning of treatment

The choice of an antibiotic according to its spectrum of action

The choice of an antibiotic according to the sensitivity 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 after the normalization of a clinical status and body temperature

Allergic test at the start of treatment

Attention to the age, physiological status of the patient, concomitant diseases, the location and severity of infection.

COMMON ANTIBIOTICS SIDE-EFFECTS

Allergy, an anaphylactic shock. For prevention – an allergic test before the first administration of the drug

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 activation of Candida fungi. For prevention – to take antifungal drugs (nystatin, itraconazole) together with a wide spectrum antibiotics.

CLASSIFICATION

A. *Inhibitors of cell wall synthesis*
Penicillins
Cephalosporins
Carbapenems and monobactams
Glycopeptides
B. *Protein synthesis inhibitors acting on ribosomal subunits 30S*
Aminoglycosides
Tetracyclines
C. *Protein synthesis inhibitors acting on ribosomal subunits 50S*
Macrolides and azalides
Chloramphenicols
Lincosamides
D. *Antibiotics which disturb functions of nucleic acids* 1. Rifampicins
E. *Antibiotics which disturb the structure and functions of cell membranes*
Polyenes
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).

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 (benzylpenicillin, penicillin G)*
A short acting
– Benzylpenicillin sodium (penicillin G)
– Benzylpenicillin potassium
– Penicillin V
A long acting
– Penicillin G procaine

– Benzathine benzylpenicillin (Bicillin-1)
– Benzathine benzylpenicillin + benzylpenicillin procaine + Benzylpenicillin sodium (Bicillin-3)
– Benzathine benzylpenicillin + benzylpenicillin procaine (Bicillin-5)

B*. Semisynthetic penicillins*

A penicillinase resistant
– Oxacillin
A wide spectrum
– Ampicillin
– Amoxicillin
– Carbenicillin
Combined penicillins
– Ampiox
– Amoxiclav (Augmentin).

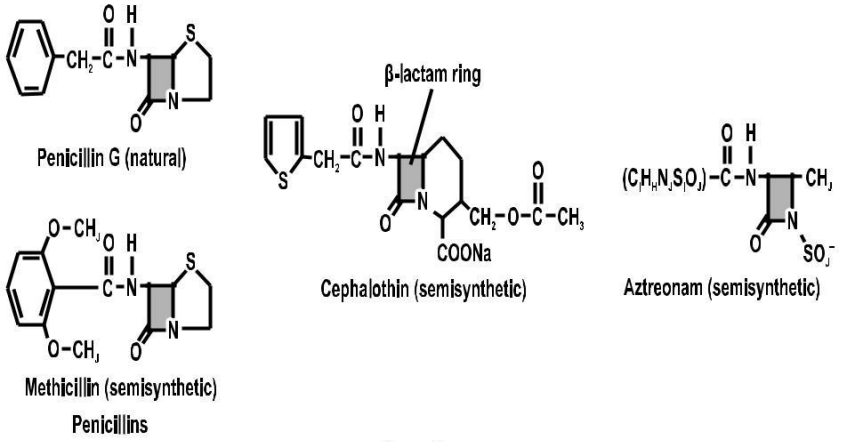

Fig. 31.1. Chemical structure of β-lactam antibiotics.

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.

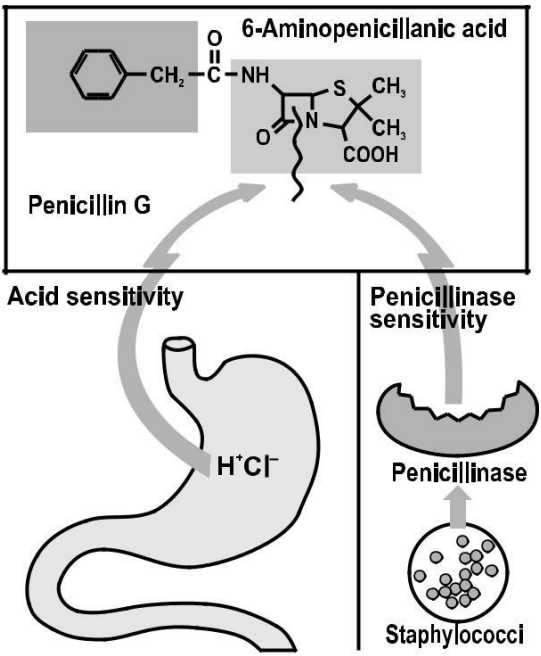

Fig. 31.2. Site of cleavage of penicillin by acid or by bacterial penicillinase *(by. H.Lüllmann, 2000)*.

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 in 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.

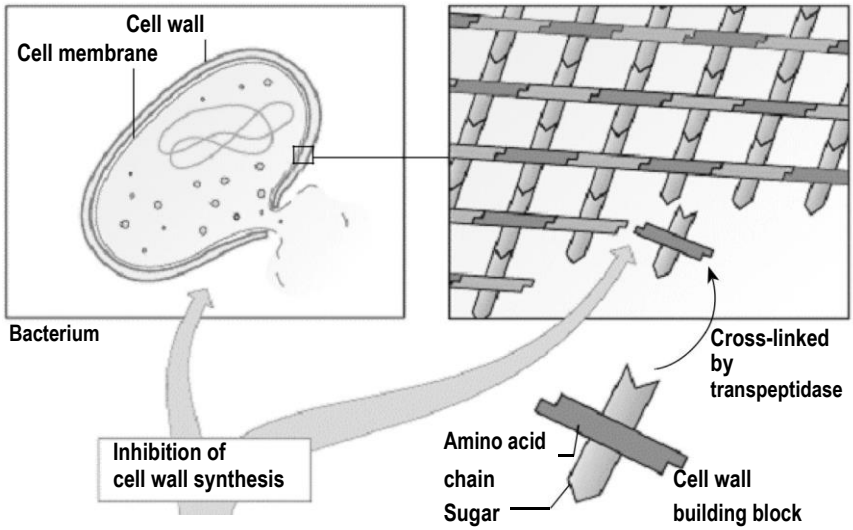

Fig. 31.3. Mechanism of bactericidal action of penicillins *(by H.Lüllmann, 2000)*.

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

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
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 toxic action of potassium on CNS and the heart.

Benzathine penicillin (Bicillin-1) is long-acting natural penicillin, has 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 long-acting natural penicillin containig benzylpenicilln sodium (or potassium), benzatine benzylpenicillin, and benzylpenicillin procaine in the equal amounts, has 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, 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 semisynthetic penicillin, is an 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 nu-merous strains that are now resistant to these agents - so-called methicillin-resistant staphylococci (MRSA).

Ampicillin is semisynthetic penicillin, is an 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 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 bacteræmia 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

The 1st generation

– Cefazolin (Kefzol)

– Cephaloridine
– Cephalexin

The 2nd generation
– Cefamandole
– Cefuroxime
– Cefaclor

The 3rd generation
– Cefotaxime
– Ceftriaxone
– Cefixime
– Cefazidime
– Cefoperazone

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 the 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

Allergy (there is some cross-sensitivity with the penicillins: 1-20% of patients exhibit sensitivity to both classes of antibiotics)
Dyspepsia
Renal disturbances (cephaloridine is the worst offender)
Changes in the blood film, the suppression of the bone marrow resulting in granulocytopenia (relatively rare)
A decrease in the prothrombin amount in blood
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 preven-tion 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 the 3rd generation cephalosporin; is administered IM 2-3 times a day, well penetrates CNS, tissues, and liquids of the body; is used in severe infec-tions of the respiratory and urinary pathways, sepsis, meningitis, osteomyelitis; is the antibiotic of choice in 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 inhib-iting 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 hypopro-thrombinemia and disulfiram-like reaction as side effects.

Cefpirome is highly effective against Gram-positive and Gram-negative 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 into 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, 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 actions 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 rarely, seizures in high doses (meropenem is less likely to cause seizures).

MONOBACTAMS

Aztreonam is an antibiotic from the monobactams group:

has the 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, in-hibiting 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) character-ised 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 spec-trum 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 peni-cillase 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.

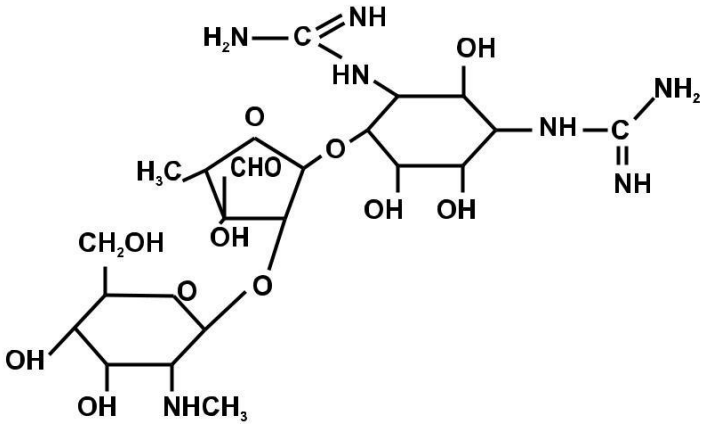

Fig. 31.4. Chemical structure of streptomycin.

CLASSIFICATION

The 1st generation
- *Streptomycin*
- *Neomycin*
- *Kanamycin*

The 2nd generation
- *Gentamycin*

The 3rd generation
- *Amikacyn.*

Pharmacokinetics

are not absorbed after 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).

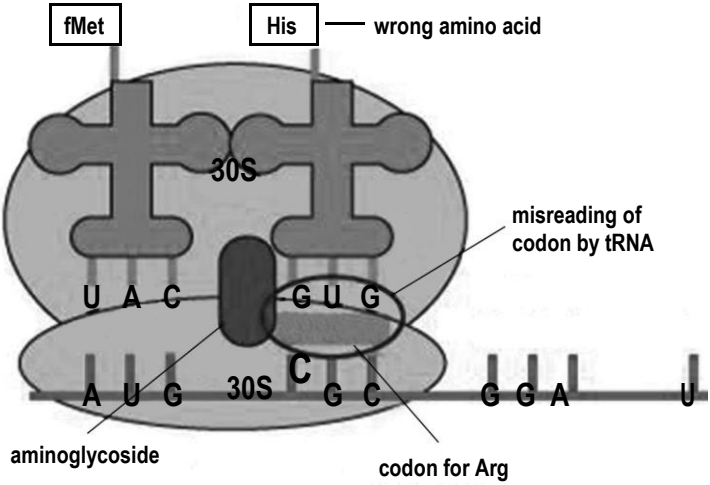

Fig. 31.5. Aminoglycosides' mechanism of action (http://www.picsearch.com).

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.
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 the 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, 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.

Peculiarities of preparations

Streptomycin is effective against the organisms which cause plague, tularemia and, in 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. S. *aureus*); because of its serious toxic effects, it is used topically to treat wounds. infected burns, 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, includ-ing *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 *M. tuberculosis* and is an alternative preparation in this disease.

Kanamycin has a more limited spectrum of activity than gentamycin. It is inef-fective against *Pseudomonas* and most Gram (-) organisms, but is active against *M. tuberculosis* and can be used as 2nd-line preparation in this disease.

Side-effects

Ototoxicity
Nephrotoxicity

Neurotoxic effects, including dysfunction of the optic nerve, neuromuscular junction blockade when an aminoglycoside is given at high doses or in combination with antidepolarizing drugs.

Allergic reactions.

TETRACYCLINES

Tetracyclines contain 4 heterocyclic rings in their molecules (fig.31.6).

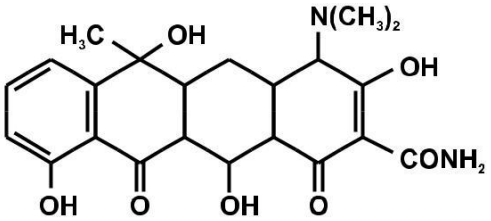

Fig. 31.6. Chemical structure of tetracyclines.

CLASSIFICATION

Natural
- Tetracycline

Semisynthetic
- 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)

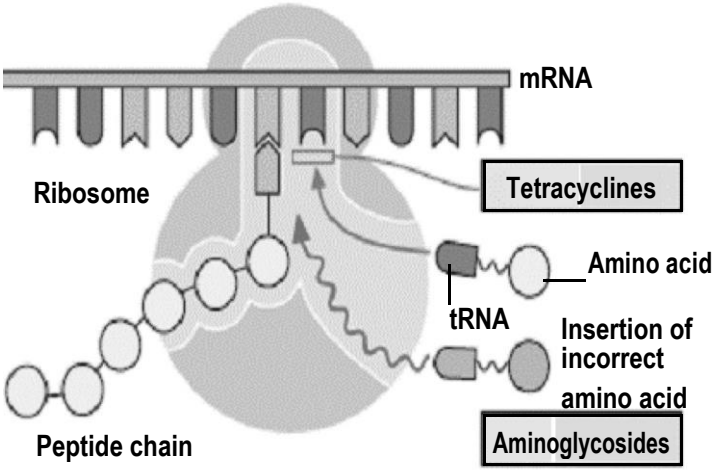

Fig. 31.7. Mechanism of action of tetracyclines in comparison with the mechanism of action of aminoglycosides *(by. H.Lüllmann, 2000)*.

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.

Spectrum of action

Tetracyclines are broad-spectrum antibiotics with activity against Gram (+) bac-teria (*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

Gastrointestinal disturbances
Hepatic dysfunction
Dermatitis, phototoxicity
Teratogenic action ("tetracycline teeth")
Yellow-brown discoloration of the teeth and depressed bone growth if tetracyclines are given to children
A pseudotumor of the brain
Dysbacteriasis and superinfection which can result in staphylococcal enterocolitis, candidiasis, and pseudomembranous colitis.
Stomatitis, gingivitis.

Contraindications

Diseases of the liver and kidney
Pregnancy
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, lymphoid tissue; is excreted with urine (40% of the dose).

CHLORAMPHENICOLS

CHLORAMPHENICOL

Levomycetin (Chloramphenicol) is a nitrobenzene derivative (fig.31.8).

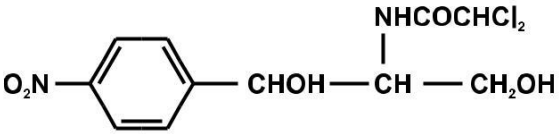

Fig. 31.8. Chemical structure of chloramphenicol.

Pharmacokinetics

is administered orally, applied topically (ointment, eye drops)
is absorbed rapidly from the GI tract
undergoes entero-hepatic cycling
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 peptide chain (fig. 31.9).
The drug is primarily bacteriostatic although it may be bactericidal to some strains.

Spectrum of action

Chloramphenicol has a wide spectrum of antimicrobial activity, including: many Gram (-) organisms*;* anaerobic organisms (*Bacteroides* species*); 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).

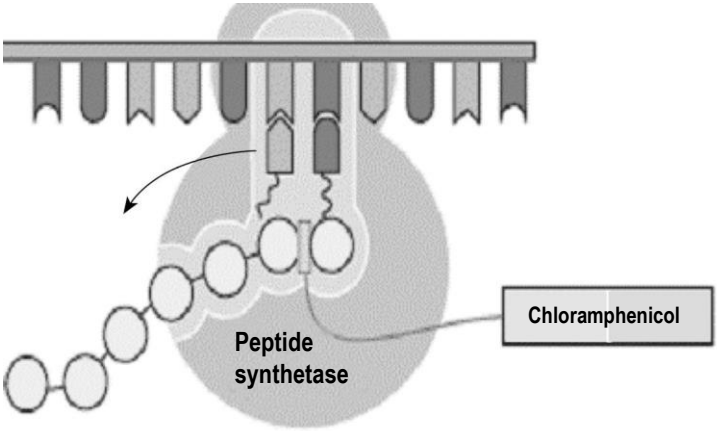

Fig. 31.9. Mechanism of action of chloramphenicol *(by. H.Lüllmann, 2000)*.

Side-effects

Allergic reactions
The inhibition of leukopoesis and erythropoesis
Superinfections including candidiasis and acute staphylococcal enterocolitis.
A gastrointestinal upset
The gray-baby syndrome (this condition is seen in neonates, especially premature infants, who have been given relatively large doses of chloram-phenicol. Cyanosis, respiratory irregularities, vasomotor collapse, abdominal distention, loose green stools, and an ashen-grey color characterize this often fatal syndrome. The condition develops because of the immature hepatic conjugating mechanism and the inadequate mechanism for renal excretion in neonates)
Endotoxic reactions.

MACROLIDES AND AZALIDES

Macrolides and azalides are the antibiotics that have a large lactone ring struc-ture. These may be 14- or 16-membered rings.

CLASSIFICATION

The 1st generation
- Erythromycin

The 2nd generation
- Azithromycin
- Clarithromycin
- Spiramycin.

ERYTHROMYCIN

Erythromycin is the first generation macrolide (fig. 31.10). It was the first drug in this family.

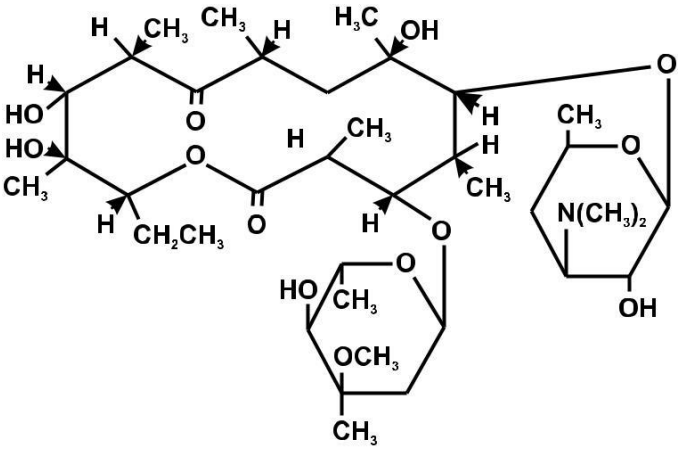

Fig. 31.10. Chemical structure of erythromycin.

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.
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.

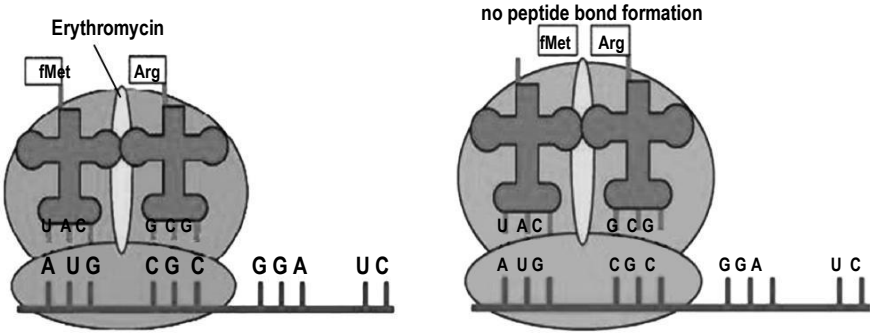

Fig. 31.11. Mechanism of action of erythromycin (http/www.picksearch.com).

Indications

Non-severe infections of the respiratory system, synusitis, otitis
Pneumonia due to *Mycoplasma*
Legionnaires' disease
Diphtheria
Urogenital infection due to *Ureaplasma*
Chlamidial infections
Syphilis
Acne.

Side-effects

Erythromycin has a very low incidence of serious side-effects:
Cholestatic hepatitis, jaundice
Epigastric distress
Ototoxicity (transient deafness).

Contraindications

1. The decreased liver function.

PECULIARITIES OF OTHER PREPARATIONS

Clarithromicin 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 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 gonor-rhoeae, 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, 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 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 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 is 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 P450 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 gonor-rhoeae, 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***.

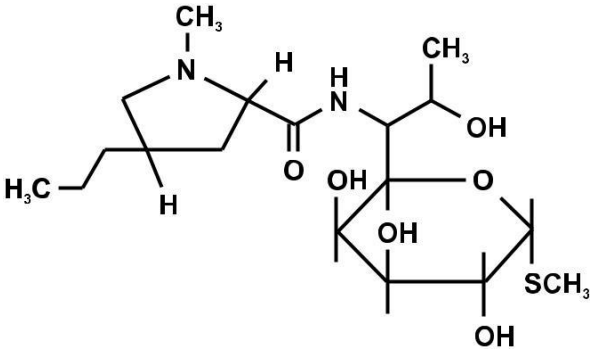

Fig. 31.12. Chemical structure of lincomycin.

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 the 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 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 (Rifampicinum) belongs to the group of complex macro cyclic antibiotics (fig. 31.13).

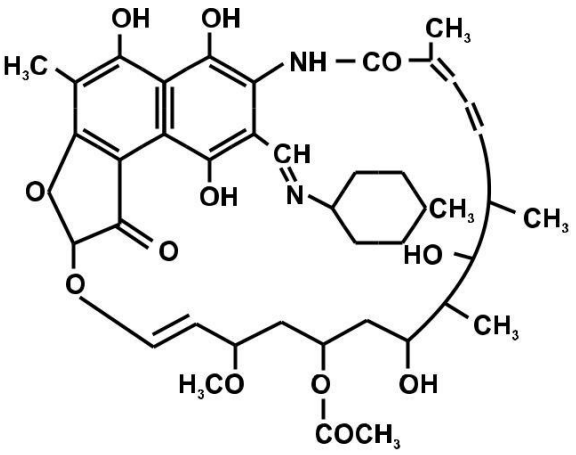

Fig. 31.13. Chemical structure of rifampin.

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).

Mechanism of action

It inhibits the RNA synthesis in bacteria and chlamydiae by binding to DNA-dependent-RNA polymerase (fig. 31.14).

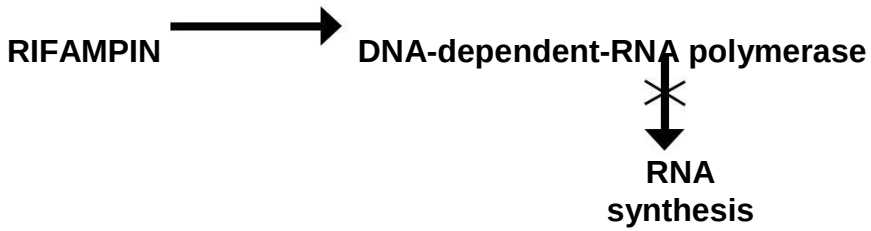

Fig. 31.14. Mechanism of action of rifampin.

Spectrum of action

Most Gram (+) and many Gram (-) microorganisms are sensitive 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 combination with other agents)
Atypical mycobacterial infections
Leprosy
Bacterial infections caused by sensitive microbes: pneumonia, cholecystitis, osteomyelitis, etc. (as an alternative antibiotic).

Side-effects

Red discoloration of urine, sweat, tears, and contact lenses
Proteinuria and impaired antibody response

Changes in the half-life of a number of co-administered drugs metabolized by cytochrome P-450 system

Rash

Gastrointestinal disturbances

Renal damage

Jaundice and severe hepatic dysfunction.

ANTIBIOTICS INFLUENCING STRUCTURE OF 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.

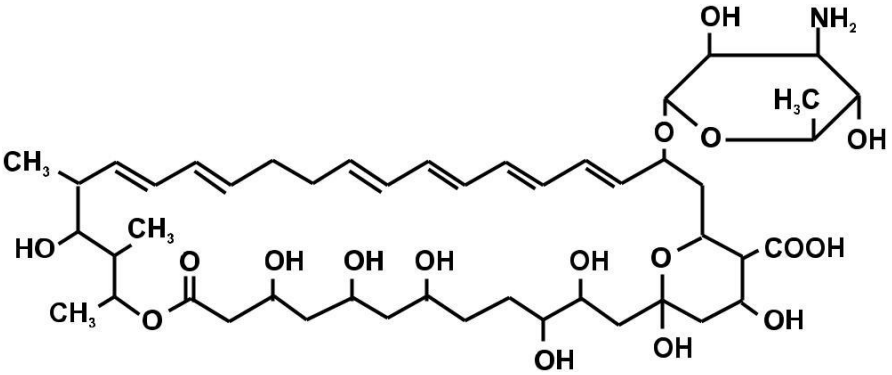

Fig. 31.15. Chemical structure of nystatin.

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 chemi-cal 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 infections of the skin, mucous membranes, and intestinal tract: thrush (oral candi-diasis) and vaginitis are treated by topical application, whereas intestinal candidiasis is treated by 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* species, *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 cell membrane.

The membrane lipid structure is distorted with an increase in permeability to polar molecules resulting in marked changes in cell metabolism.

Spectrum of action

The spectrum of action is narrow and includes Gram (-) bacteria (*P. aeruginosa, Salmonella, Shigella, Escherihia coli, Pasteurella, Brucella, Haemophilus influen-zae,* 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, 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:
Cefalexin
Cefasolin
C. Ceftriaxone
Cefaclor
E. Cefpirome.

№2. All the concerning the mechanism of action of penicillins is true, except:
They inhibit cell wall synthesis
They inhibit transpeptidase
They have a bactericidal action
They cause disturbances of the structure and function of the cell membrane
They act on microbes in the growth phase.

№3. Erythromycin is:
Destroyed by the gastric acid
Destroyed by intestinal enzymes
Entered the phagocytes
The crossing blood-brain barrier
Mainly excreted with bile.

№4. Tetracycline is stored in the body in:
The liver
Some malignant tumors
Hairs, nails, skin
Bones and dentition
Fat tissue.

№5. A 6-year old boy was admitted to 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.
Tetracycline
Azithromycin
Bicillin-5
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 a few stages from the primary tissue affect to the systemic disorders in CNS and other organs.

ANTISPIROCHETAL DRUGS

Drugs for the treatment of syphilis and other spirochetal infections are named ***antispirochetal drugs.***

CLASSIFICATION

A. *Antibiotics*

Basis antibiotics
- Benzylpenicillin sodium
- benzylpenicillin (Bicillin-1)
- Benzathine benzylpenicillin + benzylpenicillin (Bicillin-5)

Alternative antibiotics
- Cefaloridine
- Erythromycin
- Chloramphenicol (Levomycetin)

B. *Bismuth preparations*
- Bijochinol.

ANTISPIROCHETAL ANTIBIOTICS

Benzylpenicillin sodium is the inhibitor of the cell wall synthesis with short duration of action and a narrow spectrum. It is effective against *Treponema palidum* and used as the basis 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 the 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, 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 cell wall to many agents
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 eradi-cate 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 toxicity. The efficacy of the 2nd line preparations is lower, but they act on resistant strains of mycobacteria.

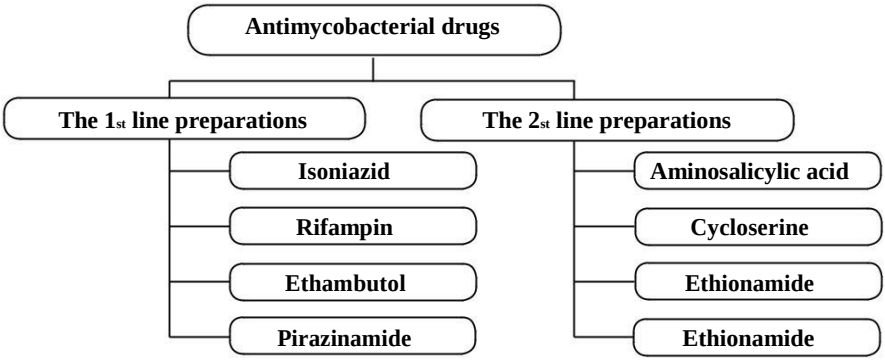

Fig. 32.1. Classification of antimycobacterial drugs according to their activity.

ISONIAZID (INH)

It is the hydrazide of the isonicotinic acid, a synthetic analog of pyridoxine (fig. 32.2). Isoniazid is the most potent anti-tubercular agent.

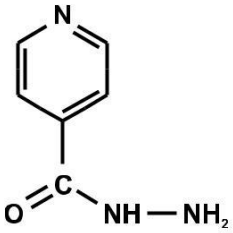

Fig. 32.2. Chemical structure of isoniazid.

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 an autosomal dominant (fig. 32.3)

is excreted with urine, parthialy with saliva, sputum, and milk.

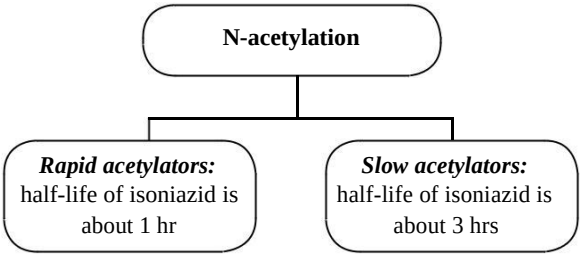

Fig. 32.3. Groups of patients according to speed of isoniazid's acetylation.

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

Hypersensitivity
Peripheral neuritis (paresthesia)
Mental abnormalities, psychotic episodes, euphoria, convulsions
Optic neuritis
Hepatitis

Neurological side-effects are due to 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 the DNA-dependent-RNA polymerase, suppresses the initiation step of transcription in procaryotes. It is bactericidal for both intracellular and extracellular my-cobacteria. Rifampin is the 1_{st} line preparation in tuberculosis and the most effective anti-leprosy drug. For detail information – see Chapter 31.

PYRAZINAMIDE

is a pyrazine analog of nicotinamide
is taken orally and widely disrtributed in the body, penetrates into 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 anti-tubercular 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 into CNS
is ethylenimine derivative, blocks nucleic acids synthesis and inhibits arabi- nozyl transferases involved in the synthesis of arabinogalactan, a component of the mycobacterial cell wall
is a bacteriostatic anti-tubercular agent
is the 1st line anti-tubercular 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 folate metabolism, is bacteriostatic, is taken in a high dose (10-15g per day) and causes many side-effects (dyspepsia, crystalluria, the enlargement of the thyroid gland), is used rarely.

Ethionamide is a structural analog 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 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 fluorquinolones, 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. They are small particles the main structure elements of which are the nucleic acid (DNA or RNA) and the protein coat (capsid), require the active participation of cell metabolism to survive.

A life cycle of virus consists of adsorption and penetration, uncoating, early protein synthesis, nucleic acid synthesis, assembly and budding (release of virions). Viruses have some specific enzymes which are the targets for antiviral drugs (reverse transcriptase, HIV-specific protease, DNA polymerase).

In the body there are natural antiviral substances interferons produced by immune competent cells.

ANTIVIRAL AGENTS

Antiviral drugs are preparations for the treatment of viral infections.

CLASSIFICATION

According to the mechanism of action

Inhibitors of attachment to host cell or penetration into host cell
- Amantadine
- Remantadine

Inhibitors of DNA polymerase
- Acyclovir
- Gancyclovir
- Famcyclovir
- Valacyclovir
- Vidarabine

Inhibitors of RNA-dependent RNA polymerase
- Ribavirin

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
   – Laferonum (IFN-α-2β)

According to the clinical usage

For influenza and respiratory virus infections
- Amantadine, Remantadine
- Ribavirin
- Zanamivir and other neuroaminidase inhibitors

For herpes and cytomegalovirus infection
- Acyclovir and other inhibitors of DNA polymerase

For HIV infection
- Zidovudine and other reverse transferase inhibitors
- Sanquinvir and other HIV protease inhibitors

Preparations with a wide antiviral spectrum
- Laferonum and other interferons

PREPARATIONS FOR TREATMENT OF INFLUENZA

REMANTADINE

It is a midantan derivative, structurally related to amantadine.

Pharmacokinetics

is taken orally
does not penetrate into CNS
is excreted by the cells of the epithelium of the upper respiratory pathways
is metabolized in the liver
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 release of new virions.

Spectrum of action

The virus of influenza A_2, the virus of encephalitis.

Indications

The treatment of influenza A_2
The prevention of influenza
The prophylaxis of epidemic encephalitis.

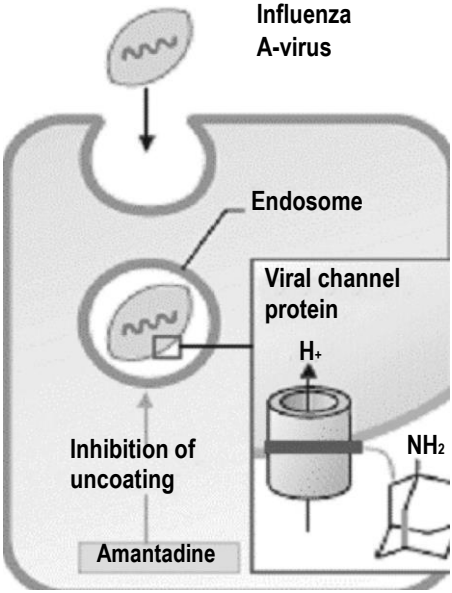

Fig. 32.4. Mechanism of action of midantan derivatives *(by H.Lüllmann, 2000)*.

Side-effects

Headache
Hallucinations
Ataxia
Disturbances of speesh
Insomnia
Confusion
Seizures.

PECULIARITIES OF OTHER DRUGS

Amantadine is structurally similar to remantadine, 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, pregnancy.

Zanamivir (Relenza) is 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 bioavail-ability, 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 a competitive inhibitor of influenza's neuraminidase and prevents new viral particles from being released. It is taken orally, has bioavail-ability over 80% and half-life about 1-3 hrs (for its active metabolite T1/2=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, haemorrhagic colitis and Stevens–Johnson syndrome.

PREPARATIONS FOR TREATMENT OF HERPES AND CYTOMEGALOVIRUS INFECTION

ACYCLOVIR

It is a synthetic purine nucleoside analog (acycloguanosine) (fig. 32.5).

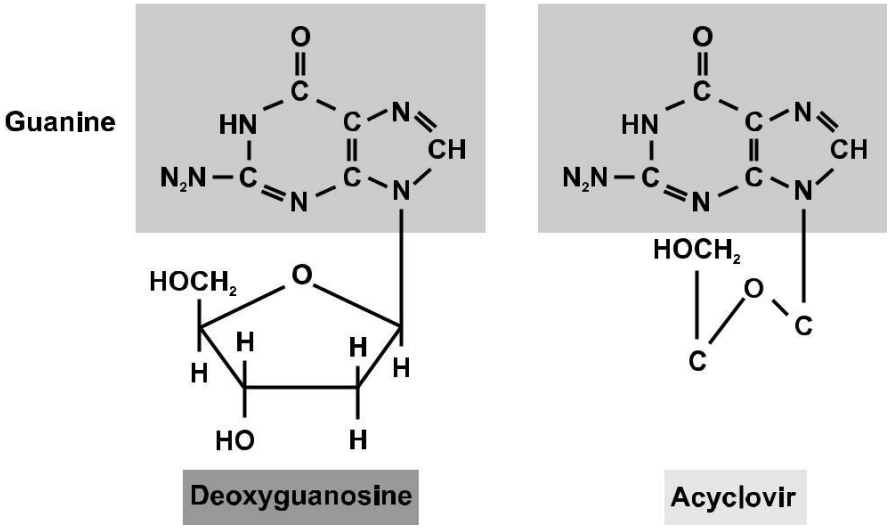

Fig. 32.5. Structural resemblance between acyclovir and guanine-containing nucleotide (http://www.picsearch.com).

Pharmacokinetics

is administered orally, IV, or topically
is widely distributed through the body
penetrates into CNS
is partially metabolized and excreted with urine.

Mechanism of action

Aciclovir transforms into triphosphate, interferes with the viral DNA polymerase and inhibits the viral DNA replication (fig. 32.6)
It is also incorporated into DNA and leads to premature chain termination
Acyclovir inhibits only actively replicating viruses.

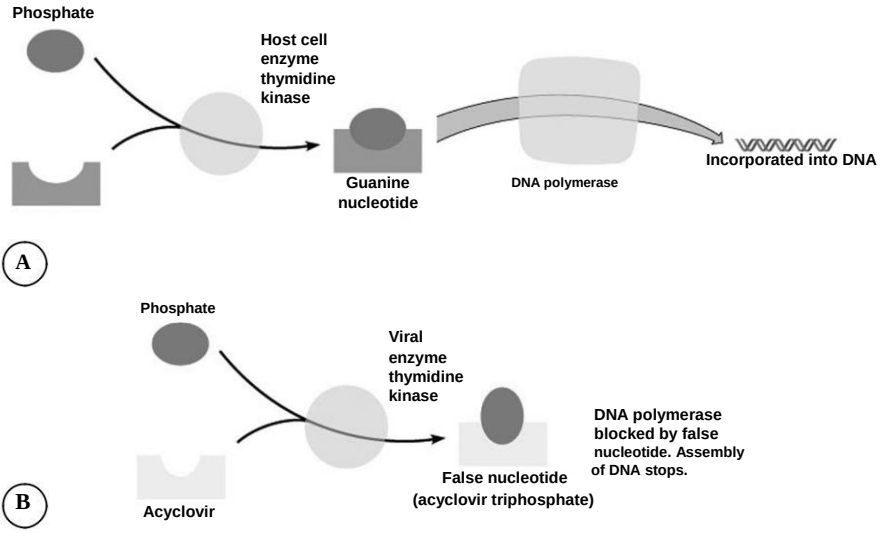

Fig.32.6. Mechanism of acyclovir's action: A – synthesis of normal viral DNA guanine nucleotide; B – synthesis of false viral DNA nucleotide with acyclovir (adapted from http://www.picsearch.com).

Spectrum of action

Herpes simplex virus types I and II, varicella-zoster virus, Epstein-Barr virus, cytomegalovirus.

Indications

Primary mucocutaneous herpes infection
Recurrent mucocutaneous herpes infection
Herpes genitalis
Herpes simplex encephalitis
Prophylaxis of herpes infection before and after tissue transplantation (in seropositive patients).

Side-effects

Local discomfort, itch (after the topical application)
Nausea, vomiting
Headache, encephalopathy (after IV administration)
Nephrotoxicity.

PECULIARITIES OF OTHER PREPARATIONS

Gancyclovir is a nucleoside analogue, blocks DNA-polymerase of cytomegalovirus, is used for the treatment of cytomegalic retinitis in immune suppressed patients.

Famcyclovir is an acyclic analogue of deoxyguanosine, is only used for the treatment of acute herpes zoster.

Valacyclovir is a prodrug converted to the active drug aciclovir via hepatic first-pass metabolism, has greater bioavailability than aciclovir. 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 the Epstein-Barr virus in subjects afflicted with acute mononucleosis), can prevent the establishment of viral latency.

Vidarabine (ara-A) is adenine arabinoside, is one of the most effective nucleoside analogues, is the least toxic, is used for the treatment of herpes infection and herpes zoster.

PREPARATIONS FOR TREATMENT OF VIRAL HEPATITIS

RIBAVIRIN

Ribavirin is an antiviral medication administered orally. is a prodrug.

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 muta-tions 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.

Indications

Ribavirin is used primarily to treat hepatitis C and viral hemorrhagic fevers. For hepatitis C ribavirin is used in 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.

Side effects

Feeling tired, headache, nausea, fever, muscle pains, and an irritable mood
Serious side effects include red blood cell breakdown, liver problems, and allergic reactions.
Use during pregnancy results in harm to the embrio and fetus. Effective birth control is recommended for both males and females for 7 months after use.

PREPARATIONS FOR TREATMENT OF HIV INFECTION

ZIDOVUDINE (AZT)

It is a nucleoside 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 analog 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

AIDS
The prophylaxis of HIV infection through accidental needle sticks

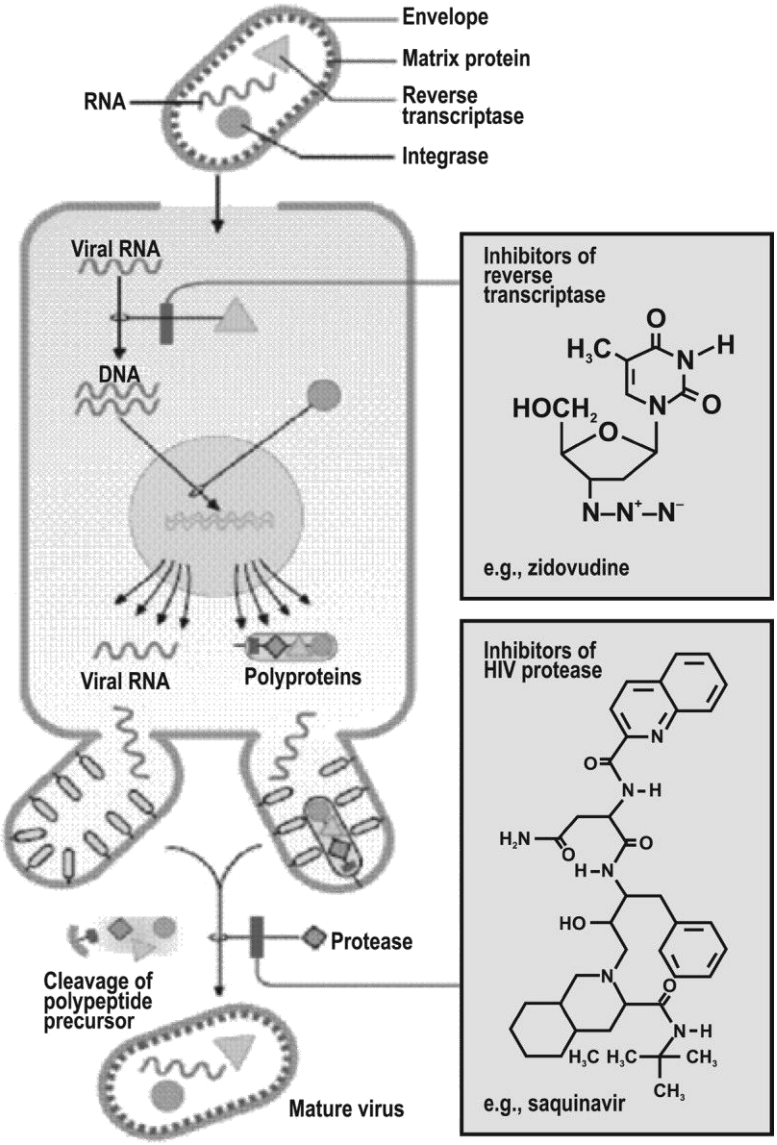

Fig. 32.7. Chemical structure and mechanism of action of NRTI and HIV protease inhibitors *(by H.Lüllmann, 2000)*.

The prevention of vertical HIV transmission from the mother to the neonate.

Side-effects

Anemia, neutropenia
GI distress
Headache, agitation, insomnia
Myalgia
Hepatitis and cholestasis.

PECULIARITIES OF OTHER NRTI

Didanosine is used for AZT-resistant HIV-infection.

Zalcitabine is used in a combination with AZT or as monotherapy in patients who can not tolerate AZT.

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.

AGENTS OF WIDE ANTIVIRAL SPECTRUM OF ACTION

INTERFERONS

They are glycoproteins produced by leukocytes (INF-α), fibroblasts (INF- β) and immune cells (INF-γ). Nowdays they are synthesized by recombinant DNA technology.

Mechanism of action

Interferons interact with receptors on host cell membrane and induce the formation of protein kinase that leads to phosphorilation and blockage of peptide chain initiation

They alsoinduce phosphodiesterase activation that leads to degradation of terminal nucleotides of tRNA.

Spectrum of action

Interferons have wide antiviral spectrum of action. They also have anti-cancer, anti-toxic, and immune stimulating properties.

Indications

INF-α is used to treat viral hepatitis A and B, Kaposi's sarcoma, papillomatosis, hairy cell leukemia.
INF- β is applied for treatment of multiple sclerosis.
INF-γ is used for chronic granulomatous disease.

Side effects

Fever
Lethargy
Bone marrow suppression
Heart failure
Hypersensitivity.

TESTS FOR SELF-CONTROL

№1. Bijochinolum:
Is a synthetic anti-tubercular drug
Is the basis antibiotic for treatment of syphilis
Is the bismuth preparation for the treatment of syphilis
Is administered orally
Is used only in syphylis.

№2. Antiviral agents that inhibit viral nucleic acid synthesis do not include:
Remantadine
Acyclovir
Gancyclovir
Famcyclovir
Vidarabine.

№3. Isoniazid:
Is highly effective against tuberculosis
Inhibits the synthesis of mycolic acids
Is the 2nd line preparation for the treatment of tuberculosis
Does not act on intracellular mycobacteria

E. Is less neurotoxic if given together with pyridoxine.

№4. Zidovudine has such properties as:
Inhibits HIV reverse transcriptase
Is taken orally
Can be used for the treatment of herpes and cytomegalovirus infection
Significantly reduces mortality and morbility from AIDS
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 anti-tubercular drug became the cause of such complications?
Isoniazid
Rifampin
Ethionamide
Streptomycin sulfate
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 vec-tor)*** (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:

> **Presumptive treatment.** Tests for malarial parasite should be done in all cases of fever, and presumptive treatment with the first full dose of chloro-quine should be administered. Chloroquine is highly effective as schizonti-cidal 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.

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

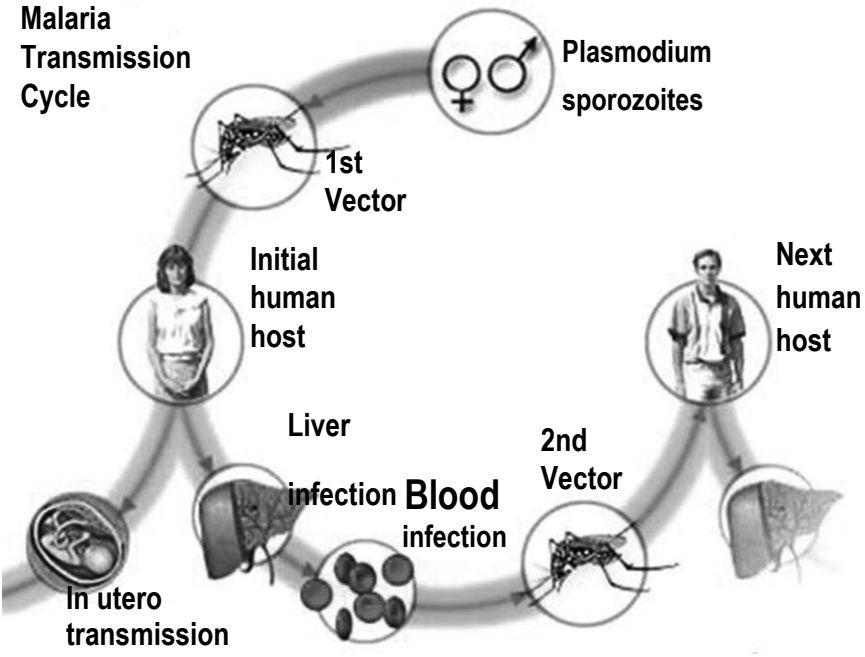

Fig. 33.1. Transmission cycle of malaria (http://www.picsearch.com).

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.

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.

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.

Chemoprophylaxis: Travelers to endemic areas and high risk individuals living in endemic areas (pregnant, elderly, 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

4-Aminoquinolines
- Chloroquine

Quinoline-methanols
- Quinine
- Mefloquine

8-Aminoquinolines
- Primaquine

Sulfonamides and sulfone
- Sulfadoxine
- Sulfamethopyrazine
- Dapsone (pyrimethamine + sulfonamide)

Diaminopyridines
- Pyrimethamine (Chloridinum)

Biguanides
- Chloroguanide (proguanil)

Hydroxynapthoquinone
- Atavaquone

Other preparations
- Halofantrine
- Artemisinin
- Fansidar.

According to the antimalarial action

Hemato-shizonticidal agents
- Quinoline-methanols
- 4-Aminoquinolines
- Sulfonamides and sulfone
- Hydroxynapthoquinone
- Diaminopyridines

Tissue-shizonticidal agents
- 8-Aminoquinolines

Gameticidic agents
- 4-Aminoquinolines
- 8-Aminoquinolines
- Diaminopyridines.

CHLOROQUINE

Choroquine is the most potent antimalarial agent, 4-aminoquinoline derivative (fig. 33.2).

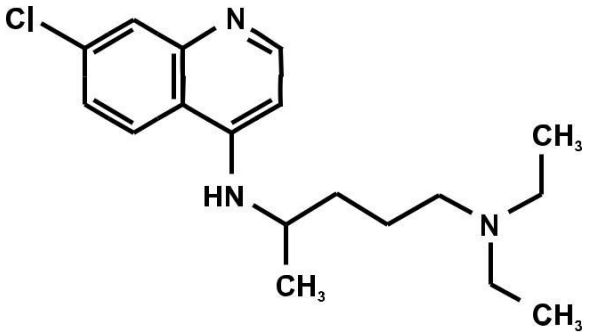

Fig. 33.2. Chemical structure of chloroquine.

Pharmacokinetics

is administered orally and IM

is rapidly and completely absorbed after 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).

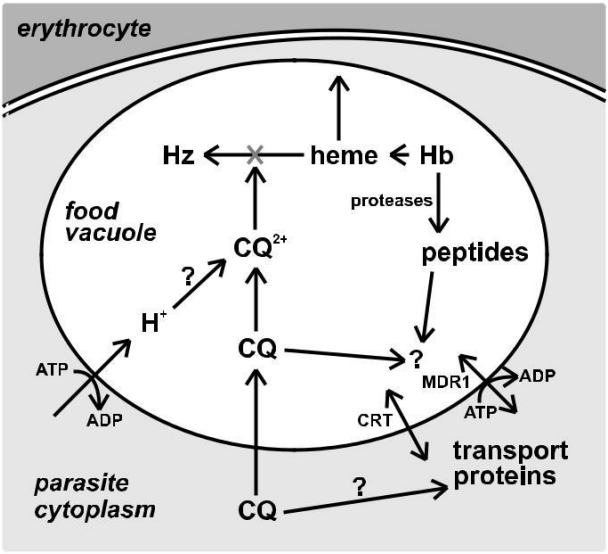

Fig. 33.3. Mechanism of action of chloroquine: CQ – chloroquine, Hb – hemoglobin, Hz – hemozoin (http://www.picsearch.com).

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.

Spectrum of action

Erythrocytic shizontes of *Plasmodium falciparum*, *Plasmodium vivax* (less ef-fective), gametocytes of *Plasmodium falciparum*, *Entamoeba histolytica*.

The drug also has an anti-inflammatory, weak cytostatic action, suppresses immunity, excerts anti-arrhythmic effect in the human body.

Indications

An acute attack of malaria
Malarial coma
The prevention of the spread of malaria
Individual chemoprophylaxis
Extra-intestinal amebiasis
Rheumatoid arthritis
Discoid lupus erythematosus.

Side-effects

A gastrointestinal upset
Headache
Skin rash, itch
Visual disturbances
Depigmentation of nails beds, hair, and mucous membranes
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 ***blood shizonticide***; realizes its action by complexes with double-stranded DNA to prevent strand separation resulting in 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 a M-cholinomimetic 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, vertigo, 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 ***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 anti-arrhythmics.

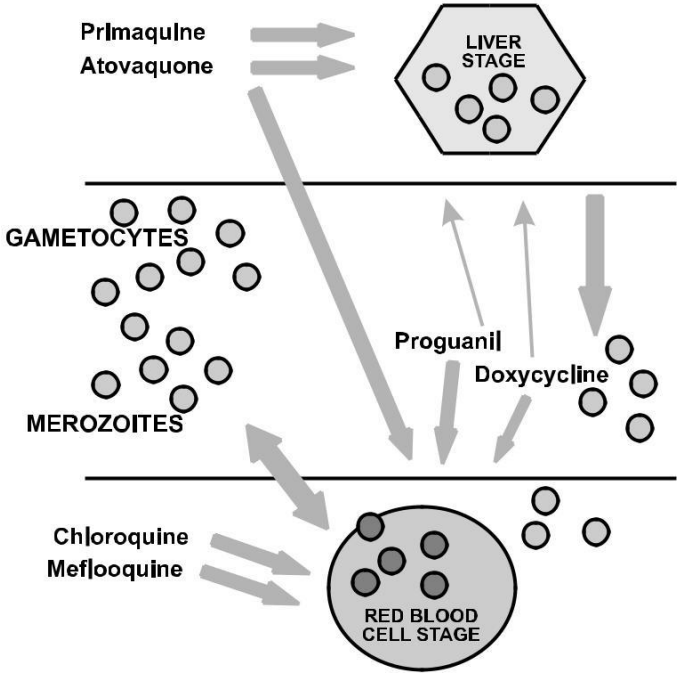

Fig. 33.4. Stages in the plasmodium life-cycle when antimalarial drugs act (http://www.picsearch.com).

Primaquine is a 8-aminoquinoline derivative; is administered orally, is well absorbed in the gut, rapidly oxidized, and excreted with urine; has the mechanism of action connected with an oxidative damage of 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; 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 in-ability 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 anlalogs of PABA and are converted into non-metabolizable adducts by DHPS. This leads to a 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 ***blood shizontocide and strong sporonticide*** in the mosquito's gut, is effective against *Plasmodium falciparum* in a combination with a 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 py-rimethamine. It violates the metabolismof folic acid in plasmodium, also is effec-tive 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, purpura), lethargy, headache, fever, polyneuritis, pulmonary infiltrates, cough, dyspnea, skin reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome).

Artemisinin and its semi-synthetic derivatives are a group of drugs used against Plasmodium falciparum malaria It was isolated from the plant Artemisia annua and 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 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 a 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 insti-tutions 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, the formation of trophozoites, the penetration of intestinal wall, the multiplication of trophozoites within the colon wall, excretion of cysts with feces. If amoebas enter the blood and travel to another organs, they cause systemic invasion.

CLASSIFICATION

Mixed amebicides (for all localizations)
- Metronidazole

Tissue amebicides
- Metronidazole

– Tinidazole
– Emetine hydrochloride
– Chloroquine

Luminal amebicides
– Iodoquinol
– Tetracyclines
– Diloxanide furoate
– Quiniodochlor.

METRONIDAZOLE

It is a nitroimidazole derivative (fig. 33.5).

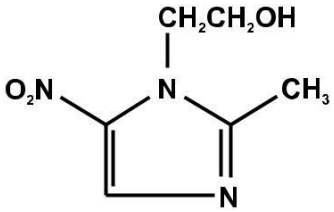

Fig. 33.5. Chemical structure of metronidazole.

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, 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)

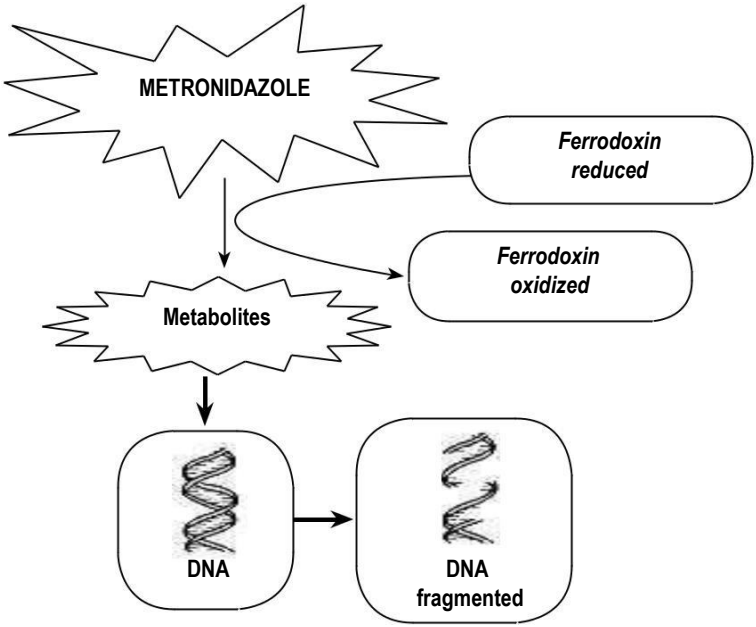

Fig. 33.6. Mechanism of action of metronidazole.

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 metroni-dazole 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 sensitive microbes (IV)
Respiratory infections, infections of the intestine and urinary pathways caused by sensitive microbes
Pseudomembranous colitis
Prophylaxis of anaerobic infection before 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

Red-brown discoloration of urine
Changes in pharmacokinetics of some other drugs (e.g.; ethyl alcohol, lithium salts).

Contraindications

1. Hemopoiesis disturbances
2. Organic lesions of 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 the alternative drug in the treatment of tissue amebiasais; is toxic and causes nausea, vomiting, cardiotoxicity, weakness, dizziness.

Diloxanide furoate is a luminal amebicide; is used to treat intestinal amebiasis; is well tolerated, but may cause flatulence, dry mouth, itch, 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 (urine canal) is the most common 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, gas.

Although most people will recover from giardiasis without treatment, medica-tions, 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, brain tissue, accumulates; binds to membrane phospholipids, blocks phospholipase A_2, disturbs functions of DNA, also binds to acetylcholine receptor; may cause diz-ziness, headache, vomiting, liver lesions, yellow pigmentation of the skin, psychosis.

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. When kids have symptoms, they vary depending on the child's age and the immune system's response to the infection.

Toxoplasmosis infections in people fall into three basic patterns:

congenital toxoplasmosis, in which a child becomes infected before birth; 2) toxo-plasmosis in otherwise healthy kids (with the same symptoms a pregnant woman may have); 3) toxoplasmosis in kids with weakened immune systems.

Toxoplasmosis is treated with ***pyrimethamine*** which is described as an antima-larial agent and its combinations with sulfonamides (***sulfadiasine***).

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

The drugs for the treatment of cutaneous leishmaniasis

- Quinacrine
- Metronidazole
- Monomycine
- Amphotericin B

The drugs for the treatment of visceral leishmaniasis
- Sodium stibogluconate
- Pentamidine.

SODIUM STIBOGLUCONATE

is the 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 inhibi-tion 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, 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:
Chloroquine
Primaquine
Quinine
Pyrimethamine
Mefloquine.

№2. The mechanism of the action of chloroquine is connected with:
The conversion of the nitro-group into the toxic anion radical
Blockade of SH-groups
Prevention of hemoglobin digestion
Disturbances in DNA reduplication
Folate antagonism.

№3. The indications for the use of metronidazole are:
All forms of malaria
All forms of amebiasis
Giardiasis
Trichomoniasis

E. Visceral leishmaniasis

№4. The correct statements concerning antiprotozoals are:
Quinine is used for the radical cure of malaria
Chloroquine is used for malaria and amebiasis
Metronidazole may cause disulfiram-like adverse reaction
Sodium stibogluconate is antimony compound for leishmaniasis
Sodium stibogluconate is a folate antagonist for toxoplasmosis.

№5. A patient with an acute attack of malaria was presctibed with an 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:
Pyrimethamine
Chloroquine
Quinine
Metronidazole
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 spe-cies 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).

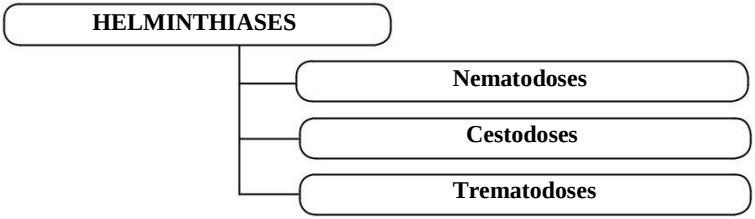

Fig. 34.1. Main classes of helminthiases.

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).

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

Drugs for treatment of nematodoses
a. For intestinal nematodoses
– Pyrantel pamoate
– Piperazine adipinate
– Levamisole
b. For extraintestinal nematodoses
– Diethylcarbamazine
– Ivermectin
Drugs for treatment of cestodoses
For intestinal cestodoses
– Niclosamide (Phenasal)
For extraintestinal cestodoses
– Albendazole
Drugs for treatment of trematodoses
For intestinal trematodoses
– Perchloroethylene
For extraintestinal trematodoses
– Praziquantel
– Chloxyl
Drugs of wide spectrum of action

– Praziquantel.
– Albendazole
– Mebendazole

MEBENDAZOLE

Mebendazole is a benzoimidazole derivative (fig. 34.2).

Pharmacokinetics

is taken orally
is poorly absorbed in the gut (10%); absorption is increased in the presence of fatty meals
is rapidly metabolized
is excreted with urine and bile within 24-48 hrs.

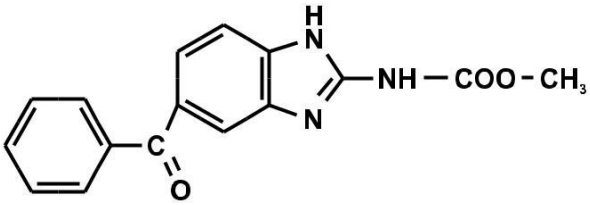

Fig. 34.2. Chemical structure of mebendazole.

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 a 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 microtu-bules. 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, cestodes (adult beef tapeworms (Taenia saginata), pork tapeworms (Taenia solium); cysticercosis caused by the larval form of the pork tapeworm; echinococcosis of the liver, lung, 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 ban-crofti or Brugia malayi; gnathostomiasis; hookworm infections, including cutaneous 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 bronchi, rarely dizziness, paraesthesias, vertigo, 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, leukopenia.

PYRANTEL

is taken orally, is poorly absorbed and acts in the gut
is the 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, 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 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 antihelmintic
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 haema-tobium, 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 different countries. Examples of naturally occur-ring 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 (*P. acutifolia or P. 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.

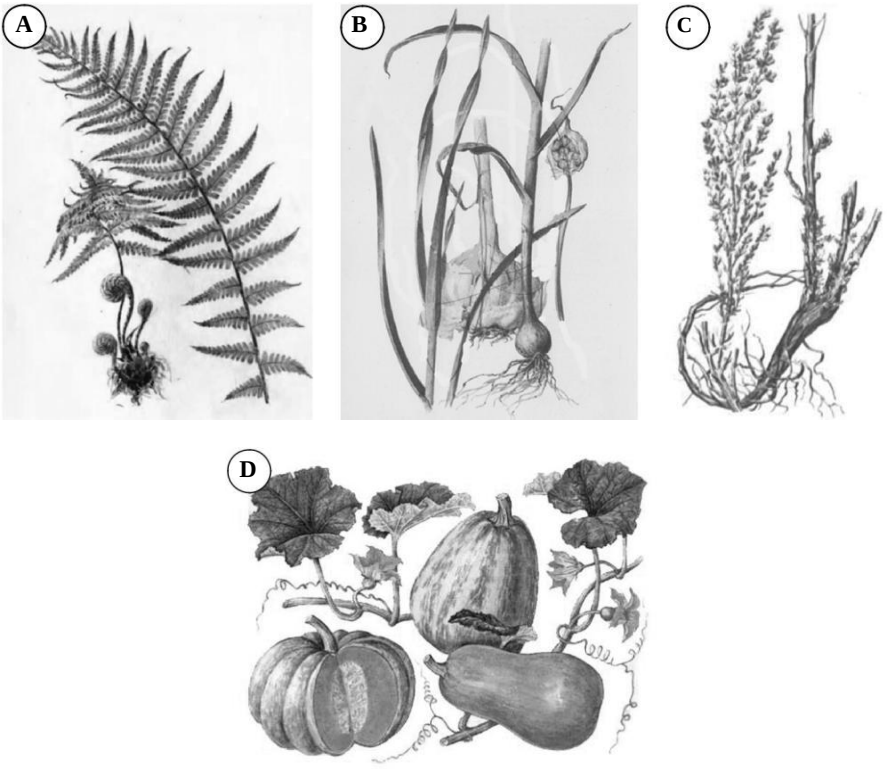

Fig. 34.3. Some medicinal plants used as antihelminthics: A – *Dryopteris filix-mas*; B – *Allium sativum*; C – *Arthemisia cina*; D – *Cucurbita pepa*.

TESTS FOR SELF-CONTROL

№1. All the listed drugs are antihelminthics, except:
Mebendazole
Metronidazole
Niclosamide
Pyrantel pamoate
Piperazine adipinate

№2. The antihelminthic affecting microtubular function in nematodes is:
Praziquantel
Niclosamide
Piperazine adipinate
Mebendazole
Ivermectin.

№3. The correct statements concerning the mechanisms of action of antihelminthics are:
Mebendazole disturbs parasite's microtubules and glucose uptake
Niclosamide causes paralysis of microfilariae
Pyrantel is depolarizing neuromuscular blocking agent for nematodes
Ivermectin interferes with receptors of parasite's chloride channels
Praziquantel stimulates GABA receptors in parasitic worms.

№4. The true indications for to the use of antihelminthics are:
Roundworm disease is treated by pyrantel pamoate or mebendazole
Pinworm disease is treated by niclosamide
Filariasis is treated by diethylcarbamazine
Tapeworm disease is treated by niclosamide
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?

Mebendazole
Pyrantel pamoate
Niclosamide
Piperazine
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 the 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, 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: a spasm of bronchi, pulmonary edema, a respiratory arrest, asphyxia

GI 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:

detoxication therapy (non-specific)
symptomatic therapy (non-specific)
antidote therapy (specific).

DETOXICATION THERAPY

The main purposes of detoxication therapy are to reduce poison absorption and to enhance the removal of poison.

For the reduction of absorption the following is used:

The irrigation of the skin and mucous membranes with cold water, an isotonic solution of sodium chloride, in some cases with special antidotes (e.g. a 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)

The lavage of the stomach with potassium permanganate (in poisoning with alkaloids), cold water (in poisoning with acids or alkalis), etc.

Emesis induced with apomorphine (parenterally), a solution of ammonia (dissolved in water, per os), or mechanically

The use of adsorbents (activated charcoal, enterosgel)

The use of astringents (tannin, milk, egg-white)

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:

Forced diuresis with furosemide or mannitol

The altering of urinary pH (alkalinization for acidic substances and acidification for alkaline drugs)

Peritoneal dialysis, hemodialysis, hemosorbtion
The use of osmotic purgatives (magnesium sulfate, sodium sulfate)
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)
Analeptics for the stimulation of respiration and an increase of the excretion of poison through the lungs (Carbogenum, 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 oxybutyrate (IV, IM)
– magnesium salts: magnesium sulfate (IV, IM).

– N-cholinergic agonists: Cytitonum (IV), 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), Carbogenum (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 anti-foam agents (vapor of ethanol).

– α- and α,β–adrenergic agonists: phenylepiphrine (IM, SC, or IV), noradrena-line 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

Sulfur containing compounds

– Dimercaprol (Unithiol)
– Sodium thiosulfate
– Acetylcysteine

Chelating agents

– Sodium edeteate (trilon B, EDTA–Natrium)
– Tetacin-calcium (Calcium-EDTA)
– Deferoxamine (desferral)
– Penicillamine

Cholinesterase reactivators

– Pralidoxim (PAM)
– Alloxim
– Dipiroxim
– Isonitrosine

Antagonists of opioids
- Naloxone
- Naltrexone

M-cholinoblockers
- Atropine sulfate

Anticholinesterases
- Neostigmine (Proserinum)

Preparations of other groups
- Cromosmonum (Methyleni coeruleum)
- Ethanol (Spiritus aethylicus)
- Potassium permanganate
- Activated charcoal (Carbo activatus).

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, dimercaptoprol)
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, the treatment of alcoholism
may cause nausea, tachycardia, dizziness, paleness.

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, 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 (paracethamol). In the last case it is used for the replacement of depleted essential substance (as glutathion substitute).

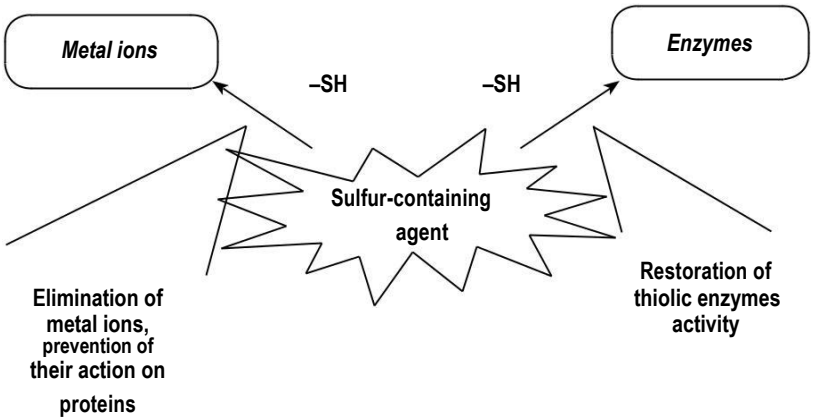

Fig. 35.1. Mechanism of action of sulfur-containing drugs.

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.

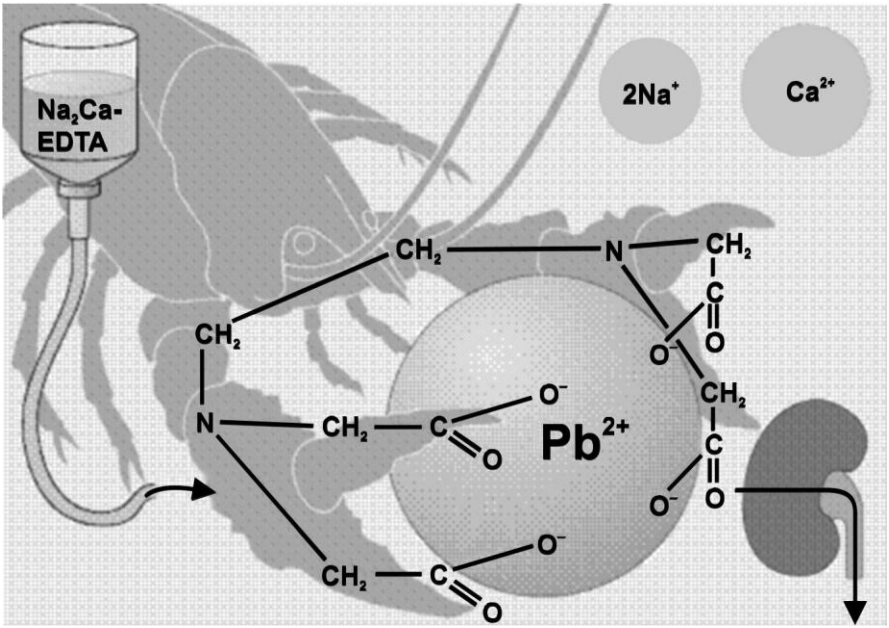

Fig. 35.2. Mechanism of action of chelators *(by H. Lüllmann, 2000)*.

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, yttrium
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, 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, gastrointestinal disturbances.

DEFEROXAMINE

is administered IM, IV, orally, or used for the lavage of the stomach
binds to free ions of iron and to iron from ferrous-containing proteins (fer-ritin 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, hemo-chomatosis, hemosiderosis
may cause skin rash, collapse (after a quick IV injection).

CHOLINESTERASE REACTIVATORS

Cholinesterase reactivators (alloxim, dipiroxim, isonitroside, 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.

METHYLENE BLUE

is an antiseptic with the properties of a donator and acceptor of hydrogen
is administered IV in the form of sterile solution (**Chromosmonum**)
is used for the treatment of acute poisonings with cyanides, carbon oxide, hydrogen sulfide. Under the conditions of cyanide poisoning Methylenum coeruleum 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 methy-laldehyde forming.

POTASSIUM PERMANGANATE

is an antiseptic from oxidazers group
is an antidote in poisonings with morphine, some alkaloids, and phosphor
is used for the 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 intoxi-cation 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 lungs, convulsions, unconsciousness.

Emergency help:

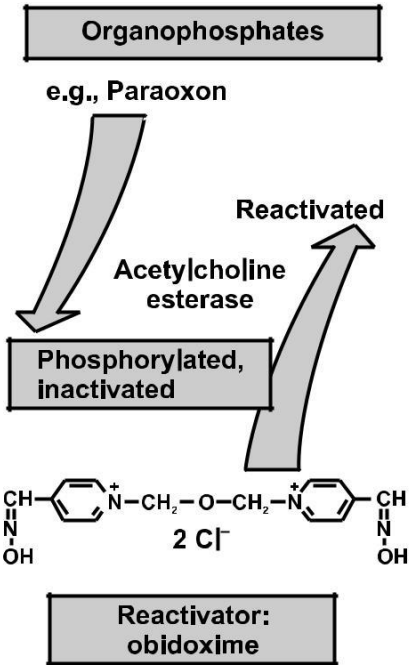

Fig. 35.3. Reactivation of acetylcholine esterase with obidoxime *(by H. Lüllmann, 2000)*.

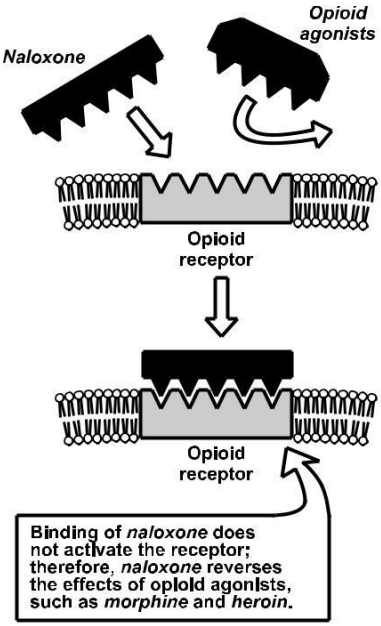

Fig. 35.4. Competition between morphine and naloxone *(by R. Finkel et al., 2000)*.

Reactivators of cholinesterase (dipyroxim, alloxim, izonitrozin), IM
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; hypotermia; involuntary urination and defecation.

Emergency help:

Lavage of the stomach with the solution of potassium permanganate
Analeptics (bemegride)
Glucose, insulin, and vitamins preparations (IV)
Nootrops (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, a spasm of the intestine and bowel.

Emergency help:

The lavage of the stomach with 0,5% solution of potassium permanganate
Naloxone, IV (an antagonist of narcotic analgesics)
Atropine (for a decrease in the vagal action of morphine).

Acute poisoning with cardiac glycosides

Signs:

bradycardia, then tachycardia and arrhythmia (premature ventricular beats, fibr-tillation); changes in ECG; an increase in signs of CHF; anorexia, vomiting, nausea; headache, fatigue, hallucination; vision disturbances (xantopsia, micro- and macropsia).

Emergency help:

The abolishing of cardiac glycoside
Drugs containing potassium (potassium chloride, panangin)
SH-group donator (dimercaprol, or unithiol)
Anti-arrhythmic agents (phenitoin, lidocaine, propranolol, an atropine for AV block)
Digoxin antibodies (digibind)
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:

The lavage of the stomach
The alkalinization of urine and forced diuresis
Hemodialysis
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:

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

The lavage of the stomach with cold water

The administration of covering drugs, astringents, and local anesthetics into the stomach

In poisoning with acids – sodium bicarbonate (IV) for the correction of metabolic acidosis

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, irritateability, irritability.

Emergency help:

The lavage of the stomach

The administration of activated charcoal and astringents in the stomach

Dimercaprol (unithiol), tetacin-calcium, or sodium thiosulfate

Atropine for a decrease in a spasm of the GI tract

Morphine

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 is, its fatal and nonfatal effects, includ-ing 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 off the body.

CLASSIFICATION

Thiols and other SH-containing compounds
- – Cysteine
- – Cystamine
- – 2-mercaptoethylguanidine
- – Thiourea
- – Thiouracil
- – Dithiocarbamate

Indolalkylamines:
- – Tryptamin
- – Serotonin
- – Mexamine

Arylalkylamines
- – Epinephrine
- – Norepinephrine
- – Dopamine

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, 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; well penetrates into vari-ous 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, 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
Potassium permanganate is used for the lavage of the stomach
Apomorphine is an ideal emetic in poisonings with acids and alkalis
Specific antidotes are not available for all poisons.

2. Deferoxamine is:
A. A sulfur-containing compound
B. An acetylcholine esterase reactivator
A chelating agent used in poisoning with ferrous compounds
An antidote in mercury poisoning
A drug for the treatment of hepatocerebral dystrophy.

3. The treatment of mercury poisoning includes:
A. Deferoxamine
B. Unithiolum C.
Penicillinamine D.
Atropine
E. Hemodialysis.

№4. Forcsed diuresis is:
A. Specific antidote therapy
B. Realized by the hydratation and further administration of furosemide
Non-specific detoxication therapy
Used to hasten the elimination of poison from blood through the kidney
Realized by the dehydratation and use of potassium-sparing diuretics.

№5. A patient with symptoms of the phosphororganic poisoning was admited to the emergency department. Which combination of drugs must be used as fist aid?

A. Naloxone and atropine

Unithiolum and potassium chloride

C. Neostigmine and chlorpromazine D.

Unithiolum 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 comma.

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 taking 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 (inside, a gargle, for injections and 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 prescrip-tion is made with the help of *"Repetatur!"*

Prescribing poison or drastic substance in the dose which exceeds the maximum one a doctor must write out a dose of this substance in words and put an exclama-tion 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 prescrip-tion is written out as a special form. For the majority of medicinal forms we use "Form №1" (fig. 36.1). Form №2 is for the prescribing of drugs which are free of charge. Form №3 is for narcotic and poisonous drugs.

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 drug and are dosed by patient. Dosed medicinal forms are divided into non-liquid (solid), liquid, soft, and sterile forms (fig. 36.2). 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. 36.3). The positive qualities are: stability, a convenient tak-ing, the exactness of closage, protection from the action of destroying enzymes for some forms. For dragee, it is an opportunity of incompatible medicinal substances' combinations. The defects are: a slow action, the impossibility to prescribe to little children, to patients in faint state, etc.

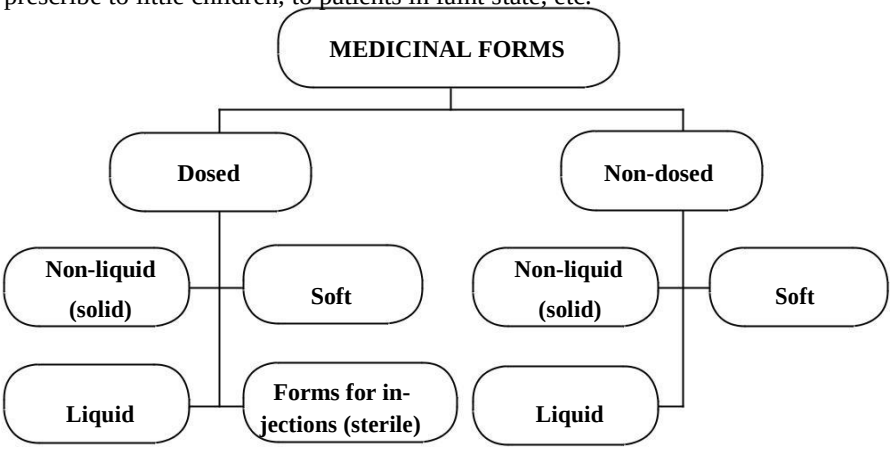

Fig. 36.2. Classification of medicinal forms.

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 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

Hospital...	Code of establishment	

Medical documentation. Form F1

PRESCRIPTION
(adult, children's – underline that's necessary)
"____" _____ 2009

_____
(Patient's family-name, initials and age)

_____
(Physician's family -name and initials)

Gr.	Cop.	Rp.:
Gr.	Cop.	Rp.:
Gr.	Cop.	Rp.:

_____.
(Physician's signature and stamp)
Prescription is real during 10 days, 1 month – underline that's necessary

Fig. 36.1. Form №1 for prescribing of most of drugs.

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. 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.

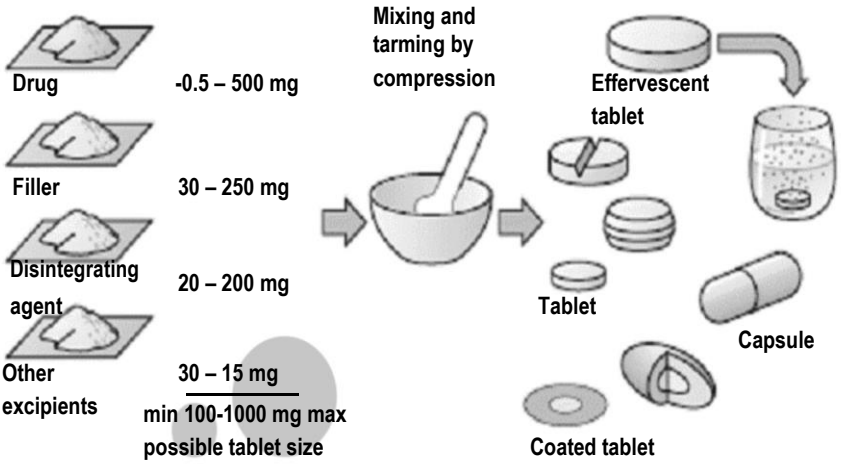

Fig. 36.3. Non-liquid (solid) medicinal forms *(by H. Lüllmann, 2000)*.

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:

Powder *(pulvis)*

1. A simple powder 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. A powder with a weight less than 0,1 (Sugar should be added in the 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.

#

Capsule *(capsula)*

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.

Tablet *(tabuletta)*

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 *(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 a faint state (in the state of uncon-

sciousness). The negative qualities are: pain, the necessity of sterility, the possibility of vessel damage, the transmission of infection, etc.

For injections, drugs are often given as solutions and, less frequently, in crystalline suspension for IM and SC injection. An 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. 36.4; 36.5).

From ampoules and flacons the solution is aspirated via a needle into a syringe (fig. 36.4). 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. 36.4).

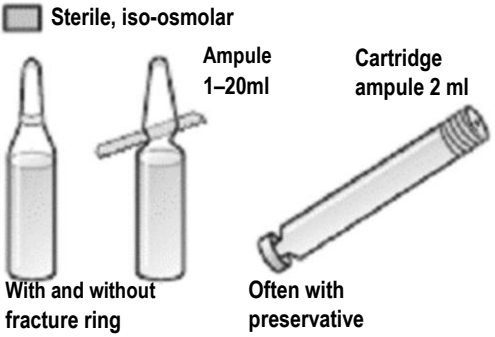

Fig. 36.4. Ampoules with sterile medicinal forms *(by H. Lüllmann, 2000)*.

An infusion refers to a 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 for one occasion has its packing (an ampoule), in *Subscriptio* after the amount of doses *"in ampullis"(in ampull.)* is written.

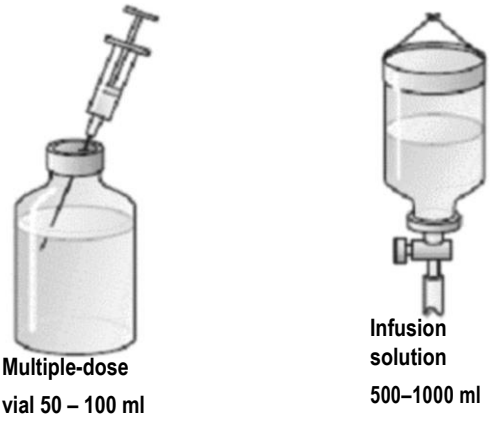

Fig. 36.5. Flacons containing sterile solutions *(adapted from H. Lüllmann, 2000)*.

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 bottles):

Ampoule *(ampulla)*

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.

Bottle *(flacon)*

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. 36.6). 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 tem-perature, 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 is used and the method of a single dose. 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, are written the name of *Basis* and *Adjuvans*, their doses, then *–"Olei Cacao 3,0"*. In subscription it should be indicated: *"Misce ut fiat suppositorium rectale. Da tales doses numero 10."*

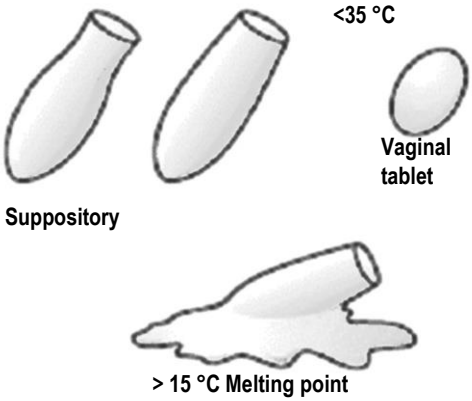

Fig. 36.6. Suppositories as soft dosed medicinal form *(by H. Lüllmann, 2000)*.

Prescribing of ***vaginal suppositories*** is similar and differs in the dose of *Ol. Cacao* (4,0) and the indication *"in 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. (supposi-torium vaginale), M. f. supp. rect. (Misce ut fiat suppositorium rectale), M. f. supp. vagin. (Misce ut fiat suppositorium vaginale).*

Examples of suppositories prescribing:

Rectal suppository
(suppositorium rectale)

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.

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 suppository
(suppositorium vaginale)

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.

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.

#

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 sucked and act quicker; 2) they are convenient for children; 3) they are suitable for prescribing hygroscopic substances. The disadvantages are: less portability, unsteadiness, 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 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. 36.7).

All liquid medicinal forms which are prescribed for taking inside and are measu- red by spoons are only prepared with distilled water.

Solution is a liquid dosed medicinal form that consists of a solvent and a soluble 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 des- sertspoon – 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 dis-solved 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 prepared from poisonous or drastic substances and 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.

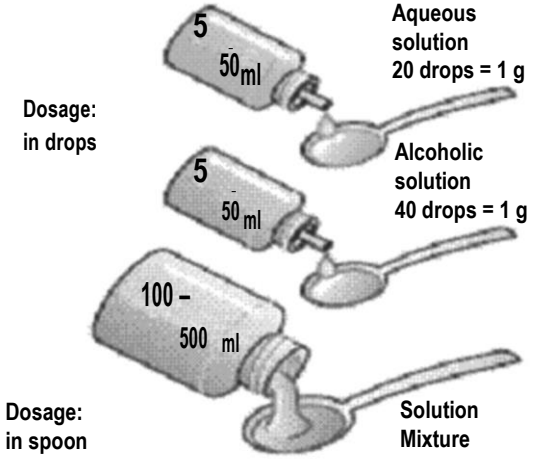

Fig. 36.7. Dosage of liquid medicinal forms for taking inside *(adapted from H. Lüllmann, 2000)*.

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 cal-culated 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, mixings of 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 preparations 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, for example magnesium sulfate, bismuth, etc. ***Potion*** is liquid dosed medicinal form, which includes pharmacologically active substances, water and various syrups. In fact, these are sweetened mixtures. ***Lemonade*** is a sweet or acidified liquid for internal use. ***Elixir*** is transparent, aromatic, pleasant liquid taste, 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 nitro-gen-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 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 spray, modern medicinal form of industrial manufacture for inhalation (dosed aerosol) or external use (non-dosed aerosol). As a rule, al above mentioned forms are prescribed in the short form.

Main abbreviations: *Sol.(solutio), inf. (infusio), dec.(decoctio), tinct. (tinctura), extr.(extractum).*

Examples of prescribing of liquid dosed medicinal forms:

Solution *(solutio)*

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% – 10ml
D. S. Take 5 drops 2 times a day.
#

Infusion *(infusio*)
or decoction *(decoctio)*

Rp. Dec. cort. Quercus 10,0 – 200 ml
D. S. Take 1 tablespoon 2 times a day.
#

Tincture *(tinctura)*

Rp.: Tinct. Valerianae 30 ml
D. S.Take 30 drops 3 times daily.
#

Liquid extract
(extractum fluidum)

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 – 180ml
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 ear or a nose, infusions, decoctions, tinctures, liquid extracts and mixtures for external use), ***soft*** (ointments, liniments, pastes, plasters, applicitions, poultices).

The powder for external use is a very fine powder *(Pulvis subtillissimus)*, 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 pre-scribed 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 abbrevia-tion *"Steril.!"*(fig. 36.8).

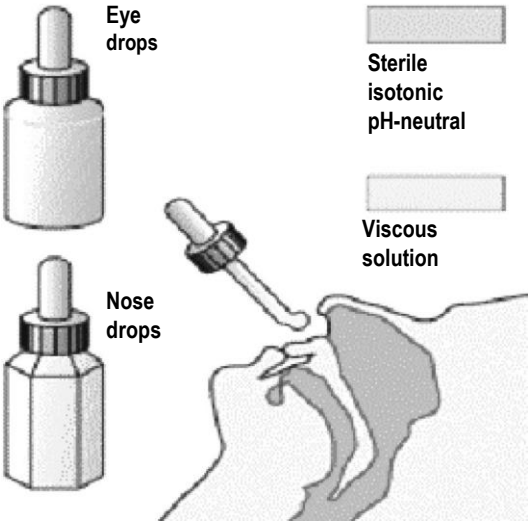

Fig. 36.8. Eye drops and nasal drops as liquid non-dosed medicinal forms *(by H. Lüllmann, 2000).*

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 the dry me-dicinal 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. 36.9). Ointment basis is represented by different lipids *(Vaselinum, Lanolinum, Adeps suilis depuratus, etc.)*. Ointments may be prescribed in a short and full forms. 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. 36.9). To form paste such inert substances as *Talcum, Zinci oxydum,* etc. are added to medicinal substances and ointment basis.

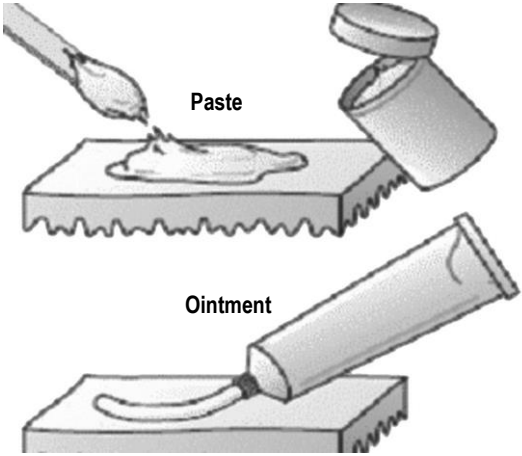

Fig. 36.9. Soft non-dosed medicinal forms *(adapted from H. Lüllmann, 2000)*.

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 soft medicinal form, made as plastic mass, which is capable of soften-ing 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 officinal 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 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. (subtillissimus), 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 *(aspersio)*

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 the 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% – 10ml
D. S. For the processing of small
cuts of the skin.

#

Infusion and decoction for external use

Rp.: Dec. cort. Quercus 200ml
D. S. For gargling.

#

Tincture and liquid extract

Rp.: Tinct. Calendulae 50ml
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 *(unguentum)*

Rp.: Ung. Prednisoloni 1% – 10,0
D. S. Apply on the skin.

#

Rp.: Ung. “Synalar”10,0
D. S. Apply on the skin.

#

Liniment *(linimentum)*

Rp.: Lin. Synthomycini 10% – 50,0
D. S. Apply on the wound.

#

Paste *(pasta)*

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:
Powders of Thyreoidinum (0,02). Take 1 powder 3 times a day.
Tablets of Pentoxylum (0,2). Take 1 tablet 3 times daily.
Tablets “Ascorutinum”. Take 1 tablet twice a day.
Capsules of Celecoxibum (0,1.). Take 1 capsule 3 times daily.

Dragee of Aminazinum (0,025). Take 1 dragee 2 times a day.
5% solution of Natrii salicylas for internal use. Take 1 tablespoon 3 times a day.
4 % solution of Dibazolum as drops for internal use. Take 10 drops 2 times a day.
Tincture of Arnica. Take 30 drops 3 times daily.
Ampoules each containing 1 ml of 50% solution of. Analginum. Administer IM.

10. Flacons each containing Insulinum in a dose of 5 ml (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 the 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.

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