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ANTICHOLINERGIC BURDEN IN AGING PATIENTS AND ITS ROLE IN THE DEVELOPMENT OF BLADDER DECOMPENSATION

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Anticholinergic load is considered as a cumulative effect of medicine with anticholinergic activity. The article presents data of the role of anticholinergic load in the development of bladder decompensation in patients with benign prostatic hyperplasia. 381 patients with benign prostatic hyperplasia in the stage of subcompensation and decompensation of the bladder were examined. Anticholinergic load in elderly patients can develop both as a result of taking drugs with high potential anticholinergic activity and as a result of long-term use of drugs with low potential anticholinergic activity. Medicine with high potential anticholinergic activity reduce the symptoms of overactive bladder in patients with benign prostatic hyperplasia, but anticholinergic load becomes a deepening factor in the decompensation of bladder, which worsens the results of surgical treatment.

Key words: benign prostatic hyperplasia, anticholinergic load, low-potential anticholinergic activity, high-potential anticholinergic activity, bladder decompensation.

Г.Л. Пустовойт, Л.П. Саричев, Р.Б. Савченко, Я.В. Саричев, Р.Л. Устенко, С.А. Сухомлин АНТИХОЛІНЕРГІЧНЕ НАВАНТАЖЕННЯ У СТАРІЮЧИХ ПАЦІЄНТІВ ТА ЙОГО РОЛЬ У РОЗВИТКУ ДЕКОМПЕНСАЦІЇ СЕЧОВОГО МІХУРА

Антихолінергічне навантаження розглядають як кумулятивний ефект від прийому препаратів з антихолінергічною активністю. У статті наведено дані про роль антихолінергічного навантаження в розвитку декомпенсації сечового міхура у хворих на доброякісну гіперплазію передміхурової залози. Обстежено 381 пацієнтів із доброякісною гіперплазією передміхурової залози в стадії субкомпенсації та декомпенсації сечового міхура. Антихолінергічне навантаження у пацієнтів літнього віку може розвиватися як в результаті прийому препаратів з високою потенційною антихолінергічною активністю, так і в результаті тривалого застосування препаратів з низькою потенційною антихолінергічною активністю. Препарати з високою потенційною антихолінергічною активністю зменшують симптоми гіперактивного сечового міхура у пацієнтів з доброякісною гіперплазією передміхурової залози, але антихолінергічне навантаження стає фактором поглиблення декомпенсації сечового міхура, що погіршує результати хірургічного лікування.

Ключові слова: доброякісна гіперплазія передміхурової залози, антихолінергічне навантаження, низькопотенційна антихолінергічна активність, високопотенційна антихолінергічна активність, декомпенсація сечового міхура.

The work is a fragment of the research project "Clinical and pathogenetic characteristics of urinary tract remodeling in the elderly and senile people", state registration No. 0120U104459.

At untimely elimination of an obstructive component at patients with a benign prostatic hyperplasia (BPH) remodeling of a urinary bladder passes a stage of compensation which demonstrates prostatic symptoms accompanied with overactive bladder (OAB) in a subcompensation stage, and the stage of decompensation, which is accompanied by an increase in the volume of post void residual (PVR), the development of ureterohydronephrosis, recurrent urinary tract infection, stone formation and renal failure [7].

It is known that acetylcholine is synthesized in cholinergic neurons and acts as the main neurotransmitter of the cholinergic system: activation of peripheral M-cholinoreceptors is accompanied by a contraction of urinary bladder smooth muscles. The mechanism of action of anticholinergic drugs is aimed at blocking the M-cholinoreceptors of the central and peripheral nervous system [2]. The inclusion of anticholinergics in the spectrum of drugs, due to the elimination of the symptoms of OAB, has significantly improved the quality of life of patients with BPH. However, according to F.C. Burkhard et al. (2020), due to adverse reactions, most patients stop taking anticholinergic drugs in the first three months of therapy [5]. During long-term use of anticholinergic drugs F. Jacquia et al. (2015) observed a decrease in uroflowmetric parameters, an increase in the maximum cystometric capacity, and increase in the volume of PVR [9]. Based on European recommendations, the use of anticholinergic drugs is not indicated for the amount of PVR>150 ml [5].

To date, more than 600 drugs are known to be used in clinical practice, including antispasmodics, antidepressants, antihistamines, antiparkinsonian, psychotropic, mydriatic and a number of other drugs that have anticholinergic activity (AA). In addition, a number of drugs, the mechanism of action of which is directed to other receptors, can cause side effects due to AA [8].

According to D. Bishara et al. (2020), up to 60 % of older people take one, and from 7 % to 17 % take several drugs with AA [4].

Anticholinergic load (AL) is considered as a cumulative effect of taking drugs with AA. First it was described in 1966. Due to the decrease in cholinergic reserves of the body, the elderly and senile are at risk of anticholinergic reactions, due to a number of factors: a decrease with age in the production of proteins required for the synthesis of acetylcholine; reducing the number of acetylcholine receptors; reducing the rate of excretion of chemicals. AL can develop both in overdose of drugs with AA, and as a result of a pathological reaction of the body to therapeutic doses [11].

The purpose of the study was to establish the role of anticholinergic load in the development of urinary bladder decompensation in patients with benign prostatic hyperplasia.

Materials and methods. In the urology department in 2018–2020 381 patients were operated due to BPH (age 67.49 ± 5.95 years), among them there were 232 patients (60.89 %) in the stage of urinary bladder subcompensation (group I). The duration of the disease in patients from the onset of the first clinical symptoms varied from 2 to 12 years: the duration of the disease up to 5 years was noted by 153 patients (65.9 %), from 5 to 10 years – by 65 patients (28.0 %) and more than 10 years – by 14 patients (6.0 %). From the anamnesis, 82.8 % of patients took α -blockers for 62.02 ± 31.01 months and 18.5 % of patients with OAB received high potential anticholinergic activity drugs (solifenacin, tolterodine, oxybutinin) for 9.4 ± 3.2 months and 21.9 % of patients with concomitant pathology (hypertension, bronchial asthma, sleep disorders, gastric ulcer, hay fever, gout, coronary heart disease) took drugs with low potential anticholinergic activity (diazepam, colchicine, prednisolone, rosuvastatin, amantadine, loratadine, digoxin, warfarin, pantoprazole, omeprazole, nifedipine, levocetirizine, etc.) for 15.1 ± 9.2 months.

In the stage of urinary bladder decompensation (group II) there were 149 patients (39.11 %) operated in two stages. The duration of the disease varied from 7 to 20 years: the duration of the disease up to 10 years – 104 patients (68.8 %) and more than 10 years – 45 patients (30.2 %). According to the anamnesis, 90.6 % of patients took α -blockers for 114.77 ± 52.18 months, 20.81 % of patients due to OAB took drugs with high potential anticholinergic activity for 21.61 ± 9.04 months and 19.46 % of patients with concomitant pathology – drugs with low potential anticholinergic activity for 74.64 ± 80.48 months. Indications for cystostomy were acute urinary retention or chronic urinary retention with complications such as paradoxical urinary incontinence (51.01 %), ureterohydronephrosis (31.54 %), urinary tract infections (92.26 %), stone formation (3.36 %) and renal failure (36.91 %).

Clinical trial data was statistically processed by the method of variation statistics. We performed the statistical analysis for the obtained scientific data using standard software package “Data Analysis” in Microsoft Excel for Windows 2010. We calculated the following arithmetic mean values – arithmetic mean (M), mean arithmetic error (m), and differences probability (p). Interpretation of the obtained data reliability was performed by the conventional parametric method according to the Student’s t-test. Reliability was determined when its value was at least 95 % (0.05)

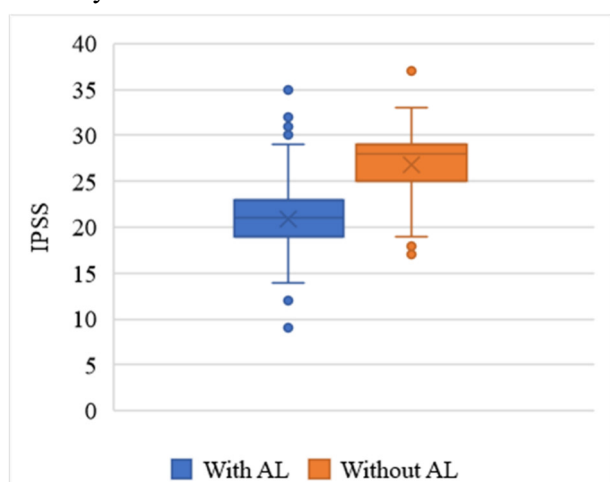


Fig. 1. Comparison of IPSS in patients of group I depending on AL.

the effective volume of urination was 23.1 % lower (151.3 ± 40.9 and 196.7 ± 43.7 , respectively, $p < 0.001$).

In patients taking drugs with high potential anticholinergic activity, IPSS points were 12.2 % higher (19.6 ± 4.1 and 22 ± 3.7 , respectively, $p = 0.019$), the volume of PVR – 41.2 % greater (136.6 ± 75.5 ml and 192.9 ± 94.1 ml, respectively, $p = 0.010$), Q_{ave} – 35.5 % lower (3.1 ± 2.0 and 2 ± 1.3 , respectively, $p = 0.016$),

Results of the study and their discussion.

In group I of patients, before operation IPSS was 24.7 ± 4.4 points, PVR – 126.8 ± 68.3 ml, Q_{max} – 9.4 ± 2.3 ml/s, Q_{ave} – 2.9 ± 1.2 ml/s, effective urination volume – 180.4 ± 47.3 ml. At the same time, in patients with AL due to the reduction of symptoms of OAB, IPSS was 24.9 % lower (20.8 ± 3.8 and 26.9 ± 2.9 , respectively, $p < 0.001$, fig. 1), QoL – 9.3 % lower (3.9 ± 0.6 and 4.3 ± 0.7 , respectively, $p = 0.001$).

Also, in patients with AL the volume of PVR was 57.8 % higher (165.8 ± 90.1 ml and 105.1 ± 49.4 ml, respectively, $p < 0.001$, fig. 2), Q_{max} – 17.8 % lower (8.3 ± 2.4 and 10.1 ± 2 , respectively, $p < 0.001$), Q_{ave} – 19.4 % lower (2.5 ± 1.6 and 3.1 ± 0.9 , respectively, $p = 0.016$), and

and the effective volume of urination – 22.4 % lower (136.9 ± 35.5 and 106.3 ± 16.4 , respectively, $p=0.009$) comparing to patients who took drugs with low potential anticholinergic activity.

Analysis of the relationship between the two variables revealed a strong ($r=-0.811$) inverse correlation between IPSS and Q_{max} , a strong ($r=0.911$) direct correlation between the volume of the PVR before surgery and the QoL after surgery, and also medium-strength ($r=0.559$) direct correlation between the volume of PVR before surgery and indicators on the IPSS scale after surgery, indicating incomplete recovery of detrusor function.

In the Group II of patients, at hospitalization IPSS had 34.31 ± 1.04 points, PVR volume – 884.26 ± 363.93 ml. At the same time, in patients who took drugs with AL for a long time, the volume of PVR was 81.1 % higher (1258.6 ± 539.7 ml and 695.2 ± 300.1 ml, respectively, $p<0.001$, fig. 3), while IPSS and QoL did not differ significantly. In patients taking drugs with high potential anticholinergic activity, the volume of PVR was 46.9 % higher (975.3 ± 476.1 ml and 1432.3 ± 507.7 ml, respectively, $p=0.001$) compared with patients taking drugs with low potential anticholinergic activity.

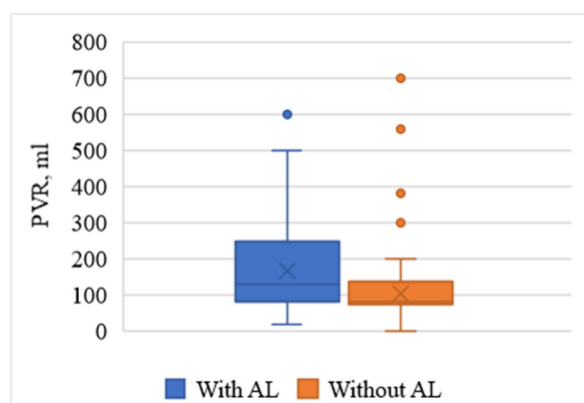


Fig. 2. Comparison of the PVR volume in patients of group I depending on AL.

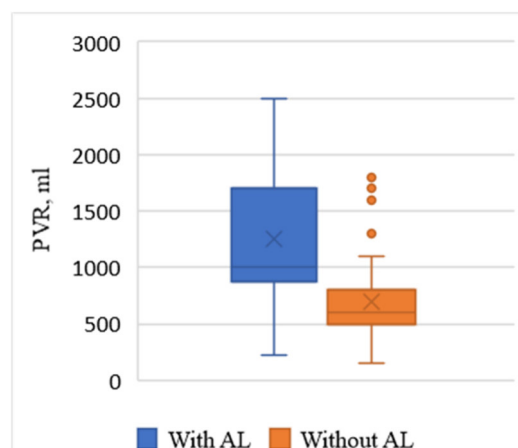


Fig. 3. Comparison of PVR indices in patients of group II depending on AL.

Analysis of the relationship between the two variables revealed a strong ($r=0.869$) direct correlation between the volume of the PVR before surgery and IPSS 6 months after surgery, strong ($r=-0.925$) inverse correlation between the volume of the PVR before surgery and Q_{max} 6 months after surgery, and a strong ($r=-0.893$) inverse correlation between the volume of PVR before surgery and Q_{ave} 6 months after surgery. Which indicates incomplete recovery of detrusor function, probably due to irreversible structural changes in the urinary bladder wall and show that in BPH patients AL may be an additional "masking" factor in the decompensation of urinary bladder.

Thus, despite the interest of researchers to the problem of AL, there is still no unified approach to both understanding their pathogenesis and choosing the best preventing method and treatment modality with the minimal likelihood of complications. Prolonged AL leads to an increase in the volume of the PVR. Drugs with high potential anticholinergic activity reduce the manifestations of urinary tract symptoms in patients with BPH, but AL becomes a deepening factor in the decompensation of urinary bladder, which worsens the results of surgical treatment.

Our research confirms the data of F. Jacquia et al. (2015) about the decrease in uroflowmetric parameters in patients with AL and shows more reliable data of urinary bladder dysfunction due to AL [10].

Diagnosis of AL causes significant difficulties both due to the polymorphism of manifestations and due to lack of awareness of the general medical community. To eliminate the clinical manifestations of AL, preference is given to drugs that are able to penetrate the blood-brain barrier and accumulate as much as possible in the areas of cholinergic metabolism between the central and peripheral nervous systems [1]. Plasma AA has been proposed to predict side effects. However, due to the high cost of the procedure, this method has not found application in clinical practice. In addition, side effects from the central and peripheral nervous systems do not always correspond to plasma AA. Despite the degree of subjectivity, the AL risk assessment method has become a practical tool for predicting side effects. Several AL scoring scales have been proposed. The features of each scale are determined by the purpose for which it was created. Thus, large-scale clinical studies have proven the high validity of the "AEC/Medichec Rating Scale" (2016), which includes drugs with AA, which are most often prescribed to elderly patients [3].

AL on the side of the central nervous system can manifest itself in hypoactive and hyperactive forms. Hypoactivity is accompanied by changes in the neuropsychological state, which vary widely – from

sedation and mild cognitive impairment to coma. Hyperactivity includes symptoms such as anxiety, fear, agitation, visual and auditory hallucinations, short-term memory impairment, delirium, hyperthermia of central origin, ataxia, convulsions, myoclonus, seizures. To a large extent, the severity of anticholinergic reactions on the part of the central nervous system is associated with the ability of drugs with AA to penetrate the blood-brain barrier [8].

Manifestations of AL on the peripheral part of the nervous system depend on AA of drugs, which is divided into low-potential and high-potential. Adverse reactions due to the use of drugs with low potential anticholinergic activity include dry mouth, blurred vision, constipation, urinary incontinence. Adverse reactions due to the use of drugs with high potential anticholinergic activity include increased frequency and severity of the above reactions, as well as dysphagia and complications on the central nervous system in the form of confusion, cognitive impairment, depression, disorientation, delirium, dizziness [15].

An important role in the prevention of the cumulative cholinolytic effect is played by increasing the awareness of medical personnel regarding the problem of anticholinergic load and high vigilance when prescribing several drugs with varying degrees of anticholinergic activity. According to E.D. Broderick et al. (2020), with polypharmacy one should be aware of and avoid the combination of drugs that can provoke a cumulative cholinolytic effect [14].

Today, we have a limited arsenal of drugs to eliminate the clinical manifestations of anticholinergic load. A drug from the group of acetylcholinesterase inhibitors, neostigmine methyl sulfate (proserin), with limited effectiveness on the side of the central nervous system, due to an increase in the concentration of acetylcholine in neuromuscular synapses, proved to be effective in peripheral symptoms. Anticholinesterase drugs capable of penetrating the blood-brain barrier – neostigmine and physostigmine turned out to be more effective in eliminating manifestations of the cumulative cholinolytic effect [15].

The drug of the new generation ipidacrine, the pharmacological properties of which consist of a combination of two effects – blockade of potassium permeability of the cell membrane and reverse inhibition of cholinesterase, has a stimulating effect on the process of excitation in presynaptic nerve fibers and postsynaptic muscle formations, stimulates muscarinic acetylcholine receptor, creating favorable conditions for conducting excitation and further contraction of muscles. In addition, ipidacrine enhances the effect on smooth muscles not only of acetylcholine, but also of other mediator substances: adrenaline, serotonin, histamine, oxytocin [15].

Conclusion

AL in elderly patients can develop both as a result of taking drugs with high potential anticholinergic activity and as a result of long-term use of drugs with low potential anticholinergic activity. Drugs with high potential anticholinergic activity reduce the symptoms of OAB in patients with BPH, but AL becomes a deepening factor in the decompensation of urinary bladder, which worsens the results of surgical treatment.

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ANALYSIS OF THE ACHIEVEMENT OF THE GLOBAL PURPOSE OF ELIMINATION OF CERVICAL CANCER IN UKRAINE

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Based on the analysis of the epidemiological situation in Ukraine, the study assesses the probability of achieving the purposes of the Global Strategy to accelerate the elimination of cervical cancer. Cervical cancer is a significant cause of death for Ukrainian women. In 2020, 30 % of all deaths were due to malignant neoplasms of the female genital organs, and approximately one in five deaths of women aged 30–45 years as a result of neoplasms was caused by cervical cancer. A comparative analysis with developed countries showed a higher probability of dying prematurely and a more significant contribution of the disease to the formation of the Global Burden of Disease indicator in young and old age. On the other hand, in Ukraine, there is a paradoxical phenomenon of decreasing mortality from cervical cancer with age. The COVID-19 pandemic was reflected in a decrease in the level of detection of new cases of the disease and an increase in the share of those detected in the advanced stage (in 2020 – 30.5 %, in 2021 – 31.1 % of deaths). It is suggested that there may be an increase in mortality due to untimely diagnosis and treatment of cervical cancer, which occurs against the background of a high prevalence of HIV infection, lower coverage of vaccination against human papillomavirus, and the low probability of Ukraine achieving the 90–70–90 goals by 2030.

Key words: cervical cancer, neoplasms, age-related mortality, premature mortality.

Н.О. Рингач, О.Г. Курик, С.П. Григорчук, І.В. Думицька, К.В. Баздирев, С.С. Мирвода, В.В. Баздирев АНАЛІЗ ДОСЯЖНОСТІ ГЛОБАЛЬНОЇ ЦІЛІ ЕЛІМІНАЦІЇ РАКУ ШИЙКИ МАТКИ В УКРАЇНІ

У статті на основі аналізу епідеміологічної ситуації в Україні здійснено оцінку ймовірності досягнення цілей Глобальної стратегії прискорення ліквідації раку шийки матки. Рак шийки матки є вагомою причиною смерті українських жінок. У 2020 р. 30 % всіх смертей через злоякісні новоутворення жіночих статевих органів, і приблизно кожну п'яту смерть жінок у віці 30–45 років в результаті новоутворень зумовлював рак шийки матки. Компаративний аналіз з розвинутими країнами показав вищу ймовірність померти передчасно та вагомий внесок захворювання у формування показника Глобального тягаря хвороб у молодому і зрілому віці. Також в Україні спостерігається парадоксальне явище зниження смертності від раку шийки матки з віком. Пандемія COVID-19 віддзеркалилася у зниженні рівня виявлення нових випадків захворювання, зростанні частки виявлених у занедбаній стадії (у 2020 р. – 30,5 %, у 2021 р. – 31,1 % смертей). Висловлено припущення щодо можливого підвищення смертності через несвочасні діагностику та лікування раку шийки матки, що відбувається на тлі високої поширеності ВІЛ-інфекції, та нижчого охоплення вакцинацією проти вірусу папіломи людини, та малої ймовірності досягнення Україною цілей 90–70–90 до 2030 року.

Ключові слова: рак шийки матки, новоутворення, смертність за віком, передчасна смертність.

The study is a fragment of the research project "Demo-social consequences of the COVID-19 pandemic", state registration No. 0122U000425.

Cervical cancer (CC) is an example of a disease resulting from which death can be avoided with timely treatment, detection and adequate treatment. Pathology ranks fourth among common types of cancer worldwide and seventh for women in the WHO European Region. In 2020, more than 604 thousand women worldwide were diagnosed with cervical cancer (6.5 % of all oncological diseases) [12]. According to estimates, almost 342,000 women died from cervical cancer in 2020 [10].