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REALIZATION OF THE ALGORITHM PHARMAKON (MEDICINE ↔ POISON) IN MODERN ANTIBIOTIC TREATMENT

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Abstract

For rational pharmacotherapy antibiotics important is not only knowledge of their selective action (antimicrobial range), but also degree of their harmlessness. The last to depend not only on a dose, but also on the chemical structure of any xenobiotic.

The aim of the study. To analyze possible side effects of medicines from group of antibiotics.

Materials and methods. The analysis of foreign and domestic scientific publications of rather possible side effects of medicines from group of antibiotics.

Results. Among a big arsenal of modern antibiotics there are more than 200 medicines with the international non-proprietary name (INN) which belong to 30 pharmacological groups. The majority of antibiotics have a wide range of antimicrobial action and much less from them possesses a narrow range. From all groups of antibiotics the most dangerous on kardio- and gematoksichnost are ftorkhinolona, karbopenema, monobaktema, penicillin and tetracyclines. Hepatotoxicity is characteristic of karbopenem, monobaktam, cephalosporins, tetracyclines, aminoglycosides and ftorkhinolon; neurotoxicity - for penicillin, cephalosporins, tetracyclines, aminoglycosides, glycopeptides, ftorkhinolon and chloramphenicol.

Conclusions. For more effective use of medical potential of antibiotics it is necessary to know also "reverse side" of an algorithm pharmakon (medicine ↔ poison) – their side effect on which safety and efficiency of modern antibiotic treatment depends. For prevention of side effects of antibiotics the doctor and the pharmacist should be able to analyze the mechanisms of their emergence and a condition promoting their emergence.

Keywords: *antibiotics; side effect; medicine; poison.*

Among the large arsenal of modern antibiotics, there are more than 200 drugs with an international non-proprietary name (INN), which belong to 30 pharmacological groups. Of these, a significant amount of penicillins, cephalosporins, macrolides, aminoglycosides and fluoroquinolones, but few drugs among carbopenems, monobactams and aminoglycosides [22]. Most antibiotics have a wide spectrum of antimicrobial action, much less of them have a narrow spectrum of activity, but all of them have side effects (SE) [5, 24].

For rational pharmacotherapy, it is important not only to know the selective activity of antibiotics (antimicrobial spectrum), but also the degree of their harmlessness. [20, 23, 24, 26]. The latter depends not only on the dose, but also on the chemical toxicity of any xenobiotic [3].

The purpose of this ыегвн is to help the doctor, pharmacist and patient Cito (quickly) «navigate» in the safety of antibiotics for the implementation of one of the basic principles of pharmacotherapy «Do no harm! ».

Firstly, of all groups of antibiotics, the most dangerous in terms of cardio- and hematoxicity are fluoroquinolones, carbopenems, monobactems, penicillins and tetracyclines. Hepatotoxicity is typical for carbopenems, monobactams, cephalosporins, tetracyclines, aminoglycosides and fluoroquinolones; neurotoxicity – for penicillins, cephalosporins, tetracyclines, aminoglycosides, glycopeptides, fluoroquinolones and chloramphenicol [3, 23, 26].

Secondly, for the prevention of the listed SE, the doctor and pharmacist must be able to analyze the mechanisms of their occurrence and the conditions that contribute to their appearance.

In particular, the neurotoxicity of penicillins and fluoroquinolones is a consequence of their antagonism with GABA. The latter mechanism is also responsible for the neurotoxicity of carbapenens, monobactams and cephalosporins. The development of encephalopathy is possible becouse of the use of large doses of cephalosporins [10]. Norfloxacin is more likely to cause SE in the central nervous system (CNS) than other fluoroquinolones. The neuromuscular block develops due to the ability of aminoglycosides to reduce the synthesis and sensitivity of H-cholinergic receptors to acetylcholine on pre- and postsynaptic membranes [3]. Symptoms of CNS depression: stupor, lethargy, deep respiratory depression; coma may occur in infants when using high doses of aminoglycosides. Conditions that predispose to the development of seizures when prescribing fluoroquinolones are traumatic brain injury (TBI), stroke, epilepsy, meningitis. The development of seizures can be triggered by the simultaneous administration of fluoroquinolones with non-steroidal anti-inflammatory drugs (NSAID), phenytoin, nitroimidazole derivatives [9, 17, 25].

Benzylpenicillin neurotoxicity (penicillin epilepsy) can lead to patient's death [10]. The development of psychosis when taking neomycin sulfate indicates the neurotoxic effect of the drug and requires immediate withdrawal and inpatient treatment. Damage to the nervous system during treatment with polymyxins is observed in 80% of patients with kidney disease, since this leads to the accumulation of the drug [1, 9].

Cardiotoxicity and hematotoxicity of benzylpenicillins are the result of inhibition of tissue respiration and the process of converting fibrinogen to fibrin, which causes bleeding [3]. The side effect of tetracyclines on the hematopoiesis process is less pronounced than that of other antibiotics, therefore they are used to treat infectious diseases in patients with blood diseases. The mechanism of dose-dependent inhibition of bone marrow functions by chloramphenicol is similar to the mechanism of its inhibition of protein synthesis in a bacterial cell. The drug inhibits protein synthesis in various cells of the body, altering the function of mitochondria [8]. Severe bone marrow suppression is possible to be of allergic origin. The latter may be based on the reactions of sensitized blood elements and hematopoietic organs with antigens, which are formed when these drugs bind to blood plasma proteins. [16]. With parenteral use of chloramphenicol, there were no cases of bone marrow aplasia, therefore it is considered that it is not chloramphenicol itself, but its decay products in the intestine, may have a toxic effect. In this regard, it is necessary to carefully use chloramphenicol in cancer patients who were previously treated with cytostatics and radiation therapy. [27].

The hematotoxicity of carbopenicillins, monobactams and cephalosporins is associated with the inhibition of the conversion of vicasol (vit. K)

into its active form, as well as the obstruction of its synthesis due to the suppression of normal intestinal microflora (the main producer of endogenous vit. K) [3, 6, 7]. Thrombocytopenia is eliminated by the appointment of vit. K, since a decrease in blood coagulation factors (prothrombin, factors VII, IX, XI) depends on the level of vit. K, which slows down the conversion of fibrinogen to fibrin and contributes to the development of hemorrhagic phenomena.

The use of erythromycin containing benzene for intravenous injections may be accompanied by the development of Gasping syndrome in children, as well as acute drug hepatitis. Chloramphenicol accumulates in an active form in liver diseases and slows down the elimination of drugs metabolized in the liver, as it inhibits the function of liver microsomal enzymes [18].

The development of hepatotoxicity of tetracyclines is promoted by the use of high doses of the drugs, impaired liver function and a long course of treatment. Hepatotoxicity of tetracyclines is more often observed in women during pregnancy and in the early postpartum period, as well as in children, especially in the prepubertal period [26]. Decreased renal excretory function increases the risk of hepatotoxic reactions.

The nephrotoxicity of aminoglycosides and vancomycin is associated with the accumulation of these drugs in the cells of the proximal renal tubules and impaired enzyme activity (Na +-, K +-, ATP; respiratory, etc.), which leads to interstitial nephritis [12]. Hyperuricemia is a results from the elimination of cephalosporins by tubular secretion. This side effect is most typical for 1st generation cephalosporins. The simultaneous intake of alcoholic beverages potentiates the nephrotoxicity of cephalosporins. Erythromycin and oleandromycin are characterized by low nephrotoxicity and can be prescribed in an average therapeutic dose for patients with chronic renal failure [3]. Furosemide inhibits the excretion of aminoglycosides through the kidneys, therefore, with their simultaneous use, the danger of the nephrotoxic effect of the latter increases. Tobramycin is less nephrotoxic than gentamicin, and amikacin is the most nephrotoxic [23]. In the course of treatment with fluoroquinolones, patients should receive a large amount of fluid to prevent crystalluria, and nephrotoxicity is a consequence of the accumulation of fluoroquinolones in the kidneys, with the exception of pefloxacin, 30% of which is excreted in bile (with urine no more than 60%) [3, 5].

In patients with renal insufficiency, the potassium salt of benzylpenicillin at a dose of 20,000,000 IU causes hyperkalemia, which can be fatal. The combination of penicillin with chloramphenicol can be fatal. When using high doses of carbenicillin, a large amount of sodium enters the body parenterally and, if the patient has heart failure, pulmonary edema can be provoked [23].

The antimicrobial effect of fluoroquinolones decreases when administered simultaneously with antibacterial agents that disrupt the synthesis of nucleic acids (tetracycline, rifampicin, nitrofurans) and protein (chloramphenicol) [3]. Fluoroquinolones should be used with caution during the formation of the osteoarticular system and breastfeeding to prevent the development of arthropathy. [5].

All polymyxins, when administered parenterally, have pronounced neuro- and ototoxicity, contribute to the disruption of neuromuscular transmission, but rarely cause an allergic reaction [3]. The use of polymyxin in ear drops is dangerous if there is a perforation of the tympanic membrane, since the ototoxicity of these substances is even higher than that of aminoglycosides [23].

With the rapid intravenous administration of clindamycin and lincomycin, cardiovascular failure (collapse, cardiac arrest) develops, arterial hypotension. Narcotic analgesics increase the inhibitory effect of clindamycin on the respiratory center [23].

Pseudomembranous colitis is the result of intestinal damage caused by the anaerobic bacteria Clostridium difficile, found in the intestines of 3% of healthy people. It has been established that β-lactam antibiotics (penicillins, carbapenems, monobactams) and fluoroquinolones create conditions for the excessive multiplication of Clostridium difficile with the subsequent production of their toxins that cause diarrhea. Pseudomembranous enterocolitis is more often observed in elderly patients who are in the hospital. With amoxicillin, the risk of developing

pseudomembranous colitis is 7 times higher than with other antibiotics [14, 19].

During the use of penicillins, dysbiosis can develop, which in turn can lead to superinfection. The combined use of penicillin with tetracycline reduces the body's immune status and increases dysbiosis. For the prevention of fungal infections of the mucous membranes and skin, simultaneously with penicillins, it is advisable to prescribe vitamins of group B and ascorbic acid (vit. C), antifungal drugs. Ampicillin trihydrate, amoxicillin trihydrate, penamecillin, becampicillin cause dysbiosis and dyspepsia less often than others (due to 70-80% bioavailability) [26]. Hypersensitivity to penicillin is more often observed in persons who have had a fungal disease, as well as in cheese-making industry at workers who are in contact with fungi close to penicillin producers, also at doctors, pharmacists, hospital and pharmaceutical workers [2]. Patients who took two or three antibiotics at the same time, had the visceral form of candidiasis develops 3 times more often than in patients who received only one antibioticCefotaxime is less likely to cause dysbiosis, however, its concentration in breast milk after intravenous administration at a dose of 1 g can adversely affect the microflora of the child's oral cavity [23].

As for fluoroquinolones, according to the frequency of side effects from the alimentary canal, these drugs are distributed in the following order: fleroxacin ≥ sparfloxacin ≥ ofloxacin [4, 11, 23]. It was also found that an increase in the dose of antibiotics to a supramaximal dose reduces immunity. [3]. Tetracyclines in the adrenal cortex reduce the content of ascorbic acid, the metabolism of which is closely related to the exchange of corticosteroids and the body's immune responses; it is with this mechanism that the development of candidiasis lesions of the intestines is associated. In addition, tetracycline has an immunosuppressive effect, therefore, the transition of an acute form of an infectious disease to a chronic is often observed [13].

Pregnant women and patients over 60 years are not recommended to inject more than 20,000,000 IU of penicillins per day, as they penetrate into breast milk, and glycopeptides can cause dysbiosis and sensitization in a child. In addition, glycopeptides are prescribed for pregnant women only for life-long indications due to the possible risk of neuro- and ototoxic, as well as teratogenic effects. There is evidence of negative effects of clarithromycin on the fetus [3]. Therefore, glycopeptides should be used with caution in children and newborns and only for severe infections.

Chloramphenicol easily penetrates the blood-brain barrier, therefore it cannot be prescribed to pregnant women, as it provokes the phenomena of encephalitis. Rifampicin is an inducer of liver microsomal enzymes, therefore it accelerates the metabolism of many drugs. Polymyxins should be administered to newborns once a day and only for health reasons. Lincomycin is low-toxic (can be used for newborns), resistance to it develops slowly. It crosses the placental barrier and may reduce the antibacterial efficacy of penicillins and cephalosporins [3].

An allergic reaction to tetracyclines occurs 2 times less often than to penicillin preparations [2]. «Gray syndrome» develops in late pregnancy, as well as in newborns with parenteral administration of chloramphenicol in high doses, pathogenetically caused by collapse, bone marrow aplasia, intoxication. All these complications are fatal [8, 16]. The mechanism of the "gray" collapse is a violation of the synthesis and functions of respiratory enzymes mainly in the mitochondria of the myocardium as a result of the activity of unmetabolized chloramphenicol. Chloramphenicol should not be used concurrently with bactericidal antibiotics such as penicillins or cephalosporins, as their bactericidal effect in this combination is reduced. Prolonged-acting penicillin drugs pose a threat to life in patients with heart disease. Among antibiotics, macrolides are the least toxic [3, 26].

Among the side effects of antibiotics, bacteriolysis, which occurs with the release of endotoxins and the development of hypovitaminosis, deserves special attention. All drugs of the tetracyclines group have an anti-anabolic effect, since they inhibit protein synthesis from amino acids in the patient's body as well as in a bacterial cell.

Ototoxicity of antibiotics is observed when they are used over the age of 60 – a factor that predisposes to ototoxicity [15, 21].

Within 2-3 weeks after the abolition of aminoglycosides, drugs with ototoxic properties should not be used. If a violation of the vestibular apparatus is detected early, then in 50% of cases it can be reversible, and prevention of toxicity is control of auditory function, audiometry. If the patient has tinnitus, allergic reactions, protein in urine, it is necessary to stop taking neomycin sulfate [21]. The frequency of ototoxicity of kanamycin is more than 40%, but it is less toxic than streptomycin, however, when taking the latter, deaths from severe encephalopathy are a possibility [2]. The ototoxicity of kanamycin and amikacin is more pronounced than that of gentamicin or tobramycin. The frequency, severity and rate of development of ototoxicity depend on the dose of aminoglycosides (daily and course), as well as on the simultaneous or sequential use of two aminoglycosides, the functional state of the kidneys, the duration of use (more than 2-3 weeks), dehydration, diseases of the internal and secondary ear, age, combined use of aminoglycosides and other ototoxic drugs (salicylates, loop diuretics, quinine, vancomycin, capreomycin, ethacrynic acid), the presence of diseases that facilitate the entry of antibiotics into the cerebrospinal fluid of the inner ear (meningitis, birth trauma, hypoxia during childbirth, etc.) [4]. Aminoglycosides are prescribed for elderly patients only for health reasons due to the increased risk of oto- and nephrotoxicity [21]. According to the degree of influence on the vestibular function, antibiotics can be arranged in descending order of side effects as follows: kanamycin → streptomycin → sisomycin → gentamicin → tobramycin.

Netilmicin is less otoxic and nephrotoxic than other aminoglycosides. Doxycycline is less toxic than other tetracyclines, new semi-synthetic macrolides are also less toxic than natural ones [26].

Hydrocortisone, while being chemically similar to fusidic acid, inhibits its antibacterial properties. Chlormfenicol has a small range of therapeutic action, so it is better to prescribe it per os than in a vein. Chloramphenicol should not be used concurrently with bactericidal antibiotics such as penicillins or cephalosporins, since their bactericidal effect in this combination is suppressed [3].

Conclusions. The analysis of the SE of antibiotics indicates that for a more effective use of the therapeutic potential of this large and important group of drugs, it is necessary to know the «reverse side» of the pharmakon algorithm (medicine ↔ poison) – their SE, at which the safety and effectiveness of modern antibiotic therapy depends.

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