Polymyxins – a new view on well-known antibiotics

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Appearance of multi drug-resistant activators makes to reconsider the attitude to a range of preparations, which are well-known and has been used for a long time, in particular to polymyxins – a group of polypeptide antibiotics produced by Bacillus polymyxa and highly active in regard to a gram-negative microflora – Escherichia coli, Klebsiella spp., Enterobacter spp., Salmonella spp., Shigella spp., Haemophilus influenzae, Brucella spp., Pseudomonas aeruginosa, Acinetobacter spp., etc. All types of Proteus spp., Serratia marcescens, gram (+) bacteria and many anaerobic bacteria, in particular Bacteroides fragilis, are insensitive to action of polymyxins. In clinical practice, polymyxin B and colistin (polymyxin E) are used, which in current conditions can be administered only as preparations of a "deep" reserve in the treatment of infections, caused by gram-negative microorganisms with multi drug-resistance to other classes of antibiotics.

Introduction

Actuality of the problem of therapy of infectious diseases, caused by multi drug-resistant strains of bacteria, is beyond question. Possible solutions of this problem can be either synthesis of new antibacterial agents, or optimization of application of the present preparations [1].

Today creation and marketing of new antibiotic are associated with expenses from 100 to 350 mln US dollars [22, 33]. Communication of resistance often proceeds to marketing of active preparation. Rational use of existing antibiotics is considered more preferred solution for domestic conditions. In this context, we would like to discuss the perspectives of administration of a well-known group of antimicrobial agents – polymyxins, which are effective in regard to gram-negative infectious agents, including multi drug-resistant ones.

Polymyxins make up a group of polypeptide antibiotics with molecular weight near 1000, synthesized by an aerobic sporogenous rod Bacillus polymyxa [44]. They has been isolated at the end of 1940th, this is precisely why the main investigations and publications on this preparations belong to the beginning of the second part of the XX century. Of 5 isolated groups of naturally occurring compounds, only 2 are used in humans – polymyxin B and polymyxin E (colistin). In Russia, polymyxin B sulfate и polymyxin M sulfate are registered (in fact, colistin).

Mode of action of polymyxins

All polymyxins affect a cytoplasmic membrane of a bacterial cell, reacting with phospholipids. They bind with anionic segments of membrane, and remind of cationic detergents by the nature of action. Damage of membrane structure leads to modification of its permeability both for intracellular and for extracellular components [44, 66].

Detergent-like action is a base for some clinically significant effects of usage of polymyxins – toxicity and neutralization of biological effects of endotoxins. Nephrotoxicity, occurring in 20% of patients in the first few days of therapy in the form of proteinuria, haematuria and increase of creatinine level in blood serum, is especially noteworthy. In case of high concentration of polymyxin in serum, oliguria and tubular necrosis are observed [77]. Neurological and dyspeptic disorders are possible as well.

Polymyxins interact with ATP -dependent calcium channels of insulin-releasing cells, that lead to suppression of insulin-stimulating transformation and transport of glucose, decrease in absorption of glucose by muscles and their fat tissue [88, 99]. Strengthening of antiinsulin effect of other preparations is possible [10].

Binding of phospholipids by polymyxins explains their biological activity in the form of blocking of effect of endotoxins- lipopolysaccharides (ELPS). Polymyxins inhibit ELPS-dependent isolation of interleukin-1 by monocytes, tumor necrosis factor by alveolar macrophages [11, 12]. Experimentally it is shown by elimination of cardiovascular, metabolic and other effects of ELPS [13]. At the same time, the clinical significance of such action of polymyxins remains unexplored in connection with a limited number of clinical observations in burn patients [14, 15] and in patients with obstructive jaundice [16].

Antibacterial activity of polymyxins

Antibacterial activity of polymyxins includes only gram-negative microflora (see the table): Escherichia coli, Klebsiella spp., Enterobacter spp., Salmonella spp., Shigella spp., Haemophilus influenzae, Brucella spp., Pseudomonas aeruginosa, Acinetobacter spp.

Polymyxin activity in regard to several pathogenic bacteria: MIC (mg/L) and/or qualitative evaluation (R - resistance) [55]

Microorganism	Colistin sulfate	Colistin sufometate	Polymyxin B sulfate
Staphylococcus aureus	64 (R)	(R)	64 (R)
Streptococcus pyogenes	32 (R)	32 (R)	16 (R)
Группа Streptococcus viridans	32 (R)	32 (R)	32 (R)
Enterococcus faecalis	R	R	R
Haemophilus influenzae	0.5-1.0	–	0.03
Escherichia coli	0.01-32	0.05-64	0.03
Klebsiella pneumoniae	0.01-1.0	0.01-4.0	0.03-0.5
Enterobacter spp.	0.03-32	0.5-R	0.03-16
Proteus spp.	R	R	R
Salmonella spp.	0.01-1.0	0.03-0.5	0.01-1.0
Shigella spp.	0.01-1.0	0.1-0.25	0.01-1.0
Pseudomonas aeruginosa	0.03-4.0	2.0-320.03-4.0	

In many cases, polymyxin remains a highly active antibiotic, in regard to bacteria, resistant to the majority of antimicrobial drugs [17]. Minor activity is shown against anaerobes. All species of Proteus spp., Serratia marcescens, gram(+) bacteria and many anaerobes, including Bacteroides fragilis, are insensitive to the action of polymyxins. Acquired bacterial resistance is developing slowly and is usually associated with lowering of permeability of membranes for polymyxins [18, 19].

Polymyxins demonstrate in vitro synergistic action with some other antibacterial agents in regard to particular infectious agents. For example, synergism with trimethoprim against S. marcescens [20], with bacitracin and miconazole – against Staphylococcus aureus and Staphylococcus epidermidis [21], have been detected. Polymyxin B increases the activity of amphotericin B against

Coccidioides immitis [22], and combination of colistin with rifampicin could suppress the vital activity of multi drug-resistant strains of Acinetobacter baumannii [23]. Nevertheless, the detected in vitro synergism was not studied in the controlled clinical studies.

Pharmacokinetics of polymyxins

Polymyxins are practically not absorbed in oral administration. After intramuscular administration, a peak concentration in blood serum (2–8 mg/L) is formed in 1–2 h with gradual reduction within 8–12 h. Intravenous bolus administration of polymyxin B with subsequent slow infusion allows to maintain its high level (5–6 mg/L) within the whole period of administration [24].

After parenteral administration, polymyxins are distributed in the organism, accumulating in kidneys, liver, heart, muscles and lungs. Preparations are not detected in bile passages and cerebro-spinial fluid (even in case of meningitis). Polymyxin B and colistin are excreted by kidneys via glomerular filtration. Urine concentration after parenteral administration varies within 20–100 mg/L. It's usually higher in colistin.

Clinical usage of polymyxins

In humans, up to 1960-th polymyxins had been considered as the main treatment agents of infections, caused by P.aeruginosa, including bacteriaemia, pneumonia, burns, meningitis (intrathecal administration), urinary tract infections [25, 26].

In the current context polymyxin B and colistin could be used only as preparations of a "deep" reserve in the treatment of infections, caused by gram-negative microorganisms with multiple resistance to other classes of antibiotics. To a large extent, it is associated with lower effectiveness and greater toxicity of polymyxins in comparison with new antibiotics, which appeared after them, such as cephalosporins and aminoglycosides.

Moreover, polymyxins could be applied topically, often in combination with other preparations in the treatment of skin and eye diseases. Eye drops of polymyxin with neomycin and gramicidin are used for prevention of infections in patients after surgery on the eyes, as well as for the treatment of keratitis [27]. Polymyxin so far is included in the schemes of selective decontamination of intestinal tract in patients, who are in the intensive care unit, surgical hospitals and cancer detection centers. For this purpose, polymyxin is prescribed orally separately or in combination with one of such preparations, as gentamicin, neomycin, cefotaxime or ciprofloxacin [28, 29]. These schemes showed high efficiency in prevention of hospital-acquired infections, caused by multi drug-resistant strains of a gram-negative microflora.

In literature, the limited data on application of polymyxins for therapy of hospital-acquired infections are provided. In particular, colistin was successfully used in 60 patients with nosocomial contamination with P. aeruginosa and A. baumannii strains, resistant to cephalosporin, monobactam, carbapenems, aminoglycosides and fluoroquinolones (60% efficiency) [30]. The best results were obtained in patients with urinary tract infections, meningitis (in 4 of 5 patients, generally, in case of intrathecal introduction), sepsis and surgical pathology (peritonitis). However, there was improvement only in 5 of 20 patients with pneumonia. The authors notice high rate of kidney dysfunction – in 27% patients with initially normal values of creatinine level and in 58% with already existed disorders. These conditions require close control of kidney function in all patients, receiving polymyxin.

In regard to low respiratory tract infection, there is conflicting information on efficiency of polymyxins. It concerns generally preventive administration of colistin in patients, who are in the intensive care units, or in patients with mucoviscidosis. In particular, T. Feeley et al. [31] discovered an increase in the rates of development of pneumonia, caused by microorganisms, resistant to polymyxin B (S. maltophilia and Burkholderia cepacia), after inhalation use of preparation. On the other hand, K. Unertl et al. [32] specify, that administration of pastes with polymyxin B in the form of applications in nasopharynx and oral pharynx or orally reduced colonization of gulp and bronchi by multi drug-resistant microorganisms. In turn, it decreased the rate of development of nosocomial pneumonia in comparison with thereof in patients, who didn't receive such therapy.

Colistin appeared to be effective solution for secondary prevention of pneumonia in patients with mucoviscidosis [33], infected by human immunodeficiency virus [34], and patients with neutropenia [35, 36]. The data, received in the Danish center of mucoviscidosis in Copenhagen, on assessment of efficiency of a three-stage treatment regimen with colistin (inhalant) and ciprofloxacin (orally), are of interest [37]. Only in 8 (17%) of 48 patients, a chronic infection, caused by P. aeruginosa, has developed within the subsequent 3.5 years, after a three-month therapy with high doses. In the control group (43 patients), there were 72% such patients.

G.S. Bauldoff et al. [38] evaluated efficiency of inhalation administration of colistin in patients with mucoviscidosis – candidates for lung transplantation. All patients were colonized by multiple drug-resistant strains of P.aeruginosa. Colistin administration in 20 patients led to disappearance of multiple drug-resistant strains and colonization of lungs with the strains of Pseudomonas aeroginosa, sensitive to antibiotics within 45.0±20.2 days. In the control group, such microorganisms have been isolated only after 144±48 days only in 3 of 10 patients. The authors concluded that colistin could be used for assistance of appearance of P. aeruginosa strains sensitive to preparations in patients, who are going to have lung transplantation.

Meningitis, caused by the activators resistant to multiple antibiotics, remains an extremely serious problem. The methods of treatment of such pathology forms by carbapenems and inhibitory-proof penicillins, are described [39, 40]. However, the development of resistance to these preparations is already an ordinary event. In particular, the strains Acinetobacter spp., resistant to carbapenems and sulbactam among others, are a serious problem [41, 42, 43]. According to multiple publications, such strains often remain sensibility to polymyxins [44, 45].

The report of P. Fernandas-Viladrich et al. [46] on the treatment of 5 patients with regard to ventriculitis with subarachnoid haematomas or operate with regard to brain neoplasm, are of interest. After intravenous administration of meropenem, sulbactam and tobramycin, as well as tobramycin intraventricularly, 3 patients died within a week after development of ventriculitis, caused by carbapenem-resistant strains Acinetobacter baumannii. Along with the listed therapy, colistin was prescribed intrathecally (within 20 days) for 2 patients that led to improvement of their condition and sterilization of cerebro-spinial fluid. The authors concluded, that exactly colistin promoted life sustaining for these patients, as neither meropenem (MIC – 4–256 mg/L), nor tobramycin (MIC – 8 mg/L) created in cerebrospinal fluid concentration, enough for suppression of activator.

Therefore, in the current context, the treatment of several severe forms of infectious pathology, including hospital-acquired infections, requires reconsideration of standard approaches. Uncontrolled administration of antibacterial preparations, including, on an outpatient basis, leads to communication of antibiotic resistance, against which science and pharmaceutical industry fail to make progress in the search for effective solutions.

This is precisely why in some cases it is necessary to pay attention to the preparations, which are well-known and studied, but undeservingly forgotten. In this respect, polymyxins could be very helpful, if used reasonably, especially in such cases, when other preparations are prognosticated as possibly ineffective.

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