Original Articles

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EFFECTIVE ANTIBIOTIC THERAPY OF COMPLICATED URINARY TRACT INFECTIONS

Summary. *The article presents data from a study on the clinical and bacteriological efficacy and safety of Brakson (tobramycin) in the treatment of complicated urinary tract infections. The results demonstrated the feasibility of the administration of this antibacterial drug in patients with complicated urinary tract infections. According to laboratory tests of antimicrobial activity of Brakson, its efficiency is 87%. Also a high level of safety of Brakson (93.3%) has been shown. This allows us to recommend the use of Brakson in complicated urinary tract infections as monotherapy.*

Complicated urinary tract infections (UTIs) are infections occurring on the background of structural or functional disorders of kidneys and urinary tracts, or on the background of concomitant conditions affecting the defense mechanisms of a macroorganism and increasing the risks of development of an infection or treatment inefficiency. Complicated UTIs may be caused by a broad range of microorganisms. This range is much broader than in non-complicated UTIs, furthermore, there is a higher probability of the fact that the pathogens will be more resistant to antibiotic drugs, especially in complicated UTIs, related to treatment [1, 10].

Factors leading to complicated UTIs:

– presence of a long term catheter or a stent (an urethral, ureteral or renal one), or a periodic bladder catheterization;

– residual urine volume > 100 ml;

– obstructive uropathy of any etiology, for example, infravesicular obstruction (including a neurogenic bladder), stones and tumors;

– vesicoureteral reflux, or other functional disorders;

– restorative operations on urinary tracts with the use of an ileum segment or creation of a conduit;

– chemical or radiation injury of the uroepithelium;

– peri- and postoperative UTI;

– renal insufficiency and kidney transplantation, diabetes mellitus and immunodeficiency states [7].

The leading pathogens of complicated UTIs are enterobacteria among which *E.coli* (Escherichia coli) ranks first. However, gram-negative nonfermentative bacteria (for example, *Pseudomonas aeruginosa*) and gram-positive cocci (for example, staphylococci and enterococci) can also play an important role in development of these infections, depending on the concomitant conditions [4] (Table 1).

The tactics of treatment of complicated UTIs depends on the illness severity. Treatment consists of 3 main directions: elimination of urological disorders, antimicrobial therapy and, if necessary, supporting therapy. In order to avoid the emergence of resistant strains, the treatment should be conducted, if possible, on the basis of the results of a culture-based urine examination. If an empiric treatment will be required, the coverage of the chosen antibiotic must embrace the most likely pathogens (grade A recommendation).

The recommended drugs are: fluoroquinolones with predominant renal elimination, inhibitor-protected aminopenicillins, cephalosporins of 2nd or 3rd generation, or, if a parenteral therapy is required, aminoglycosides (level of evidence 1b, grade B recommendation) [12].

Should the initial therapy be ineffective, or in case

of a clinically severe infection, one should select an antibiotic with a more broad coverage which will be active also in relation to *Pseudomonas* spp. (level of evidence 1b, grade B recommendation), for example, fluoroquinolone (if it was not used for initial treatment), inhibitor-protected acylaminopenicillin (piperacillin), group 3b cephalosporins or carbapenem plus aminoglycoside (level of evidence 1b, grade B recommendation). The duration of treatment is normally 7–14 days (level of evidence 1b, grade A recommendation) but can sometimes be extended to 21 days (level of evidence 1b, grade A recommendation) [8] (Table 2).

It is usually impossible to ensure full recovery without infection recurrences for as long as the predisposing causes are fully eliminated. The culture-based urine examination should be performed 5–9 days after therapy completion, and then again after 4–6 weeks (grade B recommendation) [5].

The uropathogenic microorganisms causing more than 90% of urinary tract infections include bacteria of Enterobacteriaceae family as well as *P.aeruginosa*, *Enterococcus faecalis, Staphylococcus saprophyticus*. At the same time such microorganisms as *S.aureus, S. epidermidis, Gardnerella vaginalis, Streptococcus* spp., diphtheroids, lactobacillus, anaerobia, produce virtually no such infections although they also colonize rectum, vagina and skin [9].

It should be stressed that the community acquired infections of urinary tracts in the ambulance practice and in-patient facilities are predominantly caused by one microorganism – E.coli, therefore, the decisive factor for choice of an antibiotic is its natural activity vis-à-vis *E.coli* and, to a certain degree, the acquired resistance level in the population. At the same time, the importance of other uropathogenic microorganisms with an unpredictable resistance level (which is determined by local epidemiological data) increases in hospital-acquired infections [2].

Thus, the determining factor for a possibility to use an antibiotic in urogenital infections is its activity in relation to the dominant pathogens.

As reflected in multicenter national and international studies, *P.aeruginosa* acts for more than a decade as a one of the most frequent pathogens of hospital-acquired infections, in particular, in intensive care units (ICU) [3]. The frequency of a pseudomonas infection is largely determined by the nosological structure in patients, severity of their initial condition, prevalence of invasive procedures, in particular, by number of patients who need a prolonged respiratory support, bladder catheterization or a conduct of a prolonged infusion therapy.

The necessity to discuss the issues of antibacterial therapy of infections caused by this pathogen, along with their high prevalence, is also related to the growth of its resistance to virtually all widely used antibiotics and to a difficulty of eradication from tissues and high mortality.

Unlike the overwhelming majority of representatives of its genus, Pseudomonas aeruginosa possesses multiple virulence factors. Its pathogenicity is determined by the capacity to invasion and persistence in tissues as well as to the cytotoxic effect and stimulation of a generalized inflammatory reaction. Factors that have a direct impact on formation of a local and systemic inflammation, are lipopolysaccharide, exotoxin S, flagellin, nitrate reductase, pyocyanin, phospholipase C. Most of them initiate secretion of a key anti-inflammatory mediator – a tumor necrosis factor, and phospholipase also contributes to the liberation of IL-1, IL-6, interferon-gamma of monocytes, polymorphonuclear neutrophils and T-lymphocytes [4, 5]. For *P.aeruginosa*, as also for other gram-negative bacteria, the excretory system of type III has been described (peculiar "molecular syringe") which ensures elimination of exoenzymes from the internal environment of a bacterial cell and their translocation toward the interior of a eukaryotic cell, directly to targets. The substances secreted by this system, in case of a *P.aeruginosa*, include exotoxins (ExoS, ExoT, ExoY, ExoU) [16].

Table 1. Microorganisms causing various types of urinary tract infections, % [9]

Microorganism	Acute cystitis	Acute pyelonephritis	Complicated UTIs	Catheter-related infections
E.coli	68	89	32	24
St.sapr.	8	0	1	0
Proteus	6	4	4	6
Klebsiella	4	4	5	8
Enterococci	3	0	22	7
Pseudomonas	0	0	20	9
Mixed	3	5	10	11

The immediate intracellular effects under the influence of exotoxins lie in inhibition of DNA synthesis, apoptosis stimulation, changes in cell shape, loss of the ability to a local adhesion. It has been proved that secretion of mentioned exotoxins is accompanied by a reduction in the systemic arterial pressure and development of a septic shock. The *P.aeruginosa* populations are heterogenic from a perspective of a capacity for synthesis and secretion of toxicity factors: various strains of this microorganism possess different toxicity [11]. Apparently, the expression of virulence factors is influenced by environmental conditions and the process of an individual interaction of a microorganism and bacteria as well as the population density of the latter.

One of the mechanisms conditioning the expression of virulence factors is the phenomenon of cooperative sensibility (quorum sensing) inherent to P.aeruginosa. Its core is the modification of physiological functions of bacteria during a change of their number, as a result of production of extracellular signaling molecules (autoinducers), their detection and formation of a response reaction of new quality. Under the control of this system is the synthesis of all exotoxins and formation of a biofilm. The blockade of mechanisms for implementation of the phenomenon of cooperative sensibility in *P.aeruginosa* leads to a pronounced detoxification.

P.aeruginosa has a capacity for unspecific adhesion on the implantable devices (catheters, endotracheal tubes, etc.). In parallel, there is a specific adhesion mechanism: the molecules forming parts of plasma protein, are adhesins for microorganisms. The adhesion grows in the event of mucociliary clearance disorders that develop in overwhelming majority of ICU patients, during postoperative and posttraumatic periods, in acute cardiac and respiratory insufficiency, any dehydration and in all cases of artificial lung ventilation. At a later stage, microcolonies of bacteria integrate into a continuous biofilm which constitutes several layers of microbial cells covered by a common glycocalyx (a polymer of polysaccharide nature). The overwhelming majority of cells are dormant and characterized by a very low sensitivity to the effects of antibiotics. The periodic emerging areas of spontaneous proliferation are sources of excretion into the environment of free microbial cells. First of all, this process forms the basis of catheter-related infections. The spread along the extracellular spaces is provided by the secreted proteins possessing an enzymatic activity: proteases, elastase, lipase. At any localization of a primary focus of infection, development of bacteremia is possible which essentially deteriorate the prognosis for a disease [13].

Table 2. Activity of antibiotics of various classes against major pathogens of urological infections

Antibiotics	Gram-negative			Gram-positive	
	E.coli	Other enterobacteria	*P.aeruginosa*	*E.faecalis*	*S.saprophyticus*
Aminoglycosides					
— Gentamicin	+	+/–	+/–	+/–	+/–
— Tobramycin	+	+/–	+/–	–	+/–
— Amikacin, netilmicin	+	+	+	–	+/–
Macrolides	–	–	–	+/–	+
Lincosamides	–	–	–	–	
Doxycycline	+	+/–	–	–	+/–
Chloramphenicol	+	+/–	–	+/–	+/–
Vancomycin	–	–	–	+	+
Linezolid	–	–	–	+	+
Rifampicin	–	–	–	+/–	+
Fusidic acid	–	–	–	+/–	+
Fosfomycin	+	+	–	–	+/–
Nonfluorinated quinolones	+	+	–	–	–
Fluoroquinolones 1st generation	+	+	+/–	+/–	+
Fluoroquinolones 2nd generation	+	+	+/–	+	+
Nitrofurans	+	+/–	–	+/–	+
Co-trimoxazole	+	+/–	–	–	+
Nitroxoline	+	+/–	–	–	–
Metronidazole	–	–	–	–	–

The main problem is a high resistance level of *P.aeruginosa* to most of accessible antibacterial drugs. One of the drugs, to which *P.aeruginosa* is susceptible, is an antibiotic of the aminoglycoside group – tobramycin.

The aminoglycoside group comprises oligosaccharide antibiotics (or pseudosaccharide) that are related by their chemical structure, antimicrobial spectrum, pharmacokinetic properties and character of side effects caused by them. The common name "aminoglycosides" is attributable to the presence in their molecule of aminosaccharides connected by a glycosidic linkage. The aminoglycosides are marked by a broad spectrum of antibacterial action. There are aminoglycosides of the 1st, 2nd and 3rd generations. The aminoglycosides of the 1st generation include streptomycin, neomycin, monomycin, kanamycin. Practical application of streptomycin (2nd generation) is related to emergence of strains of microorganisms resistant to aminoglycosides of the 1st generation and to the high activity of this drug vis-à-vis *P.aeruginosa*.

The aminoglycosides of the 3rd generation (tobramycin, sisomicin, amikacin, dideoxy-kanamycin B, netilmicin) were created at a time when the molecular resistance mechanisms were revealed, specific ferments that inactivate these antibiotics were identified and recovered. The aminoglycosides of the 2nd and 3rd generations are distinguished by the higher antibacterial activity, a broader spectrum of antimicrobial action, and they are gradually replacing the 1st generation drugs from the traditional spheres of their application.

By degree of decrease of the antimicrobial action strength, the aminoglycosides are ranked as follows: netilmicin, isomycin, gentamicin, tobramycin, neomycin, kanamycin, monomycin.

The resistance to aminoglycosides in clinical isolates of microorganisms is partly cross-resistant. The streptomycin-resistant strains of staphylococci and gram-negative microorganisms are in most cases sensitive to all other aminoglycosides. The pathogens resistant to kanamycin are mostly resistant to monomycin but many of them are sensitive to neomycin. The microorganisms resistant to aminoglycosides of the 1st generation, are sensitive to gentamicin and other new aminoglycosides. However, the gentamicin-resistant strains are often resistant to the 1st generation drugs. The aminoglycosides of the 3rd generation are active in relation to the microorganisms resistant to gentamicin.

The resistance of microorganisms to aminoglycosides is determined by their capacity to produce specific ferments inactivating these antibiotics. Currently, three mechanisms of enzymatic inactivation of aminoglycosides have been studied and described in detail: acetylation of NH2-group, adenylation and phosphorylation of OH-group.

All aminoglycosides are characterized by a selective neuro- and nephrotoxic action which leads to the necessity of a clear justification of indications for their administration, a careful monitoring of the blood concentration, renal function and taking audiograms at least once a week. By degree of decrease of general toxicity, the drugs can be ranked in the following way: sisomicin, gentamicin, tobramycin, netilmicin, neomycin, streptomycin, monomycin, kanamycin.

Tobramycin (tobracin, tobramycetin, nebcin, obramycin) is similar to gentamicin in the spectrum of antimicrobial action. With respect to *P.aeruginosa*, tobramycin is 2–4 times more effective than gentamicin but is inferior than it as far as the activity when impacting staphylococci, klebsiella, serratia and proteus is concerned [12].

Tobramycin cannot be bind by blood serum proteins. By its main pharmacokinetic characteristics, it is similar to gentamicin. At intramuscular injection, it is well absorbed. The peak of tobramycin blood concentration is observed after 30 minutes – 1 h $T_{1/2}$ equals to 2–2.5 h. At repeated drug injections after 8 h at doses of 25 and 50 mg, or 100 mg after 12 h, no cumulation in the body is observed. The dose of 2 to 4–5 mg/kg of body weight is injected 3–4 times a day during 7–10 days.

When given intravenously, $T_{1/2}$ of tobramycin equals to 1.5 h. The concentration peak at that is not more than 12 mcg/ml. The drug is administered intravenously, by drop infusion during 1 h, at that its blood concentration reaches 5 mcg/ml. 2 h after the infusion, the concentration decreases to 3.6 mcg/ml.

In case of impaired renal function, drug elimination slows down, and its blood concentration grows. At creatinine clearance less than 2 ml/min, $T_{1/2}$ can be 56 h, at 5–10 ml/min — 20–36 hours. Tobramycin easily penetrates the majority of tissues, its largest amount is found in kidneys, the smallest amount – in brain tissues. 90% of the drug in biologically active form is excreted by the kidneys during a day. After being ingested, it does not absorb. In hemodialysis, the antibiotic blood concentration decreases on the average by 50%.

Indications for tobramycin use are the same as for gentamicin. The antibiotic is applied as a rescue medication for treating infections caused by persistent strains of P.aeruginosa. In case of a severe infectious disease and a necessity of an urgent chemotherapeutic intervention, tobramycin in combination with ß-lactam antibiotics may be administered prior to making bacteriological diagnosis and determination of antibiogram for pathogens [3].

The objective of our study was to assess clinical and bacteriological efficacy and safety of Brakson (tobramycin manufactured by Yuria-Pharm, Ukraine) in the treatment of complicated urinary tract infections in 30 patients in conjunction with other medications of pathogenetic and symptomatic therapy. All patients were aged between 18 and 78 years, the majority were women (23 female patients). The study did not include patients who had aminoglycosides intolerance in past medical history, chronic renal insufficiency and who took antibiotics during last month.

The medication was administered intramuscularly (i.m.) or intravenously (i.v.) by drop infusion. For i.m. administration, the corresponding medication dose was injected directly from the ampoule. For i.v. administration, the solution was diluted in 100–200 ml of 0.9% sodium chloride solution, or 5% glucose solution; it was injected during 20–60 minutes. The single dose in adults and children older than one year was 1 mg/kg, daily dose – 3 mg/kg, the maximum daily dose – 5 mg/kg.

Urine culture and antibiogram were performed for all patients before drug administration and 7 days after its application. The pathogens excreted from urine in clinically significant concentrations (10,000 CFU/ml and higher) were taken into consideration. The complete blood count and common urine tests were also conducted as well as detection of blood creatinine level, ultrasonography and, if required, computerized tomography.

The assessment of the treatment's efficacy was based on the examination of clinical laboratory and microbiological indicators after 7 therapy days. Key clinical and laboratory indicators characterizing the inflammatory process activity were pain, dysuria, presence of intoxication symptoms (tachycardia, nausea, vomiting, dry mouth), temperature response, fever, laboratory indicators (leukocytosis, left deviation, increase in blood sedimentation rate, leukocyturia, blood creatinine level), ultrasound monitoring of kidneys.

According to the data presented in Table 3, all patients had urine catheters installed, suggesting that they had a hospital-acquired infection.

As a result of a microbiological examination in 30 patients with complicated UTIs, a microbial pathogen was isolated and identified in 25 (83.3 ± 7.0%) of them. The analysis of antibiograms has shown that the total number of strains sensitive to tobramycin was 86.7%. Non-sensitive *in vitro* were single *Enterobacter, Enterococcus* and *Pseudomonas* strains.

Tables 4 and 5 present bacteriological and clinical treatment results respectively. 76.7% of patients had a pronounced positive effect from treatment with Brakson.

On days 2-3 of treatment, body temperature returned to the normal or subfebrile one, pain in the lumbar region and lateral abdomen areas, dysuria, intoxication symptoms regressed. The laboratory control showed a considerable improvement of the common blood and urine analyses, and in individual patients – normalization of indicators already on day 4 of the therapy.

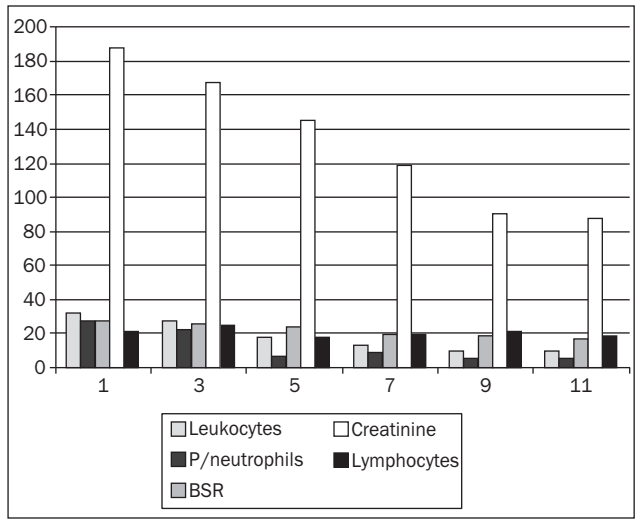

Fig. 1. Blood value dynamics in patients with complicated UTIs in the process of treatment with Brakson

Table 3. Patients with complicated UTIs who received a therapy with Brakson

Patients characteristics	Number, abs.	Number, %
Stent-associated infections	12	40
Catheter-associated infections in patients with BPH	10	33.3
Patients after endoscopic lithotripsy with nephrostome	8	26.7

Based on the results of a control microbiological examination, there was urine sterilization. An ultrasound monitoring of the kidney size and renal parenchyma thickness revealed on day 7 a positive dynamics with approximation of these indicators to the norm (Fig. 1). Given a satisfactory treatment result in 13.3% of patients, the dynamics of clinical and laboratory indicators was minimal, certain disease symptoms, changes in leukogram, leukocyturia were preserved by the time of a control examination. A decrease in the activity of infectious inflammatory process was observed with the availability of pathological changes in the common urine test.

Urine sterilization or replacement of a potentially pathogenic microorganism were recorded (Fig. 2).

In case of unsatisfactory treatment result, a subfebrile or febrile body temperature remained in 6.7% of patients. No positive dynamics was also recorded by laboratory and bacteriological criteria.

Nausea and vomiting were noted in 3 patients that could be attributed to intoxication. There are no grounds to consider these developments as side effects. Slight dyspepsia and headache did not require a withdrawal of the drug.

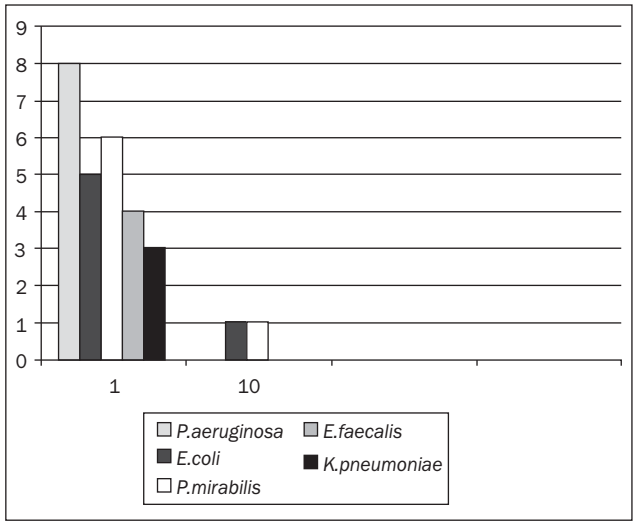

Fig. 2. Bacteriological efficacy of treatment of patients with complicated UTIs using Brakson

Conclusions

1. In the course of a study on the clinical and bacteriological efficacy of Brakson in patients with complicated urinary tract infections, the feasibility of application of this drug in this patient category has been confirmed.

2. The results of the laboratory examination of antimicrobial activity of Brakson prove its high efficacy (86.7%) in relation to the majority pathogens of complicated UTIs.

3. When applying Brakson, a high safety level, along with a substantial efficacy in 93.3% of patients, has been demonstrated in the majority of patients, which allows us to recommend it for treatment of complicated urinary tract infections as monotherapy.

Conflict of interests: not declared.

Reviewers: information is hidden.

Table 4. Bacteriological efficacy of treatment of patients with complicated UTIs using Brakson

Pathogen type	Strains number	Bacteriological result		
		Pathogen elimination	Pathogen replacement	Pathogen preservation
Enterococcus faecalis	7	6	1	0
Staphylococcus spp.	9	7	1	1
Streptococcus spp.	3	3	0	0
E.coli	5	4	0	1
Klebsiella pneumoniae	3	2	1	0
Pseudomonas aeruginosa	4	4	0	0
Absence of growth	5	–	–	–
Pathogen total	31	26 (86.7 %)	3 (10.0 %)	2 (6.7 %)

Table 5. Clinical efficacy of treatment of patients with complicated UTIs using Brakson

Clinical result	Number of patients, abs.	Number of patients, %
Good	21	70,0
Satisfactory	7	23.3
Unsatisfactory	2	6.7
Total	30	100.0

Table 6. Side effects of Brakson during combined therapy of complicated UTIs

Clinical result	Number of patients, abs.	Number of patients, %
Nephrotoxic effect	0	0
Ototoxic effect	0	0
Allergic reaction	0	0
Nausea	2	6.7
Vomiting	1	3.3

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Received on 25.11.15

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ЕФЕКТИВНА АНТИБАКТЕРІАЛЬНА ТЕРАПІЯ УСКЛАДНЕНИХ ІНФЕКЦІЙ СЕЧОВИХ ШЛЯХІВ

Резюме. У статті наведені дані дослідження щодо клінічної та бактеріологічної ефективності та безпеки препарату Браксон (тобраміцин) при лікуванні ускладнених інфекцій сечових шляхів. Відповідно до отриманих результатів продемонстровано доцільність призначення цього антибактеріального препарату у хворих з ускладненими інфекціями сечових шляхів. Згідно з показниками лабораторних досліджень антимікробної активності препарату Браксон його ефективність становить 87 %. Також було відзначено високий рівень безпеки препарату Браксон (93,3 %). Це дозволяє рекомендувати застосування препарату Браксон при ускладнених інфекціях сечових шляхів як монотерапію.

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