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Teicoplanin-TF in the treatment of severe infectious processes in children

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Teicoplanin-TF in the treatment of severe infectious processes in children

---------- Resume ----------

Article describes a traced effectiveness of the drug "Teicoplanin-TF" comprised of treatment of children's severe infectious processes, including surgical pathology. The result in all cases assessed as positive, including case of insufficient efficacy of prior antibiotic combination. Side effects and complications during use of the drug "Teicoplanin-TF" in children are not determined.

Keywords: glycopeptides, teicoplanin, severe infection, with children.

Resistance of microorganisms to antibacterial (ATB) preparations is gaining the increasing value every year [1]. It affects particularly negatively the outcomes of severe infectious processes, which are concentrating in intensive care units of hospitals of various profile. Quite often, it is necessary to include all the range of ATB-preparations which are available for the doctor in the therapy of such patients. In this regard, appearance of new antibiotics (ATB) in practical health care, which can affect the outcomes of diseases in critical patients, is extremely important. The representative of glycopeptide family - teicoplanin (TP) - which only recently appeared in the battery of clinical physicians of our country, though the experience of its use in world practice has began already in the second half of the 1980th, fully belongs to similar medicinal preparations (MP) [1]. The production of the specified MP in the present time is arranged in the Republic of Belarus at SOOO "TriplePharm". The preparation is released under the commercial name "Teicoplanin-TF" in the form of powder for preparation of solutions for intravenous and intramuscular administration in 200 mg and 400 mg bottles.

TP is a classical antibiotic of reserve which administration is reasonable upon infectious processes in most severe patients of various profiles. The mode of action of preparation is connected with the ability to block biosynthesis of a cell wall, to change permeability of cell membrane and negatively to affect the synthesis of RNA in bacterial cell [2]. It usually has bactericidal action, however, in relation to enterococci, some streptococci and the coagulase-negative staphylococcus acts bacteriostatically [1].

Is produced by Actinoplanes teichomyceticus and in chemical relation is a complex of six related compounds with differebt ATB-activity

TP activity is directed only on gram-positive bacteria (tab.). It is highly active in case of streptococcal infections including those caused by multi drug-resistant strains S. pneumonia, as well as in relation to Listeria spp. and some anaerobes (Clostridium spp., Peptostreptococcus spp., Propionibacterium acnes). The preparation works not only on coagulase-positive, but also coagulase-nerative staphylococci: St. epidermidis, St. haemolyticus, St. saprophyticus which clinical relevance has been constantly increasing during the last years [3, 4]. In the relation to the specified TP activators is, as a rule, more active than vancomycin [5,6]. The most important TP advantage is an ability to suppress methicillin-resistant strains of St. aureus and St. epidermidis (MRSA and MRSE, respectively), resistant or low-sensitivity to the majority of other ATB-preparations, including all beta lactams, aminoglycosides, macrolides, the majority of fluoroquinolones, etc. The frequency of MRSA/MRSE activators in case of staphylococcal infections in various countries reaches 24-60%, and in some regions of the USA - even 80% [2]. Quite often, the failures in the treatment of severe infectious processes in intensive care units are connected exactly with their predominance [7]. MRSA/MRSE of TP staphylococci also usually surpasses vancomycin in activity [5,6].

The most important etiological agents of many severe infectious processes are Enterococcus spp. TP belongs to a small number of ATB-preparations, which are able to suppress not only E. faecalis, but also E. faecium, which is resistant to the majority of ATB-preparations, including carbapenem. However, suppressing TP concentrations in relation to Enterococcus spp. are lower in comparison with the other representative of glycopeptide family - vancomycin (tab), which has not been used in our country for a long time.

Enterococci are able to develop the resistance to glycopeptides. However, despite the resistance, it is met more often in E. faecium, it can be developed among the strains E. faecalis as well [8]. The mechanism of resistance is associated with modification of the target of glycopeptide ATB-dipeptide D-Ala-D-Ala. The latter is a part of monomeric precoursor of peptidoglycan - UDP-N-acetylmuramylpentapeptides. Upon linking of D-Ala-D-Ala with glycopeptide synthesis of peptidoglycan is broken, therefore, creation of bacteria cell wall is damaged. There are some mechanisms of modification of D-Ala-D-Ala dipeptide on which basis some phenotypes of enterococci resistance are differentiated: vanA, vanB and vanC. In case of the two latter, variable sensitivity or complete resistance of activators to vancomycin is accompanied by TP activity maintenance [9]. According to the Republican scientific and practical center of oncology, hematology and immunology, the prevailing phenotype of E. faecium resistance among the patients observed by them was vanB: in 43.9 of 48.8% of resistant strains [10]. Therefore, TP-natural replacement of vancomycin in case of suspicion of enterococci resistance.

TP is high-active in relation to gram-positive clostridia, including C. difficile. This microorganism is an etiological factor of pseudomembranous colitis which, as a rule, is a complication of the previous ATB-therapy. The specified process is followed by the alteration mucous of intestinal tract, expressed in different degree, mainly of distal part of a large intestine, and in case of severe course can lead to death [11]. In case of pseudomembranous colitis of TP, along with vancomycin, - one of the means of the "last hope" which capable to stabilize the condition of the patient and finish the process by recovery [11,12].

Table
Antimicrobial activity of teicoplanin and vancomycin in vitro (MPK90 mg/l) in relation to gram-positive bacteria [3]

Microorganisms	Vancomycin	Teicoplanin
Staphylococcus aureus MS	2	0.5
Staphylococcus aureus MR	2	0.5
Staphylococcus spp. CN, MS	4	2
Staphylococcus spp. CN, MR	4	4
Streptococcus viridans	1	0.25
Streptococcus pyogenes	1	0.12
Streptococcus pneumoniae	0.5	0.12
Streptococcus agalactiae	0.5	0.12
Enterococcus faecalis	4	0.5
Enterococcus faecium	4	1
Listeria monocytogenes	0.5	0.25
Peptostreptococcus spp.	4	0.5
Clostridium jeikeium	1	1
Clostridium perfringens	0.5	0.5
Clostridium difficile	0.5	0.25
Propionibacterium spp.	0.5	0.25

Notes:
MS-methicillin-sensitive strains;
MR- methicillin-resistant strains;
CN- coagulase-negative staphylococci.

Actinomycetes, heterofermentative lactobacillus, Leuconostoc, Nocardia asteroides, Pediococcus, clamydia, mycoplasmas, mycobacteria, rickettsia, treponema are out of TP action area. The same concerns gram-negative activators [13]. In the latter case, the reason is the fact that the lipide layer of external membrane of gram-negative bacteria does not allow larger molecules of TP reach the layer of peptidoglycan. In case of bacteria resistance to TP, it is developing slowly, besides, the cross with preparations of other groups is absent [2].

In case of TP ingestion, it is practically not absorbed, it is in fact not metabolized by the organism (up to 80% is eliminated with kidneys intact). In this regard, during renal impairment dose correction is required. The preparation is not removed in hemodialysis. TP half-life is from 40 to 70 hours under normal function of kidneys that allows to administer it 1 time a day [1].

Indications for TP are the following: infectious processes caused by sensitive flora, including infections of respiratory and urinary tract, skin and soft tissues, bones and joints, endocarditis, peritonitis, pseudomembranous colitis. TP is one of preparations of choice in the complex therapy of sepsis. The role of gram-positive cocci in the specified disease is steadily increasing in recent years: 42% - in 1981-1983, 54% - in 1990-1992, 64.4% - in 1999 [14]. In this regard, the activators to a greater extent play a special role, the TP activity concerning them is preferable: S. aureus - 12.6%, coagulase-negative staphylococci - 37.3%, enterococci - 13.5%.

Due to the narrowness of TP action spectrum as monotherapy, as a rule, it is not used. It serves as an addition to ATB of mainly gram-negative direction or a broad spectrum: cephalosporins, carbapenems, fluoroquinolones. It is done to ensure a high activity of a combination concerning gram-positive activators, especially under suspicion of participation in the process of MRSA and MRSE of staphylococci.

Use of TP in severe infections is possible in children, starting from the early age. In this case, the development of a "red man syndrome", which is rather common for vancomycin, is unlikely [12]. In pregnancy, TP is used only in critical situations, and in case of its administration in the lactation period the breastfeeding is recommended to be stopped [13].

TP hardly penetrates the blood-brain barrier, but can be prescribed for the treatment of meningitis, caused by pneumococci resistant to penicillin [14].

TP is characterized by a low toxicity. In this regard, it is important to note that a total number of the side reactions, when using it, is much lower, than when using vancomycin [12]. A possibility of development of allergic reaction in the form of rash, itch, fever, bronchospasm, anaphylactic reactions, urticarias, angioedema, is specified, in very rare cases - exfoliative dermatitis, toxic skin necrosis, Stevens-Johnson syndrome [13]. However, the similar dangers, unfortunately, are always present in case of administration not only any ATB, but also in general of all known MP. At the same time, it is important to note that, in general, the risk of allergic reactions to glycopeptide is small, and TP in this relation is safer than vancomycin [15].

On the part of gastrointestinal tract, when using TP, nausea, vomiting, diarrhea, increase of activity of "hepatic" transaminases, increase in concentration of alkaline phosphatase, are possible. However, any of these manifestations, as a rule, does not influence significantly the possibility of preparation prescription. On the part of hemopoietic organs, agranulocytosis, eosinophilia, leukopenia, neutropenia, thrombocytopenia are described as rare side reactions [13]. For hematologic patients, the TP spectrum should be recognized as very successful, as the detection frequency of coagulase-negative staphylococcus only reaches 49 % and a phenomenon of methicillin-resistance is common in case of infectious processes in this group [8].

Most serious side effect an administration of TP is nephrotoxicity. At the same time, the risks of the latter in case of use of TP, is approximately twice (4.8 and 10.7% respectively, $p<0.0005$) lower, than vancomycin [12]. Perhaps, in certain degree, it is caused by lower therapeutic doses of the first [14]. Risks especially increase in simultaneous administration of TP and other potentially nephrotoxic MP: aminoglycosides, amphotericin In, cyclosporine, furosemide [13]. Owing to lower nephrotoxicity, the research of serum concentrations of TP is recommended only for the assessment of treatment efficacy [14], which significantly simplifies therapeutic process.

On the part of CNS secondary to TP administration, dizziness, headache, loss of hearing, sonitus, labyrinthine and vestibular disorders are possible. Local reactions in the form of dermahemia, tenderness in the place of introduction, development of thrombophlebitis or abscess are described [13]. It is necessary to notice that the majority the specified adverse events can be avoided under the right procedure of preparation introduction.

TP is usually introduced intravenously or intramuscularly [13]. In the first case, the bolus injection within 5 minutes or the infusion for 15-30 minutes is used. In the latter case the preparation is dissolved in 100 ml of infusion solution.

Initial dose for adults: intravenously 400 mg 1-2 times a day during the first 1-3 days, then - 200-400 mg a day intravenously or intramuscularly.

In case of burns and endocarditis, the maintenance dose is up to 12 mg/kg per day. For prevention of infectious complications in orthopedic or oro-maxillofacial surgery, a single 400 mg dose is introduced intravenously during anesthesia.

An initial dose for children at the age from 2 months to 16 years is 10 mg/kg intravenously in 12 hours 3 times, then - 6-10 mg/kg 1 time a day intravenously or intramuscularly; at the age under 2 months - 16 mg/kg (in the form of 30-minute intravenous infusion) on the first day, the maintenance dose is 8 mg/kg 1 time a day intravenously.

In case of pseudomembranous colitis, the way of introduction of TP is changed. The preparation is administered as 100-200 mg 2 times a day per os. The recommended dose is dissolved beforehand in 30 ml of water.

In the patients with malfunction of kidneys, dose correction begins on the 4th day for maintenance of TP concentration in serum at the level of 10 mg/l. In creatine clearance 40-60 ml/min, the maintenance dose is either decreased by half, or introduced 1 time in two days. For the patients with creatine clearance less than 40 ml/min or for the patients who are on hemodialysis, inject 1/3 dose daily or one dose 1 time in 3 days [13].

Hematotoxic TP potencies are not high, which allows using them in patients with severe hematologic pathology, as well as febrile neutropenia, when standard therapy is ineffective [10, 14].

TP is well approved in hospital practice. The present MP is a common component of the "Standards of antibacterial therapy..." in various developed countries [16, 17]. At the same time, the experience of TP administration in children, according to a number of researchers, is not enough [18]. In this regard, we give several clinical observations of successful administration of TP in children of various age with severe pathology.

The child Sh., 2.3 years old, was admitted to Vitebsk children's regional clinical hospital on 10.02.2013 with suspicion of acute appendicitis. On 11.02.2013 after the surgery, the diagnosis was established: acute gangrenous and perforated appendicitis, appendicular abscess; general fibrinopurulent peritonitis. As initial ATB-therapy, a combination of ceftriaxone, amikacin and metronidazole in age-dependent doses was administered.

The dynamics on treatment is unsatisfactory. Artificial pulmonary ventilation (APV). The fever continues to be up to 38.5 °C, expressed toxicosis, stomach is inflated, vermicular movement is absent.

13.04.2013 - relaparotomy due to suspicion of intestinal obstruction. Ongoing general fibrinopurulent peritonitis was diagnosed. The intubation of small intestine was made. Due to the severity of condition, ATB-therapy change was made: since 14.02.2013 meropenem in combination with MP "Teicoplanin-TF" was administered (10 mg/kg 3 times in 12 hours, then the same dose 1 time per day intravenously in 60 min for 100 ml of physiological solution).

On the top of already administered therapy - gradual positive dynamics of the process. Termination of APV from 16.02.2013, complete normalization of temperature by 23.02.2013. SRP decreased from 174 mg/l to 66 mg/l by 16.02.2013 and to 6 mg/l by 20.02.2013. The condition was moderate by 25.02.2013, henceforth - recovery.

Tolerance of therapy with MP "Teicoplanin-TF" is regarded as good. Urea level in the course of the treatment was within 4.0-4.7 mmol/l, other possible side reactions were not recorded.

The child K., 9 months, for the first time was admitted to Vitebsk children's regional clinical hospital in March, 2012. For the next 2 months 4 times (06.03.2012; 10.03.2012; 14.03.2012; 06.04.2012) underwent surgeries in connection with perforation of a stomach wall associated with hypoplasia of its muscular layer. Ileostomy was applied. During the treatment, he received practically all ATB-preparations available in clinics.

On admission on 07.12.2012, complaints on the increased temperature up to 39,7 °C. Established diagnosis: ARI, severe form; congenital hypoplastic stomach wall muscles (condition after surgical treatment); ileostomy; oligotrophy of the 3 degree (deficit of body weight more than 30%); candidiasis of mouth mucous and skin; bronchopulmonary dysgenesia; psychomotor retardation; rickets II, subacute course.

Ceftriaxone in age-dependent doses was administered as ATB-therapy. Temperature reaction disappeared, the condition was temporarily stabilized, however, since 27.12.2012 temperature became hectic with ranges from normal to 39,9 °C. On 04.01.2013, during the X-ray examination of lungs, bilateral focal pneumonia was revealed. Sequentially, ceftazidime, vancomycin, clindamycin, combination of ceftriaxone with amikacin were prescribed without essential result. On 23.01.2013 in the cerebrospinal fluid (CBF), the changes typical for purulent meningitis were detected: pleocytosis 536/3 in 1 mkl, protein 1.43 g/l, formula: neutrophils 32%, lympho/ monocytes 68% (it is necessary to consider that the research was conducted secondary to the massive ATB-therapy).

On 28.01.2013, the disease was already regarded as sepsis which developed owing to the immunodeficiency caused by the main pathology. The combination of cefepime and amikacin, after normalization of CSF content - MP "Stizon" + vancomycin was administered. However, the temperature reaction with rises above 38 °C remained, radiologically, only moderate positive dynamics was detected in lungs. In the specified situation, the decision to use a combination of MP "Stizon" and "Teicoplanin-TF" was made. The latter was prescribed in the dose 10 mg/kg 3 times in 12 hours and hereafter in a maintenance dose 10 mg/kg a day intravenously in the form of slow infusion (30 min) on physiological solution.

On the top of the specified therapy slow dynamics was positive. Though periodic rises in temperature remained, they became less regular, infiltrative shadows in lungs disappeared, CSF without pathology, the SRP level decreased from 42 g/l to 18 g/l. After stabilization of condition, the child was transferred to the Pediatric surgery center for further surgery treatment. The side reactions on introduction of MP "Teicoplanin-TF" (total duration of therapy more than 3 weeks) in the child were not registered, urea and creatinine values were steadily normal, the AAT and ALT level without pathology (45 IU/l and 14.8 IU/l under the norm for this age <89 IU/l and <39 ME/l, respectively).

The child M, 10 years old, was admitted to the Vitebsk children's regional clinical hospital on 09.04.2013. On 01.04.2013, in the regional hospital he underwent a surgery in relation to the acute gangrenous and perforated appendicitis, generalized fibrinopurulent peritonitis. He received ceftriaxone, cefepime, amikacin, metronidazole as ATB-therapy. It was transferred to the regional level in connection with insufficient positive dynamics of the process.

On admission, the condition was serious, adhesive obstruction was diagnosed. On 09.04.2013 relaparotomy was carried out. Adnations in the area of ileum were incised, decompressive intubation of small intestine was made. A combination of meropenem and vancomycin was administered as ATB-therapy. In this context, the child continued to have a fever up to 38,5 °C, SRP level increased from 12 mg/l to 48 mg/l. In peripheral blood leukocytosis - 11.7 x 109/l, stab shift - 22%, neutrocytosis - 92%. The stomach was uniformly inflated, intense, tendered in all segments, peristaltic noises were not audible.

Hereafter, dynamics unsatisfactory. On 13.04.2013 left-side lower lobe focal pneumonia was radiologically diagnosed. The data on the part of stomach are the same . Periodical congestion in stomach. Due to suspicion of presence of intrafilar abscesses, on 17.04.2013 relaparotomy was made, adhesive obstruction in the area of small intestine was diagnosed, signs of current purulent peritonitis. Adnations were incised, ileostomy was applied, intestinal intubation. A combination of ceftriaxone, amikacin and metronidazole in age-dependent doses was prescribed as ATB-therapy.

After the surgery, the condition of the child was very heavy. Stagnation in stomach. The temperature was subfebrile up to 37,5 °C. Peristaltic noise was weak. SRP was 72 mg/l. In peripheral blood, leukocytosis - 21.7 x 109/l, stab shift - 5%, neutrocytosis - 84%. On 18.04.2013 in connection with condition severity, insufficient effectiveness of the previous ATB-therapy, the combination of MP "Stizon" + "Teicoplanin-TF" was administered. The latter in a dose 400 mg 1 time a day intravenously in the form of slow injection on 20 ml of physiological solution.

A positive dynamics in child's condition for the first time was noted since 19.04.2013. The temperature was normalized, general well-being was significantly improved. Within several next days, abdominal distention disappeared, its tenderness decreased gradually. SRP decreased to 30 mg/l by 21.04.2013, leukocytosis and neutrocytosis in clinical blood analysis was decreased, on 22.04.2013 pneumonia resolution was detected in the X-ray imaging of lungs.

Tolerance of the administered combination of ATB was regarded as good. Side effects were not recorded. Urea level secondary to treatment was 2.25-4.5 mmol/l. On the 5th day of therapy some increase in serum level of transaminases was detected: AAT 72 U/l (norm to 50 IU/l), the ALT 64 U/l (norm (39 IU/l). However, in the setting of MP "Teicoplanin-TF", the specified shifts tended to normalization. Besides, the detected changes could be caused by the repeated severe surgical intervention, as well as the influence of the MP having similar side effects, which were received by the patient at the same period: Stizon, fat emulsions for parenteral feeding, Fluconazole, etc. [1].

In such a way, the effectiveness of MP as a part of complex therapy of children with heavy infectious processes, including in surgical pathology, was traced. The result of treatment in all cases was regarded as positive. Serious side effects, including nephrotoxicity, were not recorded. Despite various options of introduction of MP

"Teicoplanin-TF", including in the form of intravenous injection, a "red neck" syndrome (a "red man" syndrome), which we detected many times earlier in administration of vancomycin, was not observed in any patients.
The obtained data give evidence of efficiency, safety and prospects of application of HP "Teicoplanin -TF" as a part of perspective of ATB-therapy of severe infectious processes in children in conditions of intensive care units.

LITERATURE

1. Practical guidance on antimicrobial chemotherapy / under the editorship of L.S. Strachunsky, Y.B. Belousov, S. N. Kozlov. - 2004.
2. Jinjian, Fu, Xiaohua, Ye, Cha, Chen, Sidong, Chen//PLoS One. - 2013. - Vol. 8, No. 3. - P. 582-540.
3. Yakovlev, V.P., Yakovlev, S. V. Rational antimicrobial pharmacotherapy. - M.: Litterra, 2003. - P. 121-124.
4. Beloborodov, N. V. Glycopeptides (vancomycin, teicoplanin) - a place in antibacterial therapy of high-risk patients [Electronic resource]: www.rusmedserv.com/antibioroom/glyc_art.htm.
5. Tallent, S.M., Bischoff, T., Climo, M. et al.//J Clin Microbiol. - 2002. - Vol. 40. - P. 2249-2250.
6. Sieradzki, K., Leski, T., Dick, J. et al.//J Clin Microbiol. - 2003. - Vol. 41. - P. 1687-1693.
7. Wood, M.J.//J Antimicrob Chemother. - 1996. - Vol. 37. - P. 209-222.
8. Escande, M.C., Helbrecht, R.//Supp Care Cancer. - 1998. - Vol. 6, No. 3. - P. 273-880.
9. Lawrence, D.R., Benitt, P. N. Clinical pharmacology: in 2 v.; transl. from English - M.: Medicine, 1991. - T. 1.
10. Report on carrying out a pilot study of preparation "Teicoplanin-TF". - RRPC of Pediatric Oncology, Hematology and Immunology, 2012.
11. Malov, VA.//Clinical microbiology and antimicrobial chemotherapy. - 2002. - V. 4, No. 1. - P. 22-32.
12. Svetitsky, S., Leibovici, L., Paul, M.//Antimicrob.Agents Chemother. - 2009. - Vol. 53, No. 10. - P. 4069-4079.
13. Instruction on medical use of medicine Teicoplanin-TF [Electronic resource]//www.vidal.by/poisk_preparatov/teicoplanin-tf.htm.
14. Beloborodov, V.B.//Consilium Medicum. Infections and antimicrobial therapy. - 2001. - V. 3, No. 3.
15. Yu-Hor, Thong, B.//Allergy Asthma Immunol Res. - 2010. - Vol. 2, No. 2. - P. 77-86.
16. Guideline for the Empirical Treatment of Infections in Adults [Electronic resource]//www.ruh.nhs.uk.
17. Guidelines for the prophylaxis and treatment of methicillin-resistant Staphylococcus aureus (MRSA) infections in the UK//J. Antimicrob. Chemother. - 2006. - Vol. 57, No. 4. - P. 589-608.
18. Rubenstein, AA. Adverse reactions in administration of "new" antibiotics [Electronic resource]//www.antibiotic.ru

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