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Cefpirome. Literature review

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Article received: 17.07.2014. Accepted for publication: 17.09.2014.

Researchers around the world acknowledge a continuing growth of antibiotic resistance. Thus, it is especially important to select from a wide range of antibacterial agents in the pharmaceutical market the ones appropriate for specific regional sensitivity, only in accordance with clearly defined indications and in order of priority for each specific case. The most frequently used are wide range drugs, including the 4th-generation cephalosporins active against gram-positive and gram-negative microbes and most anaerobes. This review is dedicated to a representative of this group – cefpirome. The authors indicate the primary indications for use thereof and present a comparative effectiveness analysis. Cefpirome is as effective as cefepime, which is important, particularly because of growth of bacterial resistance against the 3rd-generation cephalosporins. Its significant advantage is activity against several enterococci and anaerobes. Cefpirome penetrates various body tissues fairly well and establishes there bactericidal concentrations against most known clinically significant microbes. The trials have demonstrated clinical effectiveness of the drug for various nosocomial infections, such as sepsis (62-77%), febrile neutropenia (53-84%), intra-abdominal infections (83%), complicated urinary infections (100%) etc. The drug features low toxicity: it does not exceed the one in cefepime and the 3rd-generation cephalosporins, which makes it possible to use cefpirome as the drug of the 1st choice for severe hospital-acquired infections given its wide antibacterial range and clinical significance.

Keywords: cefpirome, cefepime, nosocomial infections, sepsis, febrile neutropenia, antibiotic resistance, treatment of gram-negative infections, 4th-generation cephalosporins.

INTRODUCTION

Cefpirome is a 4th-generation cephalosporin highly active against both gram-positive and gram-negative (including *Pseudomonas aeruginosa*) microbes. Compared to the 1st-, 2nd- and 3rd-generation cephalosporins, 4th-generation cephalosporins (cefpirome and cefepime) are more effective against gram-positive microbes and *pseudomonas aeruginosa* and are sufficiently stable against class 1 chromosomal cephalosporinases (usually produced by *Enterobacter spp.*). Cefpirome features a high level of safety and an extremely low risk of nephrotoxicity [1-3]. Comparative studies have demonstrated high clinical effectiveness of the drug for bacteremias [1]. Cefpirome's wide antibacterial spectrum, low toxicity and anti-staphylococcal activity are the advantages thereof for severe sepsis, febrile neutropenia and other nosocomial infections, which are difficult to treat with routine antibiotics.

Microbiological activity

Methicillin-resistant *Staphylococcus aureus* (MRSA)-induced infections are among the most clinically significant and difficult to treat infections. Glycopeptides vancomycin and teicoplanin (only vancomycin is available in Russia) are the drugs of choice therefor; however, the therapy is not always successful [4].

Several studies have demonstrated synergism of a vancomycin (MIC 0.25-1) or teicoplanin (MIC 0.125-1) combination with ceftazidime (MIC 0.125-0.5) determined by the time of bacterial death [5]: thus, an *in vitro* study of 12 *MRSA* strains demonstrated spread of the synergic effect to glycopeptide-intermediate strains.

Similar results were obtained in a prospective randomized study of the vancomycin-ceftazidime combination's effect on the microbial death rate in the treatment of the *MRSA*-induced infections at a resuscitation and intensive care unit [6]. The study involved 20 patients with severe pneumonia or bacteremia. The first group (n = 10) was treated with vancomycin (2 g/day), the second (n = 10) – with a combination of vancomycin (2 g/day) and ceftazidime (4 g/day). Although the parameters under analysis were better in the 2nd group (microbial death rate – 40 and 60%, serum's bactericidal properties [at a 1/16 dilution] – 68 and 88.8%), the difference was not significant except for decrease in the concentration of inflammatory markers – 119.5 and 198.6 mg/l (p < 0.05) on day 3.

In general, the 4th-generation cephalosporins (ceftazidime and ceftepime) are especially effective against gram-negative microbes. However, several studies have demonstrated a surprisingly high ceftazidime activity against gram-positive aerobes [7, 8]: thus, out of the 434 coagulase-positive (CPSs) and coagulase-negative staphylococci (CNSs) extracted from clinical biomaterials, 81.3 and 91.6%, respectively, were sensitive to ceftazidime (compared to 35.1 and 26.5% sensitivity to oxacillin (sensitivity was measured by means of Mueller-Hinton agar dilution; the minimal inhibiting concentration for ceftazidime varied from 0.5 to 8 mg/l) [8]. Other authors compared this drug with the 3rd-generation cephalosporins (ceftazidime, cefoperazone, ceftizoxime, ceftriaxone) using 1,300 gram-positive and gram-negative microbes obtained from 13 medical centers [7]. Bacterial identification was performed using semi-automatic microbiological systems; sensitivity to antibiotics was measured by means of a modified Kirby-Bauer test and assessed in compliance with the CLSI (NCCLS) standards. Ceftazidime demonstrated higher activity against both gram-positive (enterococci, *MRSA* and β -hemolytic streptococci) and gram-negative strains (*Escherichia coli*, *Klebsiella*, enterobacters, protei and *Salmonella typhi*). In general, the share of *Escherichia coli*-sensitive strains was 87% for ceftazidime and 61% for the 3rd-generation cephalosporins; *Klebsiella spp.*-sensitive – 84 and 56%; *Enterobacter spp.*-sensitive – 88 and 59%; *Proteus spp.*-sensitive – 97 and 92%; *S. typhi*-sensitive – 98 and 96%; *Staphylococcus spp.*-sensitive – 86 and 59%; *Enterococcus spp.*-sensitive – 82 and 72%, respectively. The activity of ceftazidime and ceftazidime against *Pseudomonas aeruginosa* was comparable [7]. Thus, the authors have concluded that ceftazidime features a wider spectrum and higher activity against most clinically significant nosocomial microbes.

A study (Japan, 2008) of 4,228 nosocomial microbial strains from 51 medical centers was dedicated to comparative analysis of sensitivity of the 3rd- (ceftazidime and cefoperazone/sulbactam, as well as piperacillin and imipenem) and the 4th-generation cephalosporins (ceftazidime and ceftepime) [9]. CNS and CPS non-methicillin-resistant strains were 100% sensitive to all β -lactams (except for ceftazidime). *Escherichia coli* strains were the most resistant against piperacillin (24.6%), whereas the resistance thereof against other β -lactams (including ceftazidime) was below 4.5%. *Pseudomonas aeruginosa* resistance was slightly higher – from 9.1% against piperacillin to 16.3% against ceftazidime. According to the obtained data, the proportion of resistant strains slightly decreased from 2006; the authors concluded that this fact totally reflected policies of consumption of specific antibiotics at the centers involved in the study [9].

However, most authors mention increase in *Pseudomonas aeruginosa* resistance to β -lactam antibiotics around the world [3]. The study performed in Bulgaria analyzed 203 *Pseudomonas aeruginosa* strains obtained from different patients in the course of 6 years. The resistance rate was high: 56.8-93.1% for penicillins (including piperacillin + tazobactam), 59.1-79.7% for aminoglycosides, 42.3-45.5% for carbapenems and 45.8-58.2% for anti-*Pseudomonas aeruginosa* 3rd-4th-generation cephalosporins (including ceftazidime). 49.8% of the *Pseudomonas aeruginosa*

strains were multi-resistant. β -lactamases bla (OXA-group) – 41.3% - and bla (VEB-1) – 33.1% - were prevalent. Carbapenemases IMP and VIM were not observed. The authors concluded that carbapenem resistance was likely associated with protein OprD deficiency and active efflux [10]. *Klebsiella* strains were equally sensitive (97.6-99.6%) to the analyzed β -lactams, as well as enterobacter, citrobacter and serratia strains. However, an earlier study performed by the same authors demonstrated higher sensitivity of *Klebsiella* strains to ceftiofame, cefepime and imipenem [10]. Results of a similar study performed in Japan confirm equal activity of ceftiofame, the 3rd-generation cephalosporins and cefepime [11].

Another study [12] was aimed at comparing *Klebsiella spp.*-sensitivity of ceftiofame and cefepime due to increasing resistance of the 3rd-generation cephalosporins against the β -lactamase-producing *Enterobacteriaceae*. 342 microbes obtained from different pathological materials of the patients admitted to Western Romanian clinics were analyzed. Activity of both drugs was the same; the average minimal inhibiting concentration (MIC) was 1 mg/l; MIC of more than 60% of the strains was below 8 mg/l; therefore, the authors stated high activity of the 4th-generation cephalosporins – ceftiofame and cefepime – against the *klebsiella*-induced infections [12].

Huang et al. [13] analyzed sensitivity of 588 microbial strains extracted from blood of oncology patients (476 bacteremia episodes): *E. coli* – 22.4%, *Klebsiella pneumoniae* – 17.6%, *Staphylococcus aureus* – 9.7% (MRSA – 55.8%); coagulase-negative staphylococci were primarily represented by methicillin-resistant variants. Sensitivity of gram-negative microbes to the analyzed antibiotics (ceftiofame, cefepime, piperacillin/tazobactam and carbapenems) was comparable – 85% among patients with and without febrile neutropenia. The authors stated equal value of the aforementioned drugs for empiric treatment of blood flow infections in oncology patients.

Pharmacokinetic peculiarities

As most cephalosporin antibiotics, ceftiofame is poorly absorbed from the gastrointestinal tract and is thus used only parenterally (intravenously or intramuscularly). The drug's bioavailability is high in the event of intramuscular administration. The elimination half-life is ca. 2 hours (1.8-2.2 hours in patients with normal renal function); it does not depend on the dose and duration of use. The antibiotic is found in blood in therapeutic concentrations for 12 hours, which is why it is prescribed BID. The average drug's concentration in blood plasma 5 minutes after i/v administration of 1 g is 81 mg/l. Binding with plasma proteins is ca. 10%. Cumulation at repeated administration is not observed. Ceftiofame is primarily eliminated by kidneys by means of glomerular filtration (80-90% of ceftiofame is extracted with urine within the first 24 hours). The average drug's concentration in blood plasma of over-65 patients 5 minutes after i/v administration of 1 g may be as high as 127.1 mg/l; the elimination half-life increases up to 4.5 hours. Cumulation at multiple administration is not observed. Joukhadar et al. performed a pharmacokinetic comparison of ceftiofame use in 12 patients with septic shock and 6 volunteers: they analyzed permeability of the drug's dose (2 g) into interstitial fluid of skeletal muscles [14]. Results were comparable: 16.0 ± 1.1 and 18.8 ± 1.1 mg/ml per minutes in patients and volunteers, respectively ($p > 0.05$). The drug's concentration in plasma and interstitial fluid exceeded 28 mcg/ml within the observation period of 240 minutes and epy MIC for most clinically significant pathogens. The authors state reasonability of using ceftiofame for empiric treatment of sepsis. Other authors have come to the same conclusions by measuring extracellular concentration in normal lung tissue and inflamed lung tissue of patients with sepsis [15]. They demonstrated that ceftiofame concentration in both normal lung and inflamed lung and blood plasma were equal and that the drug's concentration exceeded MICs for most microbes within 12 hours after 30 mg/kg dose administration.

Indications for use: infectious inflammatory diseases induced by sensitive bacteria: sepsis/bacteremia; complicated urinary infections, including pyelonephritis, pyelitis, urethritis,

cystitis; respiratory infections, including pneumonia; lung abscess; pleural empyema; skin and soft tissue infections; wound infections; infections in patients with neutropenia.

Contraindications: intense allergy to cephalosporins, pregnancy, lactation, under-12 children. Care must be exercised when prescribing the drug to patients with gastrointestinal diseases, including ulcerative colitis, regional enteritis and severe renal failure.

CLINICAL STUDIES

Febrile neutropenia

Progress in antitumor chemotherapy may be leveled off by infectious complications, especially by febrile neutropenia (FN), which often comes secondary to the primary disease. FN is especially aggressive and difficult to treat in patients with oncohematological diseases due to duration and intensity of neutropenia. Fever is often the only clinical manifestation of FN. Broad antimicrobial action spectrum antibiotics ought to be prescribe as soon as possible. Infection is microbiologically confirmed rather rarely (25-40%).

3rd-4th-generation cephalosporins featuring anti-pseudomonas aeruginosa activity (ceftazidime or cefepime), carbapenems or “protected” anti-pseudomonas aeruginosa penicillins (ticarcillin/clavulanate or piperacillin/tazobactam) are the 1st line drugs for FN. Supplementation of the aforementioned drugs with aminoglycosides does not improve treatment results [16, 17].

F. Bauduer et al. [17] assessed results of a randomized multicenter study, where cefpirome (4 g/day) or piperacillin/tazobactam (12 g/day) were used as the 1st line drugs for chemotherapy-induced FN in patients with oncohematological diseases. 208 FN episodes were analyzed: 10 cases out of them concerned allotransplantation of stem cells, 38 – autologous transplantation thereof. The average duration of neutropenia was 17 days. The infection was microbiologically confirmed in 27% of the cases. The obtained clinical effects of cefpirome surpassed clinical effects of piperacillin/tazobactam, although the difference was not significant: fever disappearance after 2 days of therapy and negative results of bacteriological analysis were obtained in 62; 61 and 50; 55% of the cases, respectively. Use of cefpirome did not require shift to other antibiotics (no superinfection) in 59% of the cases (50% - fir piperacillin/tazobactam). Incidence of these side effects was insignificant in both groups.

The authors stated similar effectiveness of the drugs; they may be recommended as the 1st line drugs for FN.

Other authors empirically used cefpirome to treat FN in 140 patients [18]. Microbes (13 gram-positive and 9 gram-negative) were detected in 20 patients. On the average, fever disappeared after 3.1 days of therapy in 84.1% of the patients. The average time of microbial (if present) eradication was 5 days. The authors recommend using cefpirome as the 1st line highly effective and financially sound drug for FN.

G.J. Timmers et al. [19] analyzed 154 FN episodes in 106 patients with oncohematological diseases and demonstrated high effectiveness of cefpirome. The average fever duration was 4.5 days; the infection was microbiologically confirmed in 36% of the cases (44% of the strains were cefpirome-resistant); infection was clinically detected in 26% of the patients, idiopathic fever – in 38% of the patients. The average clinical effect was 53%; it was the highest at idiopathic fever – 76%; at clinically proven infections – 53%; at microbiologically confirmed infections – 27% (weak effect may be caused by resistance of some microbes to the analyzed antibiotic). No adverse effects were registered. The authors recommend prescribing cefpirome as the 1st line drug for FN; however, high risk of pseudomonas aeruginosa resistance (2 strains were identified in this study; both were cefpirome-sensitive) requires multimodal therapy.

Genitourinary infections

A comparative multicenter study (2004-2005) of patients with complicated and non-complicated urinary infections was performed in 14 medical centers in Japan [20]. The highest activity of cefpirome and cefotiam was observed against strains of escherichia coli – common causative agents of urinary infections.

A.M. Nikolovski et al. [21] achieved a 100% clinical effect and complete eradication of causative agents in 20 patients with acute and severe urinary infections, which is why they recommended cefpirome as the 1st line drug for this disease.

High clinical effectiveness of the drug was demonstrated in 88 patients with different gynecological infectious diseases, as well as for prevention of postoperative infections after vaginal hysterectomy. Clinical effect was 77%; bacterial eradication was observed in 67.8% of the cases [22].

Japanese authors [23] demonstrated effectiveness of cefpirome against a range of anaerobic microbes (*Bacteroides spp.*, *Prevotella spp.*, *Porphyromonas spp.*) in 146 patients of obstetric-gynecological clinics. Clinical effect was registered in 122 cases. Eradication of *Bacteroides spp.* was observed in 37 out of 54 patients, of *Prevotella spp.* – in 38/49, of *Porphyromonas spp.* – in 5/5. Adverse effects were observed in 4.76% of the cases. On the basis of these results, the authors state safety and effectiveness of cefpirome for use at obstetric-gynecological clinics.

Intraabdominal infections

Cefpirome takes precedence over other cephalosporins not only in the high antianaerobic activity regard. Thus, Giamarellou [24] demonstrated its uniqueness in respect of enterococci. Surgical infections are rather versatile: intraabdominal infections, obstetric and gynecological infections, musculoskeletal and soft tissue infections. Due to the peculiarities thereof, antimicrobial chemotherapy usually plays a supporting role. The most commonly used drugs are the 1st-2nd-generation cephalosporins combined with antianaerobic drugs and aminoglycosides in order to broaden the combination's antimicrobial spectrum. The 4th-generation cephalosporins were more or as effective as cefotaxime and ceftazidime [25]. *MRSA* and *Bacteroides fragilis* are not covered by the 4th-generation cephalosporins; however, some strains are cefpirome-sensitive. Moreover, cefpirome is the only effective cephalosporin against enterococci. According to the author, cefpirome and cefepime are highly indicated for empirical therapy of severe surgical infections; combination with nitroimidazoles (metronidazole) may be useful.

Sepsis and bacteremia

A group of researchers performed a multicenter comparative study of effectiveness of cefpirome (4 g/day) and ceftazidime (6 g/day) for empirical therapy of 100 patients with severe community-acquired sepsis [1]. Clinical effect of cefpirome and ceftazidime was 77 and 67%, respectively; bacteriological effect – 90 and 86% (non-significant difference). The average treatment duration was 9 days: 1-23 days in the cefpirome group and 0-25 days in the ceftazidime group. Drug monotherapy was performed in 82% of the cases in the cefpirome group and in 78% of the cases in the ceftazidime group. Other patients were additionally prescribed metronidazole and/or vancomycin and/or antifungal drugs. The most commonly observed microbes were *Escherichia coli* (35%), *Pneumococcus* (12%) and *Staphylococcus aureus* (23.8%). In total, 11 microbes were cefpirome-resistant, 10 – ceftazidime-resistant. Adverse effects were observed in 29 and 22% of the cases. In a randomized study of 3,103 cefpirome-treated patients, adverse effects (probably associated with treatment) were also observed in 22% of the cases [2]. Adverse effects were observed in 26% of the 1,134 ceftazidime-treated patients. All the other parameters, including mortality (9-12%) were almost the same (non-significant difference). The authors state effectiveness and safety of cefpirome for bacteremia. Broad antibacterial spectrum against gram-positive microbes and a possibility of administering the drug BID make it not only effective, but also more financially sound than other drugs.

Use of cefpirome in pediatric practice

Cefpirome is not indicated for under-12 children in Russia, the USA and European countries. However, experience of Japanese researchers demonstrates the safety and high activity thereof for treating various infections induced by sensitive microbes in children aged from 1 month to

12 years. The authors observed high ceftiofime concentration in cerebrospinal fluid when treating purulent meningitis (general clinical effect – 93%) and absence of adverse effects [26-28].

CONCLUSION

Thus, one of the most important properties of ceftiofime is broader antibacterial activity spectrum (stability against various β -lactamases) than in the 3rd-generation cephalosporins, which covers gram-positive and gram-negative microbes and most anaerobes. Combination of ceftiofime with vancomycin improves its clinical effect against *MRSA*; high activity against enterococci and anaerobes positively sets it apart from other 3rd-4th-generation cephalosporins. Ceftiofime is as active as cefepime and other 3rd-generation cephalosporins: several studies have demonstrated the clinical effectiveness thereof for treating patients with febrile neutropenia and sepsis. Ceftiofime penetrates various body tissues well and establishes there in the concentrations bactericidal to most clinically significant microbes. The drug is easily metered, which makes it financially sound; it features low toxicity (not higher than that of cefepime and the 3rd-generation cephalosporins). The antibiotic's effectiveness against various severe nosocomial infections has been proved; broad microbiological spectrum allows using it for monotherapy.

CONFLICT OF INTEREST

The author has indicated she has no financial relationships relevant to this article to disclose.

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