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journal homepage: <http://www.curipms.umlub.pl/>

Overview on fosfomycin and its current and future clinical significance

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ARTICLE INFO

Received 02 March 2015

Accepted 18 March 2015

Keywords:

fosfomycin,
urinary tract infections,
multi-resistant bacterial
infections.

ABSTRACT

Fosfomycin is an old antibiotic with a unique chemical structure and with broad-spectrum activity against numerous bacterial pathogens, both Gram-positive and Gram-negative, including resistant and multi-resistant strains. This antibiotic was accepted into clinical practice in the early 1970s. Its use, however, has been limited for several years for treating mainly lower uncomplicated urinary tract infections (in the form of fosfomycin trometamol taken orally). Nowadays, many clinicians and scientists are looking at this antibacterial drug for its employment in the treatment of severe infections caused by multi-resistant bacteria. Fosfomycin as an intravenous formulation (fosfomycin disodium) achieves clinically relevant concentrations in the serum and the cerebrospinal fluid, in kidney, bladder wall, prostate, lungs, bone and heart valves tissues, as well as in inflamed tissues and abscess fluid. The available clinical studies confirmed the efficacy of intravenous fosfomycin for the management of severe infections caused by multi-resistant pathogens.

INTRODUCTION

Fosfomycin, originally named 'phosphonomycin', was discovered in Spain, in 1969, being a product of native *Streptomyces* species, and its development for medical use began there in 1971. This antibiotic was initially used parenterally as the disodium salt form, for the treatment of serious infections, e.g. meningitis [4,33]. With time, its employment has been limited to treating lower uncomplicated urinary tract infections (in an oral formulation as fosfomycin trometamol) [29]. Now, in current medical practice, in the era of diminishing antibiotic options, a fosfomycin use renaissance is observable due to its good activity against resistant and multi-resistant bacteria [7,22,29,32].

FOSFOMYCIN - GENERAL INFORMATION

Fosfomycin ([[(2R,3S)-3-methyloxiran-2-yl]phosphonic acid), of the family of phosphonic antibiotics, is a unique antibiotic of a chemical structure unrelated to those of any other known antibacterial agent [4,21,29,33]. Fosfomycin

is a bactericidal agent that inhibits bacterial cell wall biosynthesis by acting on the initial stages in the synthesis of peptidoglycan precursors: the inhibition of UDP-N-acetylglucosamine enolpyruvyl transferase (MurA) [1,4,10,21,33]. This enzyme is responsible for the synthesis of UDP-N-acetylenolpyruvylglucosamine, which is a pentapeptide intermediate in the biosynthesis of the peptidoglycan layer of the bacterial cell wall [28]. Due to its different chemical structure and mechanism of action, fosfomycin does not have cross resistance with the currently used drugs [29].

Fosfomycin has a broad spectrum of antimicrobial activity, including that upon several Gram-negative and Gram-positive aerobic pathogens [14,33]. The activity of fosfomycin depends on its transport into bacterial cell by way of transport systems for L- α -glycerophosphate and hexose monophosphate, involving the presence of glucose-6-phosphate. Because of this reason, the determination of antimicrobial activity of fosfomycin *in vitro* requires an addition to the medium of glucose-6-phosphate [33].

Fosfomycin has a serum half-life of approximately 1,75 hours [1]. However, it shows post-antibiotic effects *in vitro* against *E. coli* or *P. mirabilis*, varying between 3.4 h and

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4.7 h, depending on the applied drug concentration [28]. Fosfomycin also exerts time-dependent bactericidal activity against both Gram-negative and Gram-positive pathogens [29]. The antibiotic is available as intravenous formulation (fosfomycin disodium) and as oral formulations (fosfomycin trometamol - a salt of fosfomycin with tromethamine - and fosfomycin calcium) [4,29,33].

FOSFOMYCIN AND URINARY TRACT INFECTIONS

Fosfomycin is currently used mostly as fosfomycin trometamol and is taken orally. This formulation is approved in numerous countries for treating lower uncomplicated urinary tract infections, e.g. acute cystitis, due to its good activity against common uropathogens, especially *Escherichia coli* and *Enterococcus faecalis*, as well as its good tolerability and safety. Furthermore, it reaches very high and persistent urinary concentrations (up to 48 h) [2,12,38]. A single oral dose of fosfomycin trometamol (the approved dosage) is 3 g. This antibiotic is also recommended for prophylaxis of recurrent urinary tract infections or in urological diagnostic procedures and surgery [29].

Results of the clinical trials indicate that single-dose fosfomycin trometamol has similar clinical and/or bacteriological effects comparable to 3-7-day regimens of ciprofloxacin, norfloxacin, cotrimoxazole or nitrofurantoin in women with uncomplicated lower urinary tract infections [23]. In addition, single-dose fosfomycin trometamol has similar bacteriological efficacy to a 5-day course of cefuroxime axetil or a 7-day course of amoxicillin/clavulanic acid in pregnant women with asymptomatic bacteriuria, and similar clinical and/or bacteriological efficacy to a 5-day course of cefuroxime axetil or amoxicillin/clavulanic acid in pregnant women with lower urinary tract infections [23]. It should be noted that fosfomycin trometamol is recommended for the treatment of urinary tract infections during pregnancy, and belongs to the Food and Drug Administration category B [5]. Moreover, Ruxer *et al.* [35] have confirmed the efficacy of chronic therapy with fosfomycin, co-trimoxazole and nitrofurantoin in the treatment and prevention of recurrent urinary tract infections in type 2 diabetic women, and drew a conclusion that the prophylactic use of fosfomycin was rarely associated with recurrence of these infections.

Lu *et al.* [27] studied the activity of fosfomycin against 960 strains of common uropathogens, including 3 common species of *Enterobacteriaceae* (*Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*), non-fermentative rods – *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia*, methicillin-susceptible and -resistant *Staphylococcus aureus*, vancomycin-susceptible and -resistant *Enterococcus faecalis* and *Enterococcus faecium*. It was found that *E. coli*, the most common pathogen of urinary tract infections, was invariably susceptible to fosfomycin, while the prevalence of fosfomycin-resistance among other pathogens was variable. In addition, Sultan *et al.* [36], performing studies on a total of 1840 urine samples, found that fosfomycin was 100% effective against methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant enterococci (VRE), enterococci with high-level aminoglycoside resistance (HLAR) and Gram-negative bacteria

producing extended-spectrum beta-lactamases (ESBL). Besides the aforementioned, 99% of Gram-negative bacteria producing beta-lactamases AmpC were found to be sensitive to fosfomycin. The above data indicate that fosfomycin may still be regarded as a promising option for treatment of urinary tract infections, especially in that it is useful in cases involving multi-resistant pathogens that are resistant to currently used treatments of urinary tract infections.

Although prostatic infections due to multidrug-resistant *Enterobacteriaceae* are an increasing clinical problem, Gardiner *et al.* [16] found that oral fosfomycin achieves sufficient intraprostatic concentrations in healthy men to be potentially effective in preventing prostatic infection in patients undergoing transrectal ultrasound-guided biopsy, and to be considered as a therapeutic option for patients with prostatitis caused by multidrug-resistant *Enterobacteriaceae*. However, further clinical studies are required.

FOSFOMYCIN BEYOND URINARY TRACT INFECTIONS

Nowadays, many clinicians and scientists look at fosfomycin as alternative therapeutic option in infectious diseases caused by multi-resistant pathogens [7,22,29,32]. These pathogens were recently deemed ESCAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacter* spp.) due to their “escape” from available antimicrobial agents, as well as the non-existence of newer active antibiotics [6].

Fosfomycin has not been widely used as other drugs. Indeed, the intravenous formulation has been employed for indications beyond uncomplicated urinary tract infections in only a few countries (such as Germany, France, Spain or Japan) [12]. In some European countries, however, fosfomycin has been occasionally administered for the initial empirical therapy of sepsis or soft-tissue infections. Resistance to fosfomycin is not widespread due to its limited usage, and the emergence of resistance to fosfomycin has been found to only occur in 2.3-6.7% of all cases in which this agent has been used for the treatment of infections other than uncomplicated cystitis, such as respiratory tract infections or osteomyelitis [22]. It should be noted that several mechanisms of resistance to fosfomycin have been described, including decreased drug uptake, modification of the target site and inactivation of the antibiotic [23].

Several studies have been performed on the *in vitro* activity of fosfomycin against resistant or multi-resistant bacteria. Kasse *et al.* [20], in testing susceptibility to fosfomycin in a collection of 107 carbapenem-nonsusceptible clinical isolates belonging to *Enterobacteriaceae* (of which 80 produced various types of carbapenemases), found that, overall, 78% of the strains were sensitive to fosfomycin. Beyond this work, Livermore *et al.* [26] determined the activity of some antimicrobial agents against *Enterobacteriaceae* with resistance to carbapenems, including fosfomycin. They found that fosfomycin was active against 49/81 (60.5%) of the isolates belonging to carbapenem-resistant *Enterobacteriaceae*, including 7/7 *Escherichia coli*, 16/20 *Enterobacter* spp. and *Citrobacter* spp., but only

was effective against 25/52 of *Klebsiella* spp. As reported by Fagalas *et al.* [14], fosfomycin had good antibacterial activity against the clinical isolates of *Enterobacteriaceae* that produced ESBL, being useful against 90% or more of them. Interestingly, high activity of fosfomycin has been reported against isolates of *Enterobacteriaceae* with resistance to fluoroquinolones [24]. Of note, *E. coli* seems to be the most susceptible to fosfomycin among *Enterobacteriaceae*, regardless of the isolate origin, *i.e.* clinical specimens in community- and hospital-acquired infections [14].

Fosfomycin was found to possess promising activity against carbapenemase-producing *P. aeruginosa* and *K. pneumoniae*, and to other multi-resistant strains such as methicillin-resistant *S. aureus* (MRSA) and extensively drug resistant *P. aeruginosa* [15,30,31]. Fagalas *et al.* [13] collected data published in website databases, regarding the clinical and/or microbiological effectiveness of fosfomycin in the treatment of infections caused by multi-resistant, extensively drug-resistant or pandrug-resistant non-fermenting Gram-negative bacilli. From this report comes one conclusion – fosfomycin can have an important role as a therapeutic option against *P. aeruginosa* infections. Moreover, the susceptibility to fosfomycin of multi-resistant *P. aeruginosa* isolates varied between 50% and $\geq 90\%$, depending on the study. That which was most susceptible to fosfomycin were isolates of *P. aeruginosa* of serotype O12. On the other hand, only 3.5% of all multi-resistant *A. baumannii* isolates and no isolates of *Burkholderia* spp. were susceptible to fosfomycin.

Allberger and Ingo [1] studied sensitivity to fosfomycin among 69 vancomycin-resistant isolates of *Enterococcus* spp., including: *E. faecium* and *E. faecalis* with phenotype Van A and Van B, *E. gallinarum* with phenotype Van C1 and *E. casseliflavus* with phenotype Van C2. They observed a high rate of fosfomycin-mediated inhibition of the examined enterococci, this figure being 94-97%, and concluded that fosfomycin, when used in combination with other drugs, could be a potentially useful drug for the treatment of infections caused by vancomycin-resistant enterococci. It should be realised that new therapeutic strategies are needed to combat the emergence of infections due to multidrug-resistant *Neisseria gonorrhoeae*. Fosfomycin was found to be active *in vitro* against the gonococci isolates possessing resistance to ceftriaxone and/or azithromycin [19].

Fosfomycin is effective against a wide range of infections caused by Gram-negative and Gram-positive bacteria, especially in patients suffering from multi-resistant bacterial infections. However, clinical studies to assess the efficacy of fosfomycin are limited [34]. Based on the fact that fosfomycin monotherapy with intravenous formulation should be prohibited due to the prompt emergence of resistance during therapy, the choice of the appropriate adjunctive antibiotic should be carefully investigated and must be individualized for each patient's condition [9,17]. In a prospective study, fosfomycin was given at 2-4 g intravenously every 6 h for 14 \pm 5.6 days, in combination with other antibiotics, to 11 adults hospitalized in an Intensive Care Unit due to carbapenem-resistant *K. pneumoniae* infections without definition of underlying resistance mechanisms [30]. All patients had promising bacteriological and clinical outcomes, with

all-cause hospital mortality of 18.%. Additionally, no adverse effects were reported. Chen *et al.* [9] suggest that combination therapy consisting of high-dose daptomycin and fosfomycin is an alternative treatment option for daptomycin-nonsusceptible, methicillin-resistant *S. aureus* native valve endocarditis or osteomyelitis. Especially, in that these two antibacterial agents are well known for their bacteriocidal activities and effective biofilm penetration [3,11]. Of note, infective endocarditis is a clinically significant disease with mortality ranges from 16% to 25% [11].

Beyond the aforementioned, Hamilton-Miller [18] found that fosfomycin could be a useful addition to the limited number of antimicrobial drugs, available in clinical practice effective against multi-resistant Gram-positive cocci. Fosfomycin may, thus, be regarded as a valuable option in combination therapy in the treatment of infections due to resistant and multi-resistant pathogens in haematology patients and haematopoietic stem cell transplant recipients [37]. Additionally, recent study implies that fosfomycin can be an alternative to the current ampicillin treatment of listeriosis in humans [25].

Moreover, fosfomycin is also considered as an antibacterial agent useful for perioperative prophylaxis. Chareancholvanich *et al.* [8] studying the safety and efficacy of fosfomycin and cefuroxime as antibiotic prophylaxis for knee arthroplasty, suggest using fosfomycin. They put forward that it is a safe and effective antibacterial agent – no patients had any complication and none had renal and liver function disturbance during the follow-up.

It should be noted that fosfomycin as intravenous formulation (fosfomycin disodium) possesses good pharmacokinetic properties, including its distribution into tissues. This antibiotic achieves clinically relevant concentrations in serum, kidneys, bladder wall, prostate, lungs, bone, cerebrospinal fluid, and heart valves. Beyond this, therapeutic concentrations were found to be within inflamed tissues and abscess fluid [29].

CONCLUSION

Fosfomycin is an old antibiotic and its effectiveness may be to some extent, underestimated. Nowadays, however, many clinicians and scientists are having a re-look at this antibacterial drug in the light of its good activity against multi-resistant microorganisms - these being etiological factors of severe infections both in hospitalized and ambulatory patients.

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