Fosfomycin as an alternative therapeutic option for treatment of infections caused by multi-resistant Gram-negative bacteria

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Abstract
The problem of significantly reduced drug use concerns particularly the infections caused by multi-resistant pathogens, especially Gram-negative bacteria. In this regard, interest is increasing in the known for nearly 50 years, but now frequently forgotten antibiotic – fosfomycin. Fosfomycin possesses high effectiveness for multidrug-resistant bacteria, comprising of extended-spectrum β-lactamases (ESBL), Klebsiella pneumoniae carbapenemases (KPC); commonly, the pandrug-resistant (PDR) and the extensively drug-resistant (XDR) strains, especially from Enterobacteriaceae family. Because of facilitated distribution into inflamed tissues and a very broad range of in vitro bactericidal activity, fosfomycin may have various applications in the treatment of many kinds of bacterial infections, including acute uncomplicated infections of the urinary bladder or complicated urinary tract infections, urinary tract sepsis, pyelonephritis, cystitis, prostatitis and chronic lung infections in patients with cystic fibrosis, the great majority caused by multi-resistant Gram-negative bacteria, and in infection eradicating multidrug-resistant Helicobacter pylori. Fosfomycin may limit the toxicity of other antibiotics and play a protective role in the process of bacterial resistance development during the therapy. Combinations of different antimicrobials enable the use of forgotten antibiotics in commonly occurring infections, although they are still completely incurable.

Key words
fosfomycin, multidrug-resistant bacteria, urinary tract infections, prostatitis, cystic fibrosis

INTRODUCTION

The problem of significantly reduced drug use concerns particularly infections caused by multidrug-resistant pathogens (MDR), especially Gram-negative bacteria [1]. For such infections, one or two antibiotics are the only treatment option, often with contracted indications for use (side-effects, pending primary diseases, other taints). Even though there are so many types of antibiotics with a wide range of activities, widespread availability contributed to the general abuse in therapy. Therefore, multidirectional actions to reintroduce the activity of such commonly called ‘old’ antibiotics, and enhance the effectiveness of clinical treatment, and in that way are being taken worldwide [2]. The main issue is retrospection into the principal and basic knowledge about interactions antibiotic-microorganism, as well as to keep track of rapid changes in bacteria susceptibility to many antibiotics and the emergence of new mechanisms of drug resistance. In this regard, interest is increasing in the known for nearly 50 years, but now frequently forgotten antibiotic – fosfomycin.

General features of fosfomycin. Fosfomycin (FOS), originally named fosfonomycin, was discovered in Spain in 1969 in the actinomycetes Streptomyces fradinii culture [3]. FOS, a derivative of the phosphonic acid, with a specific epoxide ring, is not classified into any of the known groups of antimicrobial agents. The lowest molecular weight gives it the possibility for rapid diffusion and penetration into many tissues of the human body, including the blood-brain barrier, where it reaches maximum therapeutic concentrations [4]. Nowadays, fosfomycin occurs in three pharmaceutical forms: two orally dispensed (pessaries for solution preparing) fosfomycin with tromethamine (commonly known as trometamol), available in Poland, and calcium fosfomycin, as well as fosfomycin disodium capsules applied by intravenous infusions [5]. It is a cell-wall active antimicrobial agent, primarily inhibiting the first step of the murein/peptidoglycan synthesis (a condensation of the UDP-N-acetylglycosamine and the phosphoenolpyruvate) through close binding to the bacterial pyruvate transferase. As a result, conversion into the UDP-N-acetylmuramic acid (UDP-MurNAc) – cell wall component protein – becomes impossible [6]. FOS also inhibits the adhesion of uropathogenic bacteria to urothelium. This is probably result of limiting the fusion of the oligomannose from bacterial cell walls to the surroundings (e.g. the mucus membrane of the urinary tract) allowing the removal of pathogens along within urine [7]. It is commonly used in the treatment of uncomplicated and complicated urinary tract infections UTIs.

Fosfomycin activity against multidrug-resistant pathogens. It is a promising fact that most of the ESBL-producing multidrug-resistant Enterobacteriaceae strains are susceptible to fosfomycin, which Falagas et al. [8] and Gupta et al. [9] have widely presented.

In the first reviewed studies, most of the identified ESBL-producing Enterobacteriaceae isolates were Escherichia coli or K. pneumoniae. All confirmed isolates were specifically
susceptible to fosfomycin in the range of 90–100% and 80–90%, respectively [8]. Secondly, among 150 \textit{E. coli} clinical isolates, over 52% of the strains were ESBL-producers, and 8% were reported as AmpC-type \beta-lactamases-producing strains. All strains were identified as fosfomycin susceptible. Due to the limited choice of antimicrobial agents in the treatment of UTIs caused by ESBL-producing bacteria, and the barely noticeable resistance rate against FOS, authors recommend its use as an alternative drug for uncomplicated UTIs [9]. In a Spanish multicentre study, the authors closely analyzed the resistance rate of \textit{E. coli} isolates. In 2009, total resistance was estimated at the low level of 3%, but its significant increase over the five previous years was also observed (from 4% in 2005 to 11.4% in 2009). This sudden increase was probably associated with the rapid rise of fosfomycin use in the community [10], which is in accordance with the studies by Oteo et al. [11]. The authors described a nearly 50% intensification of community consumption of FOS, and an unexpected extension of resistance in ESBL-positive (CTX-M-14) \textit{E. coli} clinical strains from 2.2% to 21.7% in Spain in 2004–2008. A similar study on CTX-M-15-producing \textit{E. coli} strains investigated a combination of FOS-cefoxitin for the treatment of UTIs. A bacterial resistance development was obtained in vitro at 24 hours when fosfomycin and cefoxitin were used in monotherapy in a concentrations of 4xMIC. The results of \textit{in vivo} experiments in a murine model indicated that the fosfomycin-cefoxitin combination had efficient bactericidal activity and caused kidneys sterilization. For this reason, that combination of antimicrobial agents may be successfully applied in a treatment of UTIs due to ESBL-producing \textit{E. coli} [12]. Furthermore, Pontikis et al. [13] showed \textit{in vivo} activity of FOS against the XDR and PDR strains. In a group of 26 patients, 2 described isolates were carbapenemases-producing XDR \textit{K. pneumoniae} and 15 PDR. In turn, from 17 identified \textit{Pseudomonas aeruginosa} strains, 16 were registered as an XDR and 1 as a PDR. All examined individuals were critically ill patients in the Greek intensive care units (ICUs), mostly suffering from mono- or poly-microbial primary bacteraemia, ventilator-associated pneumonia (VAP) and catheter-related bloodstream infections. Fosfomycin and other combination therapy brought a clinical cure in nearly 55% of cases. Complete bacterial eradication was noted in 56% and mortality rate reached only 40% of patients. During the therapy, a resistance to fosfomycin developed in almost 3 cases, with the minimal inhibitory concentration (MIC) value reaching from 16–32 g/mL to over 256 g/mL. All these results may suggest that fosfomycin administered in monotherapy or in a combination with other antibiotics (cotistin, tigecycline, gentamicin, meropenem and piperacillin/tazobactam) could be a good alternative for the infections caused by XDR or PDR strains, but this requires further research.

\textbf{Therapeutic applications of fosfomycin.} A high bioavailability in the human body is decidedly the most advantageous feature of fosfomycin. Significantly high concentrations are mostly achieved in the serum (lack of interactions with plasma proteins). Furthermore, the antibiotic proves a good distribution into the soft tissues, lungs, bones, heart valves, urinary bladder, prostate and seminal vesicles [4]. Additionally, it passes through the blood-brain barrier, reaching clinically high levels in the cerebro-spinal fluid (CSF), where, however, its activity against Gram-negative bacteria is apparently diminished [2, 5]. FOS also highly penetrates purulent lesions, and in almost 95% is excreted unchanged with the urine within 24 hours [5, 6].

\begin{table}
\centering
\caption{Antimicrobial activity of fosfomycin against Gram-negative bacteria}
\begin{tabular}{|l|l|l|}
\hline
\textbf{Spectrum of activity} & \textbf{Citation} \\
\hline
\textit{Escherichia coli} & 2, 14 \\
\textit{ESBL E. coli (CTX-M-14,15)} & 11, 15, 16, 17 \\
\textit{Proteus mirabilis} & 5 \\
\textit{Enterobacter spp.} & 5 \\
\textit{Citrobacter spp.} & 5 \\
\textit{Serratia marcescens} & 4 \\
\textit{Neisseria meningitidis} & 5 \\
\textit{Shigella spp.} & 5 \\
\textit{Salmonella typhi} & 5 \\
\hline
\textit{KPC, ESBL, XDR, PDR Klebsiella pneumoniae} & 2, 8, 13, 16, 18 \\
\textit{Acinetobacter baumannii} & 20 \\
\textit{MDR A. baumannii} & 18 \\
\textit{Pseudomonas aeruginosa} & 2, 4, 19 \\
\textit{MDR, XDR, PDR P. aeruginosa} & 6, 8, 18, 13, 20, 21 \\
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\end{tabular}
\end{table}

Because of facilitated distribution into inflamed tissues and a very broad range of \textit{in vitro} bactericidal activity (Tab. 1), fosfomycin may have various applications in the treatment of many kinds of inflammations. FOS is commonly administered in female acute uncomplicated urinary bladder infections and pyelonephritis [22], or uncomplicated urinary tract infections (UTIs) [2, 23]. It is also widely recommended for the UTIs treatment (also administered to pregnant women under strict medical control), and protectively in medical interventions within the urinary tract when caused by the most common uropathogens, comprising of \textit{Klebsiella pneumoniae} carbapenemases (KPC) and multi-drug resistant \textit{P. aeruginosa}. Fosfomycin is a so-called ‘urodesinfectant drug’ of proven bactericidal effect, and its potential to eradicate the UTIs pathogens reaches even 80–99% [7, 24]. The Food and Drug Administration (FDA) in the USA recommends fosfomycin-trometamol only in therapy for uncomplicated infections of the urinary bladder (cystitis) [4]. At the same time, the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products in Poland allowed its use for the therapy of uncomplicated abundant bacteruria, in a prevention of UTIs associated with surgical and transurethral diagnostic procedures [25].

FOS may also be of major importance in bacterial prostatitis, closely associated with UTIs infection. Until now, there has been no study conducted on the use of FOS and testing its accurate penetration into the prostate tissue. One of the latest researches examined a group of healthy males undergoing transurethral resection of the prostate who were treated with a single 3 g dose of oral fosfomycin tromethamine as a presurgical prophylaxis. The authors achieved satisfying concentrations of fosfomycin in most cases (with therapeutic concentrations detectable up to 17 hours). They also suggest the possibility to use it in patients with urinary tract sepsis and prostatitis due to MDR Gram-negative bacteria. Unfortunately, the authors have not investigated any antimicrobial susceptibility, or any impact
of the fosfomycin on the minimal inhibitory concentration (MIC) value [26].

There are also proposals to introduce FOS into the antibiotic therapy of Gram-negative pneumonia in patients on mechanical ventilation. A phase 1 randomized and double-blind study has evaluated the safety of 50 mg/mL amikacin and 20 mg/mL fosfomycin solution in ventilator-associated tracheobronchitis (VAT) and ventilator-associated pneumonia (VAP). The authors demonstrated that following administration, fosfomycin was rapidly absorbed and the treatment was well tolerated and safe. A second part of the clinical studies has been initiated and will consider the usefulness of 300/120 mg amikacin/fosfomycin intravenous doses as therapy in patients on mechanical ventilation against Gram-negative bacteria [27].

Due to the increasing resistance to commonly used treatment against MDR Helicobacter pylori in some countries, there is a growing need for new drugs or combinations. The authors considered the use of a regimen of rifampin or fosfomycin to eradicate that pathogen. Overall resistance rate to fosfomycin reached 8.3%, and MIC90 values were also much lower than commonly used agents (metronidazole, clarithromycin, levofloxacin). This indicates the important role of fosfomycin in eradication therapy of H. pylori [28]. These data are in accordance with earlier results [29]. The authors found that from 10 confirmed multi-drug resistant H. pylori isolates, all strains were susceptible to FOS. For that reason, it was decided to change the classical empirical treatment to a therapy containing a proton-pump inhibitor, tetracycline, bismuth subsalicylate and fosfomycin as a second-line rescue. With this, the H. pylori eradication was achieved in 95% of patients. These studies indicate a promising role of FOS as a part of empirical second-line MDR H. pylori infections treatment, especially in countries with a high prevalence of resistance to metronidazole, which requires larger controlled trials.

Apart from the very expensive process of developing new antibiotics, scientists are constantly trying to modify well-known drugs to facilitate application and multiply their effectiveness. A combination with other antibiotics, such as β-lactams or aminoglycosides, expands the activity of antibiotics, scientists are constantly trying to modify well-known drugs to facilitate application and multiply their effectiveness. A combination with other antibiotics, such as β-lactams or aminoglycosides, expands the activity of antibiotics. This was probably caused by the independent mechanisms of action and separate points of the molecular target. The authors also suggest that three-component antibiotic therapy with fosfomycin can bring satisfying results, because fosfomycin – as a relatively safe drug – may limit the toxicity of other antibiotics, such as aminoglycosides nephrotoxicity [16]. Moreover, similar antibiotic combinations have medical implications, they play a protective role and prevent the development of bacterial resistance against FOS during the therapy, and enhance the in vivo activity of fosfomycin [32].
CONCLUSIONS

The treatment of infections caused by the MDR, PDR, or even XDR pathogens, is an important clinical problem. An increase in antimicrobial resistance impedes effective therapy. Nowadays, there is a tendency to reduce the application of standard antibiotics, particularly in monotherapy. For that reason, scientists are attempting to associate the ‘old’ antibiotics with others, and broaden their spectrum of activity in the multidrug-resistant infections treatment. In this way, the adverse effects of certain antibacterial agents (e.g. toxicity) are strongly reduced. Combinations of different antimicrobials enable the use of forgotten antibiotics in commonly occurring infections which are still completely nontoxic, easy dosages, good penetration into many tissues, and little ability to display cross-resistance to other antibiotics, as well as bacterial low resistance development. All of which indicates that fosfomycin becomes an important alternative drug for various infections caused by multidrug-resistant pathogens.

REFERENCES