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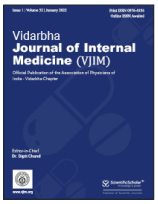

Drug Update

Fosfomycin

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ABSTRACT

Fosfomycin, a broad-spectrum antibiotic, was originally developed more than 45 years ago. Because it has both *in vitro* and *in vivo* activities against a wide range of multidrug-resistant as well as extensively drug-resistant bacteria, fosfomycin is potentially a good candidate for treating infections with these bacteria. Fosfomycin ([2R,3S-3-methyloxiran-2-yl] phosphonic acid) is the only natural phosphonic acid containing an epoxide ring, which lends good antibacterial activity to this molecule. Furthermore, fosfomycin, with a low molecular weight of 138.06 g molecular weight, is different from any other antibiotic family, indicating no cross-resistance for this drug in the clinical application. Reassessing and reevaluating 'old' antibiotics such as fosfomycin have been proposed as a possible strategy in treating drug-resistant bacterial infections.

Keywords: Fosfomycin, Antibiotic, Pharmacokinetic

INTRODUCTION

Extensive use and misuse of antibiotics over the past 50 years have contributed to the emergence and spread of antibiotic-resistant bacterial strains.[1,2] Hence, the treatment of bacterial infections suffers from the major problem of the spread of multidrug-resistant (MDR) or extensively drug-resistant (XDR) pathogens and the World Health Organization has identified antibacterial drug resistance as a major threat to global public health.[3] Given the rather limited availability of novel antimicrobial agents, the reevaluation of older antibiotic agents seems to be an appealing option.[4]

One such 'old' antibiotic is fosfomycin, a broad-spectrum antibiotic that was originally developed more than 45 years ago. Because it has both *in vitro* and *in vivo* activities against a wide range of MDR as well as XDR bacteria, fosfomycin is potentially a good candidate for treating infections with these bacteria.[5,6]

Fosfomycin ([2R,3S-3-methyloxiran-2-yl] phosphonic acid) is the only natural phosphonic acid containing an epoxide ring, which lends good antibacterial activity to this molecule. Furthermore, fosfomycin, with a low molecular weight of 138.06 g molecular weight, is different from any other antibiotic family, indicating no cross-resistance for this drug in the clinical application.[7]

PHARMACOLOGY

Mechanism of action

The drug acts by inhibiting UDP-N-acetylglucosamine enolpyruvyl transferase (MurA), an enzyme responsible for catalysing the formation of N-acetylmuramic acid, a precursor of peptidoglycan, through the binding of N-acetylglucosamine and phosphoenolpyruvate, resulting in bacterial lysis. Gram-positive and Gram-negative bacteria require the formation of N-acetylmuramic acid for peptidoglycan synthesis.[8]

Spectrum of activity

Fosfomycin exhibits a promising bactericidal activity against a variety of Gram-negative and Gram-positive bacteria, including clinical isolates of *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter*, *Pseudomonas aeruginosa*, *Proteus vulgaris*, *Salmonella schottmuelleri*, *Serratia marcescens*, *Salmonella* Typhi, *Citrobacter* spp. *Enterococcus faecalis*, *Staphylococcus aureus* (including methicillin-resistant *S. aureus*), *Staphylococcus epidermidis* and *Streptococcus pyogenes*.[9] Whereas *P. aeruginosa* exhibits moderate susceptibility, fosfomycin shows improved efficacy, especially in combinations with other antibiotics, including cefepime, aztreonam and meropenem. The strains which are resistant to fosfomycin include some isolates

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of *Acinetobacter baumannii*, Vibrio fischeri, *Chlamydia trachomatis* and *Bacteroides* species.[10]

PHARMACOKINETICS AND PHARMACODYNAMICS

There are three fosfomycin formulations: A disodium formulation for intravenous infusion that consists of 1–8 g of fosfomycin disodium powder with succinic acid as the only excipient and two oral formulations (one calcium and one trometamol). Calcium salt is marketed in a few countries as 500 mg hard gelatin capsules. Fosfomycin-trometamol is presented in a 3 g packet with white granules of fosfomycin-trometamol.[8]

Fosfomycin has good oral bioavailability. A recent review by Falagas *et al*.[4] examined the kinetics of various formulations of fosfomycin. The oral bioavailability of fosfomycin trometamol ranged from 34% to 58%. Absorption occurs mainly in the small intestine.[11] The trometamol formulation is absorbed more than the calcium formulation. Peak plasma levels of 22–32 mg/L occur 2–2.5 h after a single oral dose of fosfomycin. The drug is not bound to plasma proteins. It does not undergo metabolism in the body and is primarily excreted unchanged in the urine by glomerular filtration.[11] Peak urinary concentrations occur within 4 h of dosing. It has good penetration of the kidneys, bladder wall, prostate and seminal vesicles. The serum elimination half-life (t1/2) of fosfomycin trometamol is approximately 5 h.[8]

Fosfomycin exhibits concentration-dependent bactericidal activity against strains of *E. coli*, *Proteus mirabilis* and *Streptococcus pneumoniae* and time-dependent bactericidal activity against *S. aureus* and *P. aeruginosa*.[8]

CLINICAL ASPECTS

Fosfomycin is essentially a urinary antibiotic. Intravenous fosfomycin has been recently reevaluated for the treatment of systemic infections caused by MDR bacteria[12] Fosfomycin has also been employed for treating respiratory infections, meningitis, otitis, neurosurgical infections, endocarditis, bacteraemia, cardiac surgery, nosocomial infections by XDR *P. aeruginosa* and *A. baumannii* and carbapenemase-carrying enterobacteria, gynaecological infections as well as for device-related and osteoarticular infections by methicillin-resistant and methicillin-susceptible *S. aureus*, among others.[8] Due to its extensive tissue penetration, fosfomycin has emerged as a potential therapy for treating infections in the central nervous system (CNS), soft tissues, bone, lungs and abscesses. Fosfomycin has high penetration into the interstitial fluid of soft tissues, reaching 50–70% of the levels measured in plasma, reaching sufficiently high levels to eliminate relevant pathogens.[3] Moreover, Schintler *et al*.[13] reported that fosfomycin might also be effective in treating 'deep' infections involving the osseous matrix. With respect to CNS infections, Pfausler *et al*.[14] reported that three daily IV doses of 8 g provided a steady-state concentration of 16 mg/L in the cerebrospinal fluid for more than 90% of the interval between doses.

Fosfomycin tromethamine is currently approved as a single 3 g dose for treating uncomplicated urinary tract infections (UTIs) in women, specifically UTIs due to *E. coli* infection. Fosfomycin tromethamine has also been investigated as a potential therapy for surgical prophylaxis to prevent prostate infection and even as a treatment for prostatitis due to MDR Gram-negative bacteria. The use of a multiple-dose regimen with fosfomycin tromethamine has emerged as a potential strategy for the treatment of complicated and/or recurrent UTIs, as well as infections due to MDR bacteria. In this respect, simulations of the urinary concentrations of fosfomycin have been developed to determine the optimum dosing regimen that can provide a urinary concentration above the MIC (i.e., >16 mg/L) for 7 days.[3]

One study[15] evaluated clinical outcomes among patients with carbapenem-resistant *Enterobacteriaceae* infection who were receiving a fosfomycin dosing regimen using a Monte Carlo simulation and fosfomycin minimum inhibitory concentration (MIC). The most favourable PK/PD targets for fosfomycin were observed when high doses (16–24 g/day) of the drug were administered using prolonged or continuous infusion regimens. Consequently, these high-dose regimens could be used to treat bacteria with a MIC range of 32 mg/L–96 mg/L. In contrast, usual doses (4–12 g/day) of fosfomycin could be used for bacteria with MICs at the lower end of the range or 8 mg/L–32 mg/L. Administration of fosfomycin by prolonged or continuous infusion might be more appropriate than the intermittent regimen because it allows for a longer period of drug concentration levels to be above MIC values. The findings of this study suggest that fosfomycin has good efficacy when using dosing regimens that achieve the PK/PD target. In this study, the most commonly observed adverse drug reactions were hypernatremia, hypokalaemia and acute kidney injury. One systematic review suggests that fosfomycin 8 g loading dose followed by a daily dose of 16 g or up to 24 g continuous infusion is a promising therapeutic regimen in the treatment of systemic infections including those due to MDR organisms.[12] Fosfomycin is recommended for cystitis in immunocompetent patients, according to the guidelines of the Infectious Diseases Society of America even in conditions with ESBL, as are nitrofurantoin and cotrimoxazole.

TOLERABILITY

Fosfomycin is very well tolerated. Mild and self-limiting gastrointestinal disturbances, and usual diarrhoea, are the most frequently reported adverse effects. Only one case of pseudomembranous colitis was noted in a post-marketing

study involving 35,481 patients over 6 years in Japan.[15] Other common but minor adverse effects are dizziness, headache and vaginitis.

CONCLUSION

The World Health Organization currently recognises that antibacterial drug resistance is one of the major threats facing global public health, particularly given the reduction in the number of effective antibiotics. In this respect, reassessing and reevaluating 'old' antibiotics such as fosfomycin have been proposed as a possible strategy in treating drug-resistant bacterial infections. Fosfomycin is a broad-spectrum antibiotic with both *in vivo* and *in vitro* activities against a wide range of bacteria, including MDR, XDR and pan drug-resistant bacteria.[3]

Declaration of patient consent

Patients' consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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