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Review article

Fosfomycin: Resurgence of an old companion

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ABSTRACT

Fosfomycin was discovered over four decades ago, yet has drawn renewed interest as an agent active against a range of multidrug-resistant (MDR) and extensively drug-resistant (XDR) pathogens. Its unique mechanism of action and broad spectrum of activity makes it a promising candidate in the treatment of various MDR/XDR infections. There has been a surge of *in vitro* data on its activity against MDR/XDR organisms, both when used as a single agent and in combination with other agents. In the United States, fosfomycin is only approved in an oral formulation for the treatment of acute uncomplicated urinary tract infections (UTIs), whereas in some countries both oral and intravenous formulations are available for various indications. Fosfomycin has minimal interactions with other medications and has a relatively favorable safety profile, with diarrhea being the most common adverse reaction. Fosfomycin has low protein binding and is excreted primarily unchanged in the urine. The clinical outcomes of patients treated with fosfomycin are favorable for uncomplicated UTIs, but data are limited for use in other conditions. Fosfomycin maintains activity against most *Enterobacteriaceae* including *Escherichia coli*, but plasmid-mediated resistance due to inactivation have appeared in recent years, which has the potential to compromise its use in the future. In this review, we summarize the current knowledge of this resurgent agent and its role in our antimicrobial armamentarium.

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In the current era of antimicrobial resistance, the family *Enterobacteriaceae* is one of the most problematic groups of pathogens. Many classes of antimicrobial agents used to be almost uniformly active against *Enterobacteriaceae*, including β-lactam-β-lactamase inhibitor combinations, cephalosporins, carbapenems, sulfonamides, fluoroquinolones and aminoglycosides.

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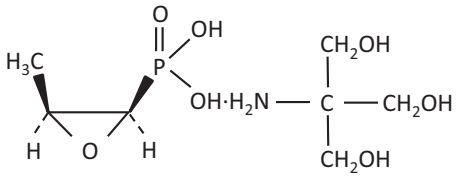

Fig. 1. Structure of fosfomycin tromethmine.

However, resistance to these classes has worsened substantially in the last decade. Taking *Escherichia coli* as an example as the prototypical and the most common *Enterobacteriaceae* implicated in human infections, approximately half of those causing UTI among inpatients are now resistant to ampicillin-sulbactam, a third are resistant to ciprofloxacin, and up to 10% are resistant to cephalosporins, primarily due to production of extended-spectrum-β-lactamase (ESBL) [1]. Notably, this worsening resistance with the spread of ESBL is occurring not only in healthcare-associated infections [2,3] but also community-associated infections [4,5].

Urinary tract infection (UTI) is an exceedingly common type of bacterial infection that affects healthy individuals as well as those with comorbidities around the world. It is estimated that one in every three women experience at least one episode of urinary tract infection (UTI) requiring treatment with antimicrobial agents by the age of 24 [6]. Given the increasing rates of resistance in urinary pathogens to agents commonly used to treat UTIs such as trimethoprim-sulfamethoxazole and ciprofloxacin, there has been a surging interest in identifying new treatment options or re-evaluate existing agents for the treatment of UTIs. One such agent is fosfomycin, which has been in existence for over four decades now. Its use has gained popularity especially since the Infectious Diseases Society of America (IDSA) and the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) updated their guidelines for the treatment of acute uncomplicated UTI and pyelonephritis in women by recommending fosfomycin as one of the first-line agents for the treatment of uncomplicated UTIs in 2011 [7].

Fosfomycin is a phosphonic acid derivative that was first identified and reported from various strains of *Streptomyces* spp. in 1969 [8]. It has been in use in most European countries for many years, but was only approved by the Food and Drug Administration (FDA) in the United States to be used, in the oral form only, as fosfomycin tromethamine, for the treatment of uncomplicated cystitis in 1996.

This review article summarizes recent studies describing the mechanism of action and resistance, susceptibility testing, pharmacodynamics and pharmacokinetic properties, dosing considerations, and clinical outcome data related to the use of this agent, including infections caused by multidrug-resistant (MDR) or extensively drug-resistant (XDR) pathogens.

1. Mechanism of action and resistance

Fosfomycin was initially reported as phosphonomycin, a broad-spectrum cell wall synthesis inhibitor produced by *Streptomyces fradiae*, *Streptomyces viridochromogenes*, and *Streptomyces wedmorensis* from the Merck, Sharp & Dohme Research Laboratories in 1969 [8]. Fosfomycin is in an antimicrobial class of its own and is structurally unrelated to any other agent currently approved for clinical use (Fig. 1). Its mode of action is inactivation of the cytosolic N-acetylglucosamine enolpyruvyl transferase (MurA), thereby preventing the formation of N-acetylmuramic acid from N-acetylglucosamine and phosphoenolpyruvate, which is the initial step in peptidoglycan chain formation of the bacterial wall [9]. Hence, fosfomycin is bactericidal in nature. The mechanisms by which fosfomycin is transported across the bacterial permeability barrier have been well described. Fosfomycin primarily utilizes the glycerol-3-phosphate transport system (GlpT) as a method of entry in almost all susceptible bacteria [10]. In addition, the hexose phosphate uptake transport system (UhpT) is induced in the presence of glucose-6-phosphate, providing an alternative to the GlpT system for its influx into cells [11].

Key resistance mechanisms to fosfomycin include the loss or reduced production of these functional transporters, reduced affinity to MurA and production of fosfomycin-modifying enzymes (Table 1). The former two mechanisms are chromosomal, whereas the latter mechanism can be chromosomal or plasmid-mediated. Mutations or insertional inactivation in one or both of the chromosomally-encoded transporter genes (*glpT* and/or *uhpT*) or their regulatory genes *uhpA*, *uhpB* and *uhpC* of the UhpT system can lead to the loss of function of these transporters and resistance to fosfomycin [12]. Modification of MurA, the target of the drug has also been reported to result in fosfomycin resistance. In *E. coli*, fosfomycin covalently binds to cysteine at position 115 of MurA. The substitution of cysteine with aspartate in this active site has been shown to result in resistance to fosfomycin [13,14]. The overexpression of MurA is another mechanism that can contribute to the development of a fosfomycin-resistant phenotype [15]. However, resistance due to MurA modification or overexpression appears to be rarer compared with the aforementioned transporter-mediated mechanisms.

Fosfomycin-modifying enzymes can be chromosomally encoded but may also be encoded on transferable plasmids, especially in *E. coli* [16,17]. Three of the four known groups of fosfomycin modifying enzymes, namely FosA, FosB, and FosX, function by nucleophilic attack on carbon atom 1 of fosfomycin to open the epoxide ring thus rendering the drug inactive. The enzymes encoded by these genes differ by the identity of the nucleophile utilized in the reaction: glutathione for FosA [18], bacillithiol for FosB [19], and water for FosX [20]. In general, FosA and FosX enzymes are produced by Gram-negative bacteria, whereas FosB is produced by Gram-positive bacteria. Another group of plasmid-mediated fosfomycin modifying enzymes, FosC, utilizes ATP and

Table 1
Mechanisms of fosfomycin resistance.

Mechanism	Protein involved	Action
Reduced permeability	GlpT	Modifications or reduced expression of glycerol-3-phosphate transporter
	UhpT	Modifications or reduced expression of hexose phosphate transporter
Target modification	MurA	Modifications or overexpression of UDP-N-acetylglucosamine 1-carboxyvinyltransferase
Inactivation of drug	FosA	Mn^{2+}-dependent glutathione-S-transferase
	FosB	Mn^{2+}/Mg^{2+}-dependent bacillithiol-S-transferase
	FosX	Mn^{2+}-dependent epoxide hydrolase
	FosC (FomA)	Mg^{2+}/ATP-dependent phosphorylation of fosfomycin