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REVIEW

Fosfomycin: an old, new friend?

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Abstract Fosfomycin (FOM) is an antibiotic which has varying application indications across the globe. European, Japanese, South African and Brazilian usage practices are much broader, involving multiple formulations of FOM than the currently limited application of FOM in the United States, where uncomplicated urinary tract infection represents the only indication for FOM-tromethamine. Based on early difficulty in determining FOMs genuine in vitro activity, there was initial skepticism about its efficacy and application range. However, in the mid 1970s, correctly executed experiments coupled with an improved understanding of microbiological concepts opened the door for broader use of FOM. During the following 40 years FOM was evaluated in pre-clinical and clinical trials in a wide range of applications and in a multitude of settings. The gathering of pharmacokinetic and pharmacodynamic data was incorporated into large scale studies in which FOM efficacy was further explored and proven. Among European nations, intravenous FOM-disodium for patients presenting with soft tissue infections, sepsis or deep seated infectious processes has become well accepted over the last two decades. The recent emergence of bacterial strains, which impede and encumber pharmacotherapy, namely, MRSA, ESBL and MSSA, lends itself to the idea of reviving long-standing, sensibly used antimicrobial agents like FOM. This review provides a comprehensive conspectus on FOM's history, mode of action, tissue penetration characteristics, resistance, antibacterial activity, combination partners and clinical uses among other facets of interest.

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History

FOM, a phosphonic acid derivative (cis-1,2-epoxypropyl phosphoric acid; $C_3H_7PO_4$), is a naturally occurring antibiotic. FOM represents its own class of antibiotics and no other member of this class is currently approved by regulatory agencies worldwide. In 1969, FOM, then called phosphonomycin, was isolated in fermentation broths through experimentation with various strains of *Streptomyces* (*S. fradiae, S. wedomorensis* and *S. viridochromogenes*) at the laboratories of MSD (Merck, Sharp & Dohme) and CEPA (Compania Espanola de Penecilina y Antibioticos) [1]. A study by Woodyer et al. provided new insights into FOM biosynthesis and offered an opportunity to augment the creation of new analogs via bio-molecular pathway engineering [2]. Today, FOM is produced synthetically.

The rise of FOMs was slow and punctuated by temporal set-backs. The mode of action of this unique antimicrobial substance was first described by Kahan et al. in 1974 [3].

One of the early set-backs was the apparent discrepancy of FOM's ability to inhibit pathogenic growth. While in vivo testing suggested a functioning alternative to existing antimicrobial therapy, in vitro results provided poor support to clinical findings. It was not until 1983, 14 years after FOM's purification, that in vitro testing was standardized by Andrews et al. [4]. They found that FOM requires glucose-6-phosphate (G-6-P) to be able to exhibit its full antimicrobial activity. Thus, the addition of physiological G-6-P allowed for in vitro tests to become more valid and mimic in vivo situations appropriately. Other studies from the late 1970s suggested that during infections suboptimal concentrations of G-6-P can be suspected [3], and the addition of G-6-P is able to enhance FOM activity in experimental infection [5]. Additionally, FOM-resistant strains have been reported to appear due to loss of the G-6-P induced transport system through spontaneous mutations [3, 6, 7].

Partly due to the disappointing in vitro results at the beginning of FOM susceptibility testing, intravenous FOM almost disappeared from the clinician′s mind in the United States [8].

Chemistry and characteristics

FOM ($C_3H_7PO_4$; MW 138.06 g/mol) easily forms salts and has a broad spectrum of bactericidal activity [9, 10]. FOM is used orally in its calcium salt form ($C_3H_5O_4PCa$;194.2) and intravenously as the more water-soluble disodium salt ($C_3H_5O_4PNa_2$; 182.03) [10]. FOM-tromethamine ($C_7H_{18}NO_7P$; 259.194), a more recent formulation, is highly hydro-soluble and offers an oral bioavailability of 34–41% [11]. It is marketed in Europe, Japan, South Africa and the United States under the brand name “Monuril” or “Monurol” at a dose of 5.61 g of FOM-tromethamine, which is equivalent to approximately 3 g of pure FOM. FOM, the only member of the group of epoxide antibiotics, inhibits cell wall and early murein/peptidoglycan synthesis in proliferating bacteria [3]. Its simple structure consists of the active, bactericidal epoxy group and a directly bonded carbon atom to the centrally positioned phosphorous [10, 12]. Figure 1 exhibits the most commonly used salts of FOM.

FOM displays broad-spectrum activity against various gram-positive and distinct gram-negative bacteria by irreversibly blocking bacterial cell wall synthesis at an earlier stage than beta-lactams or glycopeptide antibiotics. FOM inhibits an initial peptidoglycan synthesis step, triggered by uridine diphosphate N-acetyl-glucosamine-enol-pyruvyl-transferase and its co-enzyme phosphonole-pyruvate. Its target action is executed inside the bacterial cytoplasm [1, 3].

FOM utilizes one of two active transport pathways to enter the cell. The facultative hexose-monophosphate transport system (*uhpT*) depends on the presence of G-6-P, an extracellular hexose monophosphate inductor. Certain bacterial species, such as *Klebsiella, Shigella, Salmonella, Enterobacter, Enterococcus* and *Staphylococcus*, make use of this particular transport mechanism. The second pathway, the L-α-glycerophosphate transport system *(glpT),* is inducible by the glycolysis intermediate, glyceraldehyde-3-phosphate [13]. Due to the inhibitory effect of inorganic phosphates, both transport mechanisms are catabolically repressed [3].

Whereas FOM acts by directly inhibiting murein synthesis, beta-lactam antibiotics inhibit bacterial trans- and carboxypeptidases, which are responsible for interlocking of peptidoglycan precursors [3]. Glycopeptide antibiotics bind to the terminal D-alanyl-D-alanine and thereby inhibit the formation of the murein net [3].

Antimicrobial activity of FOM against *S. aureus* and other bacteria

The antimicrobial spectrum of FOM is broad. It exhibits bactericidal activity against anaerobic pathogens in addition to many gram-positive and gram-negative bacteria (Table 1). *S. aureus, Streptococcus pneumoniae, Escherichia coli, Neisseria meningitidis, Haemophilus influenzae, Klebsiella pneumoniae, Enterococcus faecalis, Serratia marcescens, Pseudomonas aeruginosa* and *Proteus mirabilis*, are among many others against which FOM is antimicrobially active [14–19]. Breakpoints of susceptibility to FOM are largely unavailable in international scientific literature. Occasional reports are offered in non peer-reviewed local medical journals presenting breakpoints between 8 and 64 μg/ml for methicillin-sensitive *S. aureus* (MSSA) and methicillin-resistant *Staphylococcus aureus* (MRSA) (Table 1). For *Enterobacteriaceae* the respective breakpoints appear to be 1–2 dilution steps lower, but are largely variable. The aberration of FOM's in vitro versus in vivo ability to effectively combat a pathogen was shown early on in a study by Miller et al. [20].

Antibiotic combinations that include FOM

Yameda et al. showed that ciprofloxacin-resistant *P. aeruginosa* strains are susceptible to the combination therapy of ciprofloxacin and FOM, especially when FOM is given second to allow for better penetration and higher kill percentages [21]. Unfortunately, data on the efficacy of FOM in combination with newly developed glycopeptide antibiotics such as oritavancin, telavancin or dalbavancin are currently not available in scientific literature (Table 1).

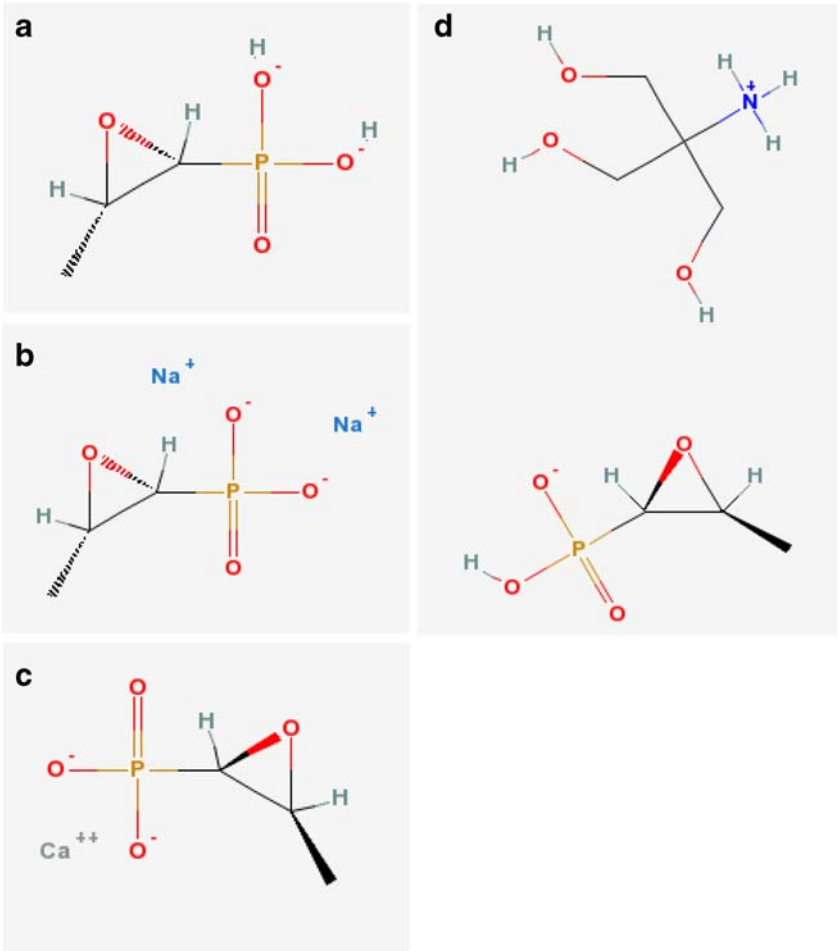

Fig. 1 Different structures and salts of fosfomycin (FOM) as detailed on PubChem [APR10, 2009; http://www.ncbi.nlm.nih.gov/sites/entrez]. **a** FOM. **b** FOM disodium. **c** FOM calcium. **d** Tromethamine

One rationale for combining FOM with a second agent for the treatment of *S. aureus* infection is to prevent the emergence of FOM resistance. In support of this concept, Thauvin et al. found that among rats with MRSA endocarditis treatment with FOM alone resulted in the development of FOM-resistant *S. aureus* in 36% of the surviving rats with positive valve cultures. However, no FOM-resistant *S. aureus* were recovered from vegetation

Table 1 MIC_{s90} for clinically relevant isolates

Bacteria	Older studies MIC_{90} (μg/ml)	More contemporary studies MIC_{90} (μg/ml)
S. aureus	1–8	8–64 [40]
S. epidermidis	32–64	na
Enterococcus faecalis	8–64	64 [49–51]
Streptococcus group A	32–64	≥64 [147]
Streptococcus group B	32–64	≥64 [147]
Streptococcus pneumoniae	8–16	na
Escherichia coli	0.5–4	≤64 [41, 43, 46, 47, 49]
Klebsiella	32–256	32–128 [41, 43, 47, 52]
Enterobacter	16–256	128 [43]
P. mirabilis	16–64	≥128 [43]
Proteus spp. (indole pos.)	512–1024	128 [43]
Pseudomonas aeruginosa	16–128	128 [52]
Serratia marescens	8–16	na
Hemophilus influenzae	2–4	na
Bacteroides fragilis	Inactive	na

na not available

cultures of animals treated with FOM in conjunction with pefloxacin [22]. The combination of linezolid with FOM has also been reported to prevent the emergence of FOM-resistant *S. aureus* [23].

In vitro synergism

In vitro checkerboard and time-kill assays have been employed to assess for synergistic activity against *S. aureus* when combining FOM with another antibiotic. Instances of synergism against MRSA have been noted when combining FOM with rifampin, linezolid, quinuprisitin/dalfopristin, moxifloxacin, trimethoprim, semi-synthetic penicillins, cephalosporins and carbapenems [23–31]. However, indifference has also been noted when combining FOM with agents such as sparfloxacin, gentamicin, trimethoprim and vancomycin [24, 30, 31]. Instances of in vitro antagonism when FOM is combined with vancomycin, methicillin, trimethoprim or gentamicin were observed [24, 31]. It is important to note that the small numbers of isolates tested in many of these studies limit the ability to draw definitive conclusions regarding the significance of the observed in vitro drug interactions. In addition, randomized investigator-blinded clinical studies are largely not available in English literature.

In vivo synergism

The efficacy of combining FOM with a second antibiotic against *S. aureus* has also been evaluated in vivo. Synergism has been noted when combining FOM with cefotaxime in an MRSA-infected fibrin clot animal model [32], a rabbit MRSA meningitis model [33], and a MRSA mouse infection model (which also demonstrated synergy between cefmetazole and FOM) [27]. Also, the combination of FOM and pefloxacin was more effective in a rat MRSA endocarditis model than either drug alone [22]. And, in a clinical study evaluating the efficacy of the combination of FOM plus cefotaxime in the treatment of 16 patients with various types of staphylococcal infections (including 12 cases of MRSA infection), Portier et al. noted 100% bacteriologic and clinical cure rates [25].

In vitro susceptibility

Currently, CLSI-approved susceptibility breakpoints for FOM exist for *E. coli* and *E. faecalis* [34] with an MIC≤64 μg/ml considered susceptible and approved for the treatment of urinary tract infections (UTIs) only. EUCAST breakpoints for fosfomycin exist for *Staphylococci*, *Enterobacteriaceae* and *Pseudomonas* with an MIC≤32 μg/ml considered susceptible [35].

There is much less contemporary data regarding FOM activity against *Staphylococci*. A Swedish study from 1983 found that among 100 clinical *S. aureus* isolates the MIC_{50} and MIC_{90} for FOM was <4 μg/ml and 8 μg/ml, respectively [36], while an Austrian report from 1984 noted that over 90% of 211 clinical *S. aureus* (irrespective of methicillin susceptibility) were inhibited with FOM concentrations ≤64 μg/ml [37]. Among a collection of 163 clinical *S. aureus* isolates from Belgium (the majority of which were collected during the mid 1980s), including 128 MRSA, the MIC_{50} and MIC_{90} for FOM were 6.2 and 12.5 μg/ml, respectively [38]. Of note, Etienne et al. found that between 1980 and 1990 the rates of FOM resistance (defined as an MIC>32 μg/ml) at a single center in France increased from 25% to 42% among coagulase-negative *Staphylococci* and 3% to 11% among *S. aureus* [39]. However, a more recent surveillance study conducted in three different regions of Germany determined that FOM activity remained high against 289 clinical MRSA isolates collected between 1998 and 2000, with susceptibility to the drug ranging between 93.75% and 99% (susceptibility defined as an MIC≤32 μg/ml) [40].

For *E. coli* and *E. faecalis,* multiple contemporary surveillance investigations conducted in geographically diverse settings have consistently revealed high rates of susceptibility, ranging between 95 and 100%, among *E. coli* strains collected from clinical urine samples [41–46]. In the largest of these studies, 99.8% of 2,292 *E. coli* isolates were susceptible to FOM (MIC≤64 μg/ml), whereas resistance to ampicillin, ciprofloxacin and co-trimoxazole was noted among 52.1%, 18.1%, and 25.2% of isolates, respectively [45]. Similarly, FOM has activity against extended spectrum beta-lactamase (ESBL) producing *E. coli*. In a collection of 290 clinically-derived, ESBL-producing *E. coli*, 99.7% of isolates were FOM susceptible [47]; among 220 CTX-M producing *E. coli*, 100% of isolates were susceptible to FOM [48]. Among *Enterococci*, a multicenter study conducted in North America found that 153 of 157 urinary-derived, clinical *Enterococcus faecalis* isolates were susceptible to FOM, with an MIC_{50} and MIC_{90} of 32 μg/ml and 64 μg/ml, respectively [49]. Other investigators have reported that FOM retains activity against vancomycin-resistant *Enterococci* [50, 51].

Extrapolating from the currently approved *E. coli* breakpoints for FOM, variable levels of drug susceptibility are found among other Gram-negative organisms [41, 43, 47, 52]. Among 138 clinical isolates of *K. pneumoniae*, 92.7% were susceptible to FOM and the MIC_{50} and MIC_{90} were 16 μg/ml and 64 μg/ml, respectively [47]. Similarly, among a collection of 30 multi-drug resistant *K. pneumoniae* (defined as resistance to at least 3 potentially effective antibiotics classes), 100% of isolates were susceptible to FOM [52]. Among 111 ampC-producing *Enterobacteria-*

ceae derived from patients with urinary tract infections, approximately 49% were FOM susceptible, though rates varied considerably depending on the species tested (82.9% of Enterobacter were susceptible, whereas no *M. morganii* was susceptible) [43]. Among 60 multi-drug resistant, non-fermenting Gram-negative organisms, Falagas et al. and colleagues found 80% of *P. aeruginosa* were FOM susceptible whereas 97% of *Acinetobacter baumanii* were non-susceptible [52].

As mentioned earlier, the addition of G-6-P to Mueller-Hinton medium produced a marked potentiation of antimicrobial activity of FOM against most bacterial species tested, but showed large variability [3] (Table 2). MICs decreased approximately 40-fold for *E. coli*, with a ten-fold increase for *Citrobacter*, *KIebsiella* and *Enterobacter* and approximately four-fold for *S. aureus* after addition of 25 μg/ml of G-6-P. In distinct cases, the augmentation of FOM antimicrobial activity achieved by the addition of G-6-P was 256-fold for *E. coli* and *Enterobacter*, 128-fold for *Klebsiella*, 64-fold for *Citrobacter* and 16-fold for *S. aureus*. In some species no corresponding G-6-P effect was detected [36]. However, in scientific literature there is not much agreement regarding the sensitivity percentage to G-6-P of the individual bacteria since different media, mostly using different concentrations of added G-6-P, were used (Table 2). The provided MICs in columns 1 and 2 are from the late 1970s or early 1980s. However, more recent surveys on the sensitivity of different bacterial species are presented in column 3.

MIC determination of FOMs should, as a matter of principle, only be carried out on agar and not in broth dilutions [53], since a relatively high likelihood of spontaneous mutation to FOM resistance may be observed [54, 55]. This leads to unclear and poorly reproducible end points when using the broth dilution technique (skip-tube phenomenon). Since FOM sensitivity rates reported in literature vary strongly, clinical results need to be taken into consideration. Thus, CLSI standards for performance of antimicrobial susceptibility testing state that the approved MIC susceptibility testing method is agar dilution. Agar media should be supplemented with 25 μg/ml of G-6-P, while broth dilution should not be performed [56].

Chromosomal resistance

For distinct gram negative bacteria, Kahan et al. demonstrated that the primary mechanism of entry of FOM into bacteria is through the L-alpha-glycerophosphate transport system (*glpT*), while an alternate uptake mechanism, the hexose phosphate transport system (*uhpT*), is induced in the presence of G-6-P [3]. FOM resistance has been demonstrated in mutants defective in either transport system [57]. In vitro experiments in *E. coli* have demonstrated that defects in the PEP:sugar phosphotransferase system (PTS) and adenylate cyclase activity, both resulting in decreased cAMP levels, were associated with FOM resistance; this resistance has been attributed to the fact that cAMP mediates induction of the glpT system [58]. In vitro generated FOM resistance in *Salmonella typhimurium* has also been associated with mutations in the PTS system [59].

Nilsson et al. reported that in vitro selection of FOM resistance in *E. coli* is associated with mutations in chromosomal genes encoding for the transport systems involved in FOM uptake (glpT or uhpT systems) as well as genes regulating cellular cAMP levels (*cyaA* and *ptsI*) [42]. However, among clinically-derived FOM resistant *E. coli*, these authors observed only mutations involving the uhpT or glpT systems, suggesting that alterations in cAMP levels may result in a biological loss-of-fitness in vivo. Furthermore, these authors also reported that despite an in vitro mutation frequency of 10^{-8} to 10^{-7} for the development of FOM resistance, the actual rates of clinically documented resistance to FOM among *E. coli* are low (see above). Based on mathematical modeling, and confirmed through in vitro growth experiments of FOM-resistant *E. coli*, these authors suggested that the growth disadvantage associated with the development of FOM resistance prevents the establishment of clinical infection [42]. Others have similarly reported on reduced virulence in *Enterobacteriaceae*, as assessed by slower growth rates and reduction in bacterial adhesion to uroepithelial cells and silicone treated latex catheters, following the development of FOM resistance [41]. In vitro studies in *E. coli* have also demonstrated that resistance to FOM can be conferred by mutations in the chromosomally-encoded phosphoenol-pyruvate:uridine diphosphate-N-acetylglucosamine enolpyruvyl transferase gene (*murA*), resulting in either reduced binding of FOM to the encoded enzyme or through over-expression of the gene [60, 61]. Similarly, intrinsic resistance to FOM found among *M. tuberculosis* has been attributed to the cysteine to aspartate substitution within the active site of mycobacterial *murA* [62]. Of note, in two clinically-derived shiga-like toxin producing *E. coli* isolates demonstrating high-level FOM resistance (MIC≥512 μg/ml), resistance appeared related to a combination of reduced uptake and increased transcription of the murA gene encoding for UDP-GlcNAc enolpyruvoyl transferase [63].

In contrast to the gram-negatives, to date, there is only one published article in the English language describing chromosomally-mediated resistance to fosfomycin in *S. aureus* [64]. The fact that these low rates mentioned here are in apparent contradiction with the ease with which resistance could arise is an argument for all those who believe in the concept that only clinical resistance data are relevant for overall decision making.

Table 2 Relevant in vitro interactions of FOM in combination with other antibiotics [14, 18, 19, 31, 52, 112, 132, 148–150]

Therapy	Combination partner	Pathogen	Combinatory effect
Penicillins	Benzylpenicilline	*N. meningitidis*	SYN
		S. pneumoniae	SYN
		S. aureus	SYN
	Ampicillin	*E. coli*	SYN
		S. aureus	SYN
	Amoxicillin	*S. pneumoniae*	SYN
	Oxacillin	*S. aureus*	SYN
	Piperacillin	*P. aeruginosa*	SYN, ANT
	Tazobactame	*S. marcescens*	SYN
		S. aureus	SYN
Monobactams	Aztreonam	*P. aeruginosa*	SYN, ANT
Cephalosporins	Cephazolin	*S. aureus*	SYN
	Cefamandole	*S. aureus*	SYN
	Cefotaxime	*S. aureus*	SYN
		S. epidermidis	SYN
		S. pneumoniae	SYN
	Ceftazidime	*P. aeruginosa*	SYN, ADD, IN, ANT
	Cefepime	*P. aeruginosa*	SYN
	Cefpirome	*S. aureus*	SYN
		P. aeruginosa	SYN, ANT
Carbapenemes	Meropenem	*S. aureus*	SYN
		S. epidermidis	IN
		P. aeruginosa	SYN
	Imipenem	*S. aureus*	SYN, ADD, IN
		S. epidermidis	SYN
		K. pneumoniae	SYN
		P. aeruginosa	SYN, ADD, IN
Aminoglycosides	Gentamicin	*S. aureus*	SYN, ADD, IN
		E. faecalis	SYN, ADD
		P. aeruginosa	SYN, ADD
		S. marcescens	SYN, ADD
	Amikacin	*S. aureus*	SYN, ADD, IN
	Netilmicin	*S. aureus*	SYN, ADD
Lincosamides	Clindamycin	*S. aureus*	SYN
Quinolones	Ciprofloxacin	*S. aureus*	SYN
		S. epidermidis	SYN
		E. faecalis	SYN
		P. aeruginosa	SYN, ADD, IN
	Levofloxacin	*P. aeruginosa*	SYN, ADD
	Moxifloxacin	*S. aureus*	SYN
		S. epidermidis	SYN
Glycopeptides	Vancomycin	*S. aureus*	SYN, ADD, IN
		S. epidermidis	ADD, IN
	Teicoplanin	*S. aureus*	SYN
		E. faecalis	SYN
Steroid antibiotics	Fusidic acid	*S. aureus*	ADD, IN
		S. epidermidis	SYN, ADD
Other	Linezolid	*S. aureus*	SYN
		S. epidermidis	SYN

Table 2 (continued)

Therapy	Combination partner	Pathogen	Combinatory effect
	Rifampicin	*S. aureus*	ANT, IN, SYN
		S. epidermidis	SYN
		E. faecalis	SYN
	Daptomycin	*E. faecalis*	SYN, IN
		S. aureus	SYN, IN

SYN synergistic, *ADD* additive, *IN* indifferent, *ANT* antagonistic

Plasmid-mediated resistance

While FOM resistance encountered among clinical isolates appears to be primarily due to chromosomal mutations, plasmid-mediated resistance has also been reported among clinically-derived bacteria. Plasmid-mediated FOM resistance was first reported in *Serratia marcescens* and is encoded by a transposable genetic element, *fosA* [65, 66]. This gene encodes a constitutively expressed enzyme that can result in the intracellular inactivation of FOM, and has been found among other *Enterobacteriaceae*, *Pseudomonas spp. Acinetobacter spp., Staphylococcus spp.,* and *Bacillus spp.* [66–70]. FosA is a glutathione S-transferase that forms a covalent bond between FOM and a sulfhydryl group in glutathione, resulting in an inactive compound [71, 72]. Another plasmid-borne gene conferring FOM resistance, termed *fosB*, has also been described in *Staphylococci*; it shares some homology to *fosA*, suggesting that the encoded protein product shares a similar mechanism of action [39, 70, 73, 74]. Among a collection of 105 geographically diverse, FOM-resistant clinically-derived *Staphylococci*, of which 39 were *S. aureus* and 27 were *S. epidermidis*, the *fosB* gene was present in 34% of isolates [39]. However, a more recent survey found that among 60 clinical, urinary-derived FOM-resistant bacteria, <10% of isolates contained either *fosA* or *fosB* [75]. Other studies reported on self-resistance of FOM, which among others may be related to inactivation of FOM through phosphorylation [76, 77].

General pharmacokinetic characteristics and aspects

In healthy men, the disodium salt of FOM shows a dose-proportional pharmacokinetic profile, has an elimination/terminal half-life of 1.5–2 hours and follows the bi-compartmental model of pharmacokinetic behavior [78–80]. FOM is not metabolized in the liver and does not undergo enterohepatic circulation [12]. Therefore, no accumulation would be expected for patients with hepatic insufficiency. After intravenous administration, FOM is actively eliminated renally at approximately 93%. Around 50–60% of its bioactive form will be excreted exclusively by glomerular filtration in the first 3–4 hours [78]. No elimination via tubular secretion has been reported. As a consequence, creatinine clearance values may be used to guide decisions regarding dose-adjustment. For patients with renal insufficiency the half-life is considerably prolonged and warrants dose adjustments, especially with creatinine clearance values of less than 40 ml/min [10, 81, 82].

FOM seems to reduce the nephro- and ototoxicity of aminoglycoside antibiotics via inhibiting their up-take by tubular epithelial cells and by protective effects on lysosomal membrane integrity [83].

Tissue pharmacokinetics and associated studies

Plasma protein binding of FOM is negligible [7]. It distributes marginally into cells and predominantly into the extracellular space fluid as documented by a volume of distribution at steady state between 18 and 27 liters [6, 84]. Early studies solidified these assumptions with evidence of tissue penetration into lungs, cerebrospinal fluid, eye, bone, muscle and secretions from skin lesions [6, 17, 85], gall bladder, the common bile duct, the appendix, ascitic fluid [86], bronchial secretions, purulent necrotic tissue and fluid, aqueous humor, lymph and lochia [10, 87]. FOM is expected to exert "*T>MIC*" killing, which means that optimal bacterial killing is observed when its concentration is moderately higher than the MIC of the causative pathogen for periods of 40–50% of the dosing interval [88].

(Diabetic) soft tissue and bone

Based on numerous clinical studies documenting effective FOM concentrations in many tissue subgroups, FOM is widely used in Austria and other EU member states for many indications including serious and life-threatening bacterial infections. For instance, in 2000 Frossard et al. showed that tissue concentrations of FOM in serum, muscle and the subcutis were significantly above the MIC for the most relevant pathogens. Subsequent in vivo PK–in vitro PD experiments utilizing *S. aureus, E. cloacae*, and *S. marcescens* underscored these findings [80]. Septic patients,

after being given 8 g of FOM intravenously, exhibited interstitial space and plasma concentrations higher than the MIC for *S. pyogenes, S. aureus* and *P. aeruginosa* [79].

In diabetic foot infections, median FOM levels were at minimum 22–25 μg/ml at a dosing interval of 8 h after a single dose in soft tissues. This level is significantly above the MIC for the most common pathogens. Measured values were comparable for inflamed and non-inflamed tissues [89] (please see "diabetic foot" section).

FOM penetrates well into osseous tissue. After 5 g or 10 g of intravenous dosing, FOM concentration in the spongiosa and corticalis were measured to be well above the MIC for most bacteria [90, 91]. The respective bone and interstitial space fluid concentrations were between 117.1 and 119.4 μg/ml and 368.4 and 451.2 μg/ml for the 5 g and 10 g dosing groups, respectively. The mean MIC_{90} range for the isolated pathogens was between 2 and 64 μg/ml.

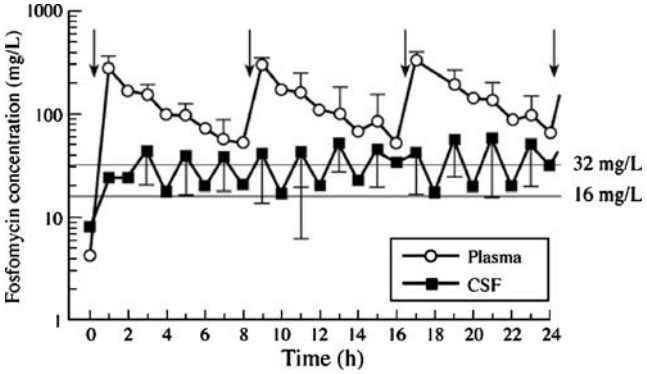

Fig. 2 Time–concentration profiles of fosfomycin (FOM) for plasma (*black circles*) and CSF (*filled squares*) after single and multiple intravenous doses of 8 g over 30 min in neuro-intensive care patients (n=6). Each *arrow* indicates intravenous administration of FOM. The *solid horizontal lines* represent MICs for SA pathogens. Data are shown as mean ± SD [88]

Cerebrospinal fluid and eye

Most antimicrobial agents minimally cross the blood–brain barrier. FOM, due to its small molecular weight and low protein binding, can cross the meninges and reach significant concentrations [92]. Maximal cerebrospinal fluid concentrations were measured at 9–10 μg/ml after 3–6 hours of 5 g of FOM, and 14–17 μg/ml after 2–3 hours of a 10 g dose [93]. In cases of inflamed meninges penetration is significantly increased. A 15-g intravenous dose of FOM achieved concentrations of 6.5–9.0 μg/ml and 20.3–39.8 μg/ml for non-infected and infected meningeal membranes, respectively [94]. In patients presenting with meningitis, cerebrospinal fluid levels of FOM of up to 150 μg/ml after 5 days of saturation were observed [95]. During a 3×8-g daily treatment of intensive care patients presenting with catheter-associated bacterial ventriculitis, FOM steady-state concentrations in the cerebrospinal fluid remained, for 98% of the observed time, above the MIC of the most relevant pathogens of 8 μg/ml, and for 92% above 16 μg/ml and 61% above 32 μg/ml (see Fig. 2) [88]. In the cerebral abscess and its capsule, concentrations of 171 μg/ml and 112 μg/ml were detectable, respectively [96].

A 4 g or 8 g intravenous dose of FOM yielded a maximum aqueous humor concentration of 28.3 μg/ml and 52 μg/ml, respectively. These levels should suffice to adequately eliminate clinically relevant pathogens. The same study showed that the infected eye harbors an even higher concentration of FOM [97]. Other studies found peak FOM concentrations of 11.46±2.12 μg/ml and 14.63±5.54 μg/ml after iv. administration of 4 g of FOM to patients undergoing cataract surgery [98]. In another study, the maximum aqueous humor concentrations of this antibiotic after an 8 g dose applied intravenously measured 35–60 μg/ml [99].

Lung and heart

For pleural space empyema and pulmonary abscesses, FOM lends itself well to antimicrobial therapeutic management because of its high target site concentration and superior penetration into pulmonary tissues [100]. In 1994, Shimada et al. showed that in a study with patients where treatment for pneumonia and lung-abscesses had failed, the combination therapy of FOM and a cephalosporin attained a 70% cure rate [101]. When dosing FOM at 2 g, serum levels attained 32 μg/ml 1–2 h post i.v. administration. Lung concentrations were measured to be 32–52% of corresponding serum levels [102].

Following cardiac surgery many pathogens such as *S. aureus, S. epidermidis* and, at times, *E. coli* and *K. pneumoniae*, can cause infections like endocarditis or mediastinitis. A 5-g intravenous application of FOM shows excellent penetration into valvular, myocardial, muscle and surrounding adipose tissue [103]. Due to its experimental treatment success, FOM has also been utilized for MSSA endocarditis [104–106]. For beta-lactam allergic, cardiac patients, FOM, in combination with an antibiotic from the quinolone group, may be an alternative [107] (Table 1). In 1990, Hirt et al. noted that a cardiogenic bypass bears no influence on FOM's kinetic behavior and penetration ability [108].

Abscess fluid

There was considerable variability in FOM concentrations in abscess fluids even after multiple doses of 8 g t.i.d. of FOM. Its concentration in pus was higher than that of relevant pathogens' MICs [109]. Most importantly, the mean half-life in pus was calculated to be approximately 32 h and suggested that continuous infusion of FOM is not

more advantageous microbiologically. No significant relationship was found between the concentrations of FOM in plasma and its concentrations in pus. However, the permeability of the abscess membrane and the ratio of the abscess volume to surface area were identified to be critical steps in the penetration process of FOM [109]. Since G-6-P is important for antimicrobial activity of FOM, the concentration of G-6-P needs to be explored, but was never determined in inflamed conditions. In normal human tissue and blood cells, G-6-P is physiologically present at concentrations of 39–127 µmol/l, which should be sufficiently high for FOM to achieve full antimicrobial activity. In infectious conditions, G-6-P can be produced in small quantities from glucose by the action of G-6-phosphatase after the addition of lyzed erythrocytes. FOM is not inactivated by very low pH values, and should therefore remain antimicrobially active in pus [110]. In this study, FOM was measured by use of capillary zone electrophoresis [111].

Therapeutic success in clinical use

Soft tissue and diabetic foot infection

Effective treatment strategies for soft tissue infections with FOM are well documented [79, 89, 112, 113]. Studies detailing the therapy of soft tissue infections caused by *S. aureus, E. coli, S. epidermidis* and *Klebsiella spp.* and treated with either FOM (8 g twice daily) plus clindamycin or FOM (8 g twice daily) plus 1–2 g thrice daily of meropenem proved successful [114, 115]. Currently, however, there are no data from controlled, well-designed clinical trials establishing combinatorial treatment regimens including FOM to be more effective than a second agent alone.

In a small explorative efficacy study in 52 diabetic patients presenting with severe bacterial foot infection, it was demonstrated that in 92.3% of patients, even after failed initial treatment with other antibiotics, ß-lactams in combination with intravenous FOM proved successful in avoiding amputation [116].

A study in 2000 by Graninger et al. demonstrated the efficient use of FOM in combination with meropenem for sepsis and FOM in conjunction with amoxicillin/clavulanic acid for diabetic foot patients presenting with phlegmone of the forefoot [117]. The study suggests further that for patients with penicillin or cephalosporin allergies, a combination of a quinolone or aztreonam with FOM or clindamycin is indicated [117].

In a very recent study, Schintler et al. showed that peak concentrations of FOM in inflamed subcutaneous adipose tissue are as high as in plasma, reaching levels of approximately 300 µg/ml after a single intravenous dose of 100 mg/kg BW administered over 30 min. By utilizing appropriate PK/PD indices, the authors concluded that a 100 mg/kg BW i.v. dose of FOM administered 2–3 times a day should be effective in the therapy of diabetic patients presenting with acute bacterial foot infection involving bone structures [118].

Gram-positive *Streptococci, Enterococci* and *Staphylococci*, gram-negative *Enterobacteria* and, at times, necrotizing anaerobic pathogens are responsible for complicated soft tissue infection and osteomyelitis.

As previously demonstrated in trials utilizing microdialysis, the condition of infection itself does not influence FOM's ability to access tissues [79, 89]. In addition, FOM demonstrates rather augmented potency against *S. aureus* in an anaerobe environment and exerts pH independent efficacy [110].

Patients on hemodialysis

Plasma protein binding of FOM is independent of its concentration and ranges around 0–2% in humans and animals [119–121]. Its hydrophilicity and low molecular weight is responsible for distributing predominantly into the extracellular water space fluid and plasma, and thus in theory FOM should be eliminated effectively via extracorporeal renal replacement devices [122].

A recent study performed with 12 intensive care patients with suspected or proven bacterial infection looked at the concentrations of FOM during continuous hemofiltration [122]. In this study, it was determined that approximately 76% of the drug is eliminated within a dosing interval of 12 hours after a single i.v. dose of 8 g. The very high rate of extraction of FOM led the authors to conclude that the current dosing regimen of 8 g twice daily, which is approved for patients with normal renal function, is also appropriate for those patients undergoing CVVH therapy.

Bacterial spondylodiscitis and osteomyelitis

Thirty four patients undergoing intervertebral disc surgery and receiving treatment with FOM in combination with either clindamycin, ceftriaxone or amoxicillin/clavulanic acid were successfully treated clinically for spondylodiscitis [123].

In a study in 2005 with 40 patients the treatment approach with twice daily 8 g FOM in combination with second generation cephalosporins over an average of 24 days proved clinically successful in 87.5% of patients [124].

The continuous increase in endoprosthetic surgeries augments the number of secondary bone and joint infections. After trauma, the incidence of expected secondary

osteitis is approximately 13% and 4% for open and closed fractures, respectively [110]. Because of its properties FOM represents a therapeutic option for these indications [110].

The broad spectrum of pathogens involved in causing osteitis or osteomyelitis calls for an antimicrobial therapy, which might consist of ß-lactams in combination with FOM. The similarity in structure of FOM and hydroxylapatite may explain the superior osseophilic behavior of FOM in contrast with other antibiotic agents [90, 91]. Furthermore, the adjuvant therapy of osteitis or osteomyelitis with FOM and/or vancomycin-enriched hydroxylapatite represents an interesting opportunity [125].

In chronic osteomyelitis the parenteral treatment regimen can last up to 6 weeks followed by oral antibiotic therapy of 6 months to a year. In acute hematogenous osteomyelitis, antibiotic chemotherapy consists of 5–14 days of intravenous therapy followed by 2–4 weeks of oral treatment [126].

In a prospective clinical trial with 60 patients presenting with posttraumatic osteomyelitis, an initial preoperative dose of 10 g of FOM was followed by thrice daily 5 g of medication. Patients were treated earlier with an average of over three antibiotics (up to 12) and received antimicrobial chemotherapy from 5 to 28 days. FOM levels in bone far superseded the MICs of the identified pathogens. Although usually higher, the therapeutic failure rate after an average 37-month follow-up window was 26.4% [91].

Another study, which included 55 patients suffering from recurring osteitis, demonstrated that the treatment with 5 g FOM 2–3 times per day for 2 weeks proved clinically successful for 89% of the patients. These patients were treated previously unsuccessfully for an average of 3.3 years [127].

Among the pediatric patient population, a study evaluating 15 days of parenteral antimicrobial therapy with cefotaxime (100 mg/kg/day) and FOM (100 mg/kg/day) demonstrated that all 20 children involved in the study were clinically healthy [128]. The therapy of acute hematogenous osteomyelitis in children is significantly shorter when treated with FOM alone or when used in combination. In this trial the most prevalent pathogens were *S. aureus* and coagulase-negative *Staphylococci* [129]. No subsequent large clinical trial was conducted verifying whether FOM monotherapy is able to significantly affect duration of therapy in children with osteomyelitis. With regard to the pediatric patient a small single-center study performed in Germany reported circumstantial evidence that FOM might be helpful in the attempt to reduce the overall prescription rate of glycopeptides in pediatric cancer patients [130].

Infections of the central nervous system (CNS)

In 2004, Pfausler et al. showed that concentrations of FOM at steady state (8 g FOM given 3 times daily) significantly exceeded MICs for the most common pathogens in the CNS fluid in patients with bacterial ventriculitis [88] (Fig. 2).

In a retrospective assessment of patients with posttraumatic intracranial abscesses and empyema, FOM was used successfully [131]. The arsenal of therapeutic strategy consists of neurosurgical intervention, external drainage and/or antibiotics. The twice daily application of 8 g FOM, mostly in combination with a third or fourth generation cephalosporin and/or metronidazole, has proven appropriate in the above-mentioned indications [96].

The treatment of infections of the cerebrospinal fluid drainage system is complicated since causative agents for shunt infections are usually nosocomial pathogens. Also, coagulase positive and negative *Staphylococci* and *Enterococci* only lead to minimal inflammatory changes in the constitution of the meningeal membranes [132, 133]. In this setting some have advocated for the following treatment plan: 200 mg/kg of patient weight of FOM in combination with a third generation cephalosporin or vancomycin, imipenem/cilastatin or rifampicin [132, 133].

Cystic fibrosis

Most patients suffering from cystic fibrosis are colonized by *Pseudomonas aeruginosa* and depend on repeated treatments with intravenous antipseudomonal antimicrobial agents for pulmonary exacerbation [134, 135]. The perpetual use of relatively few antibiotics tends to augment the presence of multi-resistant *P. aeruginosa* strains and subsequent suboptimal prognosis [135].

The combination of ciprofloxacin (oral) and FOM (i.v.) against *P. aeruginosa* infections indicated a synergistic effect in 60% and an additive effect in 40% of cases [136].

In another study, which lacks adequate control conditions, all of the 86 patients presenting with cystic fibrosis subjectively felt an improvement after treatment with FOM [137].

In 2003, Mirakhur et al. published a study where 15 patients were treated with FOM in combination with other antibiotics for 30 exacerbations. This treatment strategy consisted of two cycles per patient over an average of 16.6 days and yielded a significant improvement in FEV_1 values (pre 41.1 vs. post 49.4, $p<0.001$) [83].

Abdominal infections and prophylaxis

The authors of a multicenter, double-blind, randomized and controlled trial at nine Swedish hospitals including 517 patients concluded that a combination of FOM and metronidazole was, at minimum, equally effective and safe to a regimen of doxycycline and metronidazole in preventing, among others, abdominal infection rates after elective colorectal operations [138].

Another large randomized study at six centers reported of FOM as prophylaxis for elective colorectal operations. With regard to abdominal infections and resistance, fecal specimens obtained from patients demonstrated a fairly high prevalence of doxycycline-resistance. Resistance rates for FOM were lower and no increase in FOM resistance rates was found among aerobic isolates from infection after FOM prophylaxis [139].

A case study of a renal transplant patient with verotoxin-2 (shigatoxin) producing O157:H7 *E. coli* enterocolitis reported a full recovery for the patient after 10 days posttreatment with fluid replacement and FOM. The immuno-suppressive regimen was kept at maintenance doses throughout the treatment [140].

Urinary tract infections

A 5-year study evaluating over 19,500 uropathogens and resistance patterns suggests the expanded use of FOM (as the tromethamine salt), among a few others, for acute uncomplicated urinary tract infections (UTI) [141]. Among community-acquired urinary tract pathogens, *E. coli* is the most prevalent [142].

In a study of 52 patients and in other observations, FOM-tromethamine administered once every other day (3 g) for three cycles was found to be an inexpensive, effective and suitable alternative in the therapy of ESBL-producing *E. coli*-related lower urinary tract infection [142, 143]. In the treatment of UTIs caused by fluoroquinolone-resistant strains of *E. coli* and in regions with elevated ciprofloxacin resistance, FOM-tromethamine should be further evaluated as a first-line therapeutic approach due to excellent results [144].

A study on resistance rates showed that FOM showed the lowest overall resistance for *E. coli* in comparison to amoxicillin, co-trimoxazole and ciprofloxacin [145].

In chronic therapy with FOM, a trial with 90 women suffering from type 2 diabetes and UTIs, the data indicated that 3 months after discontinuation of antimicrobial therapy, FOM-tromethamine treated patients showed significantly reduced recurrences of UTIs as compared to women treated with co-trimoxazole or nitrofurantoin [146]. Knottnerus et al. recommended in 2008 to augment FOM-tromethamine as a treatment choice for UTIs in the next *Guidelines of the Dutch College of General Practitioners* [46]. It was further suggested that treatment with FOM-tromethamine might be equivalent to nitrofurantoin and co-amoxiclav for geriatric and pediatric patients, respectively [46].

Perspective

Intravenous FOM, a drug developed approximately 40 years ago, remains considerably effective against a wide array of gram-positive and gram-negative pathogens, including resistant organisms. This is most likely due to its restricted use, low prescription rates in distinct member states of the EU, and poor recognition in the United States. FOM is widely known as FOM-tromethamine, a salt for oral intake, and approved for the therapy of uncomplicated UTIs only. Increasing resistance of *S. aureus, E. coli* and similar pathogens to frequently prescribed antimicrobial agents may direct focus to FOM as a therapeutic alternative. ESBL and MRSA infections are becoming increasingly problematic due to resistance patterns in the United States and the European Union. Pharmaceutical drug development is a protracted process and developing new, innovative antimicrobial agents is slow-moving. One strategy in addressing this concern is to transfer responsibility to older drugs, which have been shown to be effective and safe over many decades. Thoughtful prescribing and restricted use of established medicines such as FOM may represent a solid alternative.

Conclusion

FOM is a proven and useful antibiotic in the armamentarium of anti-infectives presently available. Its unique pharmacological and pharmacokinetic characteristics combined with its limited use in the past have allowed this antibiotic to remain effective against problematic gram-positive and gram-negative pathogens such as MSSA, MRSA and ESBL. These pathogens demonstrate increasing rates of resistance against other antibiotics worldwide.

In several countries such as Austria, Germany, Spain, France, Brazil, South Africa and Japan intravenous FOM has been used successfully for almost four decades. In Europe, the use of intravenous FOM-disodium for patients presenting with soft tissue infections, sepsis or deep-seated infections has become well accepted over the last 18 years. In contrast, the United States Food and Drug Administration (FDA) has approved oral FOM-tromethamine solely for the treatment of uncomplicated lower UTIs caused by *Escherichia coli* or *Enterococcus faecalis*, because of limited FOM-related clinical research and use. Unfavorable results, predominantly in the treatment of acute gonococcal urethritis, have led to a narrowed acceptance in the United States. However, 40 years of clinical experience document that intravenous FOM is effective and well-tolerated in a variety of patient populations. Thus, FOM may be a noteworthy option in the therapy of deep seated or difficult to treat infections.

Transparency declaration

Dr. Christian Joukhadar is a consultant and speaker for pharmaceutical companies including Sandoz Gesm.b.H, the

manufacturer of intravenous fosfomycin. Dieter Steinort was a former employee of Sandoz Gesm.b.H. All other authors declare having no relationship with companies that make products relevant to the manuscript and have no conflicts of interest with this work.

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