Clinical Infectious Diseases Advance Access published June 10, 2015

Fosfomycin: the current status of the drug

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Conflict of interest: MEF participated in advisory boards of Achaogen, AstraZeneca, Infectopharm, and Pfizer; received lecture honoraria from Astellas, AstraZeneca, Merck, and Novartis; and received research support from Angelini, Astellas, and Rokitan.

Funding: None

Word counts: text 1104

Number of references: 24

The treatment of patients with prostatitis has been difficult due to the limitations of antibiotics to enter the prostate, frequently leading to the need for prolonged regimens. This challenging clinical problem has become even more complicated with the emergence and dissemination of multidrug-resistant gram-negative bacterial infections. Among them, enterobacteriaceae producing extensive spectrum beta-lactamases (ESBLs), and sometimes carbapenemases, have been the cause of various types of infections, including prostatitis, in patients in most parts of the world.[1]

While Grayson et al report on the outcome of only two patients with prostatitis, their approach, i.e. daily administration of oral fosfomycin (trometamol) for a duration beyond what is customary for orally administered fosfomycin, is interesting.[2] The authors provide clinical data complementing their work regarding the favorable penetration of fosfomycin in the prostate.[3] In a previous publication in the journal, the intra-prostatic levels after a dose of orally administered fosfomycin (evaluated with liquid-chromatography tandem mass spectroscopy) were considerable.[3] Furthermore, levels in the transitional zone of the prostate were higher than in the peripheral zone of the uninflamed prostate.[3] In their current report, the authors do not provide data on fosfomycin levels achieved in the prostate.

Fosfomycin for oral administration is not a newcomer in our armamentarium against *Escherichia coli* infections. In fact, fosfomycin per os (trometamol or tromethamine) is approved by the Federal Drugs Administration for uncomplicated urinary tract infections (UTIs), excluding pyelonephritis, due to *Escherichia coli*, if the strains are susceptible to it. A dose of 3 grams (g) of fosfomycin (contained in 5.63 g of fosfomycin trometamol) may be considered for such infections for per os administration only once. Clinical data have shown that fosfomycin even at this unusual one-off dose regimen fares well for patients with uncomplicated UTIs in comparison to other antibiotics administered for 3-7 days.[4]

Despite the availability of data suggesting the in vitro activity of fosfomycin against multidrug-resistant strains of *Escherichia coli* and other enterobacteriaceae,[5,6,7] there are sparse relevant data on clinical outcomes, including the optimal dosing. Anecdotally, it has been suggested to use oral fosfomycin every 72 hours for multidrug-resistant bacterial infections. There is currently no evidence-based recommendation to treat patients with prostatitis with oral fosfomycin. Grayson et al used the oral daily dosing regimen of 3 g of fosfomycin trometamol.[2] Of note, one of their reported patients received intravenous meropenem and showed clinical and laboratory improvement, including clearance of bacteriuria, prior to administration of oral fosfomycin.[2] Also, the authors used a protracted duration regimen of fosfomycin [12-16 weeks while antibiotic regimens of 2-4 weeks for acute and 4-6 weeks for chronic prostatitis are usually recommended (prolonged suppressive antibiotic regimens are also considered)].[8] Some other reports of treatment of patients with prostatitis with combination of oral fosfomycin and other antibiotics have recently been published.[9]

Multidrug-resistant enterobacteriaceae, including ESBLs producing strains, causing urinary and genital tract infections have become a reality that demands solutions. In clinical practice physicians often see carbapenems as a last resort to treat such infections. However, the need to treat patients with oral antibiotics in an outpatient basis makes oral fosfomycin a consideration. Obviously, microbiological confirmation of susceptibility of the pathogen to fosfomycin is a prerequisite for this type of treatment.

The cost of oral fosfomycin is less than that of most intravenous treatment options for multidrug-resistant enterobacteriaceae. Furthermore, the overall ecological burden in terms of antimicrobial resistance is probably less with the use of oral fosfomycin, at least compared to carbapenems.

Fosfomycin is also available as an intravenous agent (fosfomycin disodium) for the treatment of infections of various organs.[10,11] Tissue penetration of this small, hydrophilic molecule with almost negligible serum protein binding has been substantiated for various tissues through microdialysis techniques.[12] Specifically, tissue penetration in soft tissues, bones, central nervous system, lungs, and heart valves is good as are levels achieved in serum.[13,14] Dosage regarding the intravenous form of fosfomycin is in the range of 12-24 g in 2 to 4 divided doses, provided renal clearance is normal. In conjunction to dosage considerations, a time-dependent mechanism seems more plausible than a concentration-dependent mechanism for fosfomycin.[15] Special caution is advised when doses in excess of 16 g per day are prescribed, as sodium overload and hypokalemia are potential adverse events.

Our experience from treating patients with multidrug-resistant *Klebsiella pneumoniae* infections with intravenous fosfomycin has been encouraging[16] and has been verified by others.[17,18] Current studies are seeking to address whether intravenous fosfomycin can be used instead of meropenem in patients with bacteremia due to ESBL producing *E. coli*.[19] In an era of advanced multidrug resistance a potential role for the parenteral form of the medication is sought against other bacterial pathogens with notorious resistance profiles. Beyond enterobacteriaceae, fosfomycin, usually in combination with other antibiotics, may be helpful in a considerable proportion of *Pseudomonas aeruginosa* strains. However, in vitro studies show that fosfomycin alone is inactive against contemporary *Acinetobacter baumannii* clinical strains. The role of parenteral fosfomycin, combined with daptomycin, is also currently explored in methicillin resistant *Staphylococcus aureus* (MRSA) infections.[20]

The use of fosfomycin is not immune to the development of emergence of resistance to it. Intravenous fosfomycin is currently administered in combination with other antibiotics by most clinicians, at least for multidrug-resistant gram-negative infections. However, the likely overestimated risk of rapid development of fosfomycin resistance has not been essentially substantiated during the many years of oral fosfomycin use (although limited).[10] The levels of fosfomycin achieved in the urinary tract as well as the genital tract, are usually considerably higher than the minimum inhibitory concentration (MIC) for most contemporary relevant pathogens.[3] Nevertheless, we have witnessed resistance development to the reintroduction of another class of "old" antibiotics, namely the polymyxins, and thus one may anticipate that resistance to fosfomycin will eventually increase with its further use.[21] Therefore, although encouraging results have been reported regarding a two-dose prophylactic oral regimen of fosfomycin before transrectal ultrasound-guided prostate biopsy [22] and other regimens for endourological interventions,[23] careful consideration should be exerted regarding the potential use of fosfomycin as a prophylactic agent before transrectal biopsy of the prostate.[24]

Until more data are available from randomized controlled studies, one would probably consider treatment with oral fosfomycin, once the patient is afebrile for 48 hours in hospital or after outpatient parenteral treatment, hemodynamically stable and concurrent bacteremia effectively ruled out. Concomitant bacteremia precludes use of fosfomycin as an oral monotherapy agent. We believe that a niche for the use of oral and intravenous fosfomycin in the treatment of prostatitis may exist. Pending more robust clinical data, one should consider the use of fosfomycin in the treatment of prostatitis on an individualized patient basis according to the national guidelines of treatment of infections and local resistance data.

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