Oral Fosfomycin Formulation in Bacterial Prostatitis

Subjects: Infectious Diseases

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Bacterial prostatitis infections are described as infections that are difficult-to-treat, due to prostate anatomic characteristics along with clinical difficulty in terms of diagnosis and management. Furthermore, the emergence of multidrug resistant (MDR) bacteria, such as extended-spectrum beta-lactamase (ESBL) producer Escherichia coli, also representing the main causative pathogen in prostatitis, poses major problems in terms of antibiotic management and favorable clinical outcome. Oral fosfomycin, an antibiotic commonly used for the treatment of uncomplicated urinary tract infections (UTIs), has been evaluated for the treatment of bacterial prostatitis due to its favorable pharmacokinetic profile, its activity against MDR gram-positive and gram-negative bacteria, safety profile, and multiple synergic effect with other antibiotics as well as the low resistance rate.

Keywords: oral fosfomycin ; bacterial prostatitis ; urinary tract infections

1. Introduction

Male urinary tract infections (UTI) have an overall estimated prevalence between 1.5% and 9%, worldwide [1]. Among them, acute (ABP) and chronic bacterial prostatitis (CBP)—according to the National Institutes of Health (NIH), the classification is also known as category I prostatitis (CIP) and category II prostatitis (CIIP), respectively [2]—are considered cumbersome-to-treat infections owing to limited antibiotic choices and poor drug distribution in prostatic tissue [3]. *Escherichia coli* is considered the main causative agent of both ABP and CBP, although other organisms, including *Enterococcus* spp., *Klebsiella* spp., and *Proteus* spp., are also rising [1][3][4][5][6][7]. Furthermore, the increased prevalence of challenging antibiotic resistant microorganisms, such as extended spectrum beta-lactamases (ESBL) producing *E. coli*, as well as the increasing fluoroquinolone resistance, pose major clinical problems in choosing the appropriate therapy to treat and eradicate UTIs [3][8]. In fact, ESBLs are beta-lactamases able to provide bacterial resistance by hydrolyzing various antibiotics: penicillins, first-, second-, and third generation cephalosporins, as well as aztreonam [9]. For this reason, infections caused by ESBL producer bacteria require the administration of different antibiotic classes, such as fluoroquinolones—that may produce adverse effects due to their known toxicities—or carbapenems, which should be considered last resort drugs that should be spared and can be used only in hospital settings [7] [10]. Alarmingly, the increasing rate of *Enterobacterales* carbapenem resistance (mainly due to carbapenemases' production), adds additional complications to the treatment of both ABP and CPB [4][8]. An old and well-known ally for the treatment of UTIs sustained by these bacteria is represented by fosfomycin. Since its approval, oral fosfomycin–trometamol formulation has been used to treat uncomplicated cystitis in women provoked by susceptible micro-organisms, due to both fosfomycin's favorable capacity to gain high bladder concentrations, even after single dose, and to its capacity to not allow bacteria to develop cross-resistance [11][12].

2. Rationale for Oral Fosfomycin Administration in Patients with Bacterial Prostatitis

Among antibiotics in clinical use, fosfomycin tromethamine, with a low molecular weight of 138.059 + 121.131 g/mol, is able to reach clinically relevant concentrations in the bladder as well as in the prostatic gland. Its hydrophilicity, together with the negligible protein binding (<5%) and the overall PK/PD profile, allow the antibiotic to reach a bio-availability level of 33–50% with a 2-h concentration of 20–30 mg/L and 2000–2500 mg/L in the serum and in the urine, respectively, after a single oral dose of 3 g [13].

Following oral fosfomycin administration in animal models, Fan et al. described the beneficial effects in terms of decreased inflammation, lowering bacterial proliferation and the amelioration of prostatic damage [14].

To note, as reported by the European Committee on Antimicrobial Susceptibility Testing (EUCAST), fosfomycin epidemiological cut-offs (ECOFF) for the bacteria most frequently isolated in UTIs range from 4 mg/L for *E. coli* to 8 mg/L for *Proteus mirabilis* and 32 mg/L for *S. aureus* (even lower for MRSA) [15][16], values that are lower than the antibiotic concentration in the urine even after 48 h post antibiotic administration (100–700 mg/L) [13]. Several studies do not endorse fosfomycin administration if its MIC is >4 mg/L, due to the high risk of not achieving efficient intraprostatic concentrations [1].

The reason behind its success in the treatment of UTIs as well as the perioperative prophylaxis of prostate biopsy is due to its unchanged excretion in the urine and almost unchanged renal elimination [13]. On the other hand, this poses a problem in the administration of fosfomycin to patients with compromised renal function.

Although oral fosfomycin administration dates back to the 1970s and some mechanisms of resistances are unknown—as aforementioned—fosfomycin-resistant *E. coli* are still rare, testifying the slow adaptation rate of the bacteria to this molecule, a clear advantage for the physician. Moreover, the mechanism of action of fosfomycin, affecting the early steps involved in bacterial cell wall formation [17], suggests an additive or synergistic action in combination with other antibiotics; in fact, fosfomycin shows important synergistic effects with many other antibiotics, e.g., piperacillin/tazobactam, ceftazidime/avibactam, meropenem, colistin, and daptomycin, as well as linezolid [13][18][19][20][21][22][23][24][25][26][27][28][29].

Some issues can arise in performing fosfomycin susceptibility testing due to the aforementioned fosfomycin mechanism of entry requiring the presence of G6P. Because of that, the gold standard method for *Staphylococci*, *Enterococci*, *Enterobacterales* and *P. aeruginosa* is the agar dilution with the addition of G6P in the medium [30]. This methodology is time and consumables demanding, which is not suitable for every hospital setting. Luckily, more easy and rapid antimicrobial susceptibility testing methods have been produced by different companies and several studies have been performed demonstrating the validity of the disk diffusion and gradient test, as well as automatized methods [31][32][33][34][35][36]. The accuracy of the results depends on the choice of the most appropriate method for the isolate species, and on the strict adherence to the manufacturers' instructions, as reported by EUCAST [37].

Last but not least, when performing the disk diffusion or gradient test, it could be possible to see colonies within the inhibition zone. In accordance with the EUCAST recommendations, these colonies must be ignored. Luckily, to date, there is no correlation between their appearance and the onset of fosfomycin resistance, which remains very low [38][39].

3. Oral Fosfomycin in Chronic Bacterial Prostatitis

Bacterial prostatitis infections, both acute and chronic, are challenging to treat infections, due to the poor antibiotic penetration in prostatic tissue. CBP represents a complex setting to deal with, due to the presence of prostatic calcifications acting as a bacterial sanctuary, and the bacterial biofilm formation, which both lead to relapsing infections, persisting symptoms, and treatment failure; because of this, antibiotic treatment for CBP requires longer duration compared to acute forms, resulting in increased resistance due to selective pressure [3].

Bouiller et al. retrospectively described 17 CBP episodes treated with oral fosfomycin, 3 g every 24–48 h, for a mean duration of 5.5 weeks, achieving a microbiological and clinical cure in more than 90% of episodes. Oral fosfomycin was prescribed mostly to treat CBP due to ESBL producing *Enterobacterales* with resistance to fluoroquinolones and cotrimoxazole in patients with underlying urological disorders, which could explain the incidence of recurrences (58%) in that population [1].

Los-Arcos et al. reported 15 complicated cases of CBP, of which 14 were caused by *E. coli* (4 isolates produced ESBL), whilst in one case the identified etiological agent was *K. oxytoca*; 13 patients received 3 g every 72 h of oral fosfomycin and 2 patients received 3 g every 48 h. Overall, treatment duration was 6 weeks, attaining microbiological examination in 8 of 15 cases, whereas a clinical cure was achieved in 7 of 15 cases; 7 cases failed the fosfomycin therapy within a median follow-up period of 29 months; four out of the six patients diagnosed with prostatic calcifications relapsed within six months [40].

Karaiskos et al. described 44 CBP cases treated with oral fosfomycin, 38 of which had a positive culture for gram-negative bacteria (mostly *E. coli*): 10 isolates produced ESBL, 26 cases were MDR, whilst 6 cultures tested positive for *E. faecalis*. All patients received 3 g daily of oral fosfomycin for one week, followed by 3 g every 48 h for 6 weeks and 12 weeks, in 25 patients and in 19 patients, respectively. A microbiological cure was achieved in 86% of the cases at the end of therapy and 77% at 6 months; the clinical cure was 84% at the end of therapy and 80% at 6 months. Fosfomycin failure was observed in 18% of patients, the majority of whom had a MIC > 16 mg/L [41].

Almeida et al. described a case of *E. coli* CBP with several relapsing episodes, despite multiple previous antibiotic regimens; the patient was treated with prolonged fosfomycin therapy: 3 g daily for 10 days, then 3 g every 48 h for three months followed by 3 g weekly for 9 months. Due to intraprostatic calcifications, besides fosfomycin therapy, the patient underwent transurethral resection of the prostate (TURP), achieving a clinical cure confirmed after 9 months of post-therapy follow-up [42].

In a case report, Grayson et al., trying to enhance the antibacterial activity towards an ESBL-*E. coli* responsible for a CBP case, which relapsed after carbapenem therapy, administered 3 g twice daily of oral fosfomycin, causing intense diarrhea and leading clinicians to reduce the dosage at 3 g daily. A microbiological and clinical cure was achieved 6 months after the end of therapy [43].

Cunha et al. described the case of an ESBL *E. coli* prostatitis in a patient with a penicillin allergy and affected by prostatic hypertrophy; he did not respond to previous therapies with nitrofurantoin, doxycycline, and oral fosfomycin, showing

persisting pyuria and bacteriuria as well as persistent positive urine cultures. A prostatic ultrasound revealed intraprostatic calcifications, without abscesses, and a TURP was performed to remove them.

Therefore, a three-week regimen of 3 g daily of oral fosfomycin plus doxycycline 100 mg twice daily was made, fulfilling a sustained microbiological and clinical cure. Of note, the *E. coli* strains isolated resulted in always being susceptible to fosfomycin (MIC < 4 µg/L) [44].

Recently, Denes described a clinical case about a patient, with a medical history of prostatic surgery and urethral stenosis, who was treated with a course of oral fosfomycin (3 g daily for one week followed by 3 g every 48 h for 3 months) to treat a prostatitis due to *E. coli* resistant to fluroquinolones and cotrimoxazole, and achieved a microbiological and clinical cure in the six-month follow-up. Just as in the case of Cunha et al., previous fosfomycin administration did not result in bacteria resistance [45].

Finally, an uncommon case of persistent CBP, in a patient affected by prostatic hypertrophy and ciprofloxacin allergy due to *Raoultella planticola,* was successfully treated by Gian et al. who administer oral fosfomycin, 3 g daily, for three months [46].

The majority of reported CBP patients received oral fosfomycin as an alternative regimen to the standard of care without standardized duration and dosage, achieving microbiological/clinical eradication and a recurrence rate not so different compared with the classic agent (fluoroquinolones). Prostatic calcifications, along with urinary abnormalities, represent the main causes, which led to antibiotic failure and infection recurrence. Oral fosfomycin did not demonstrate a safety concern, except for self-limiting diarrhea, and previous fosfomycin treatments have not been associated with resistance development [1][40][41][42][43][44][45][46].

4. Oral Fosfomycin in Acute Bacterial Prostatitis

Due to prostate inflammatory status in ABP, most antibiotics, including fosfomycin, do penetrate the prostatic tissue [47]. Although the pharmacokinetic and pharmacodynamic proprieties of fosfomycin are very favorable and fosfomycin pharmacological proprieties—especially its low protein binding and high lipid solubility [2], which promote its penetration into the lipid-rich prostatic parenchyma—the use of fosfomycin for the treatment of ABP is still neglected.

Even though oral administration of fosfomycin trometamol does not represent the first choice for the treatment of ABP, it could be useful for outpatients or for those who cannot receive other drugs due to allergies, as well as being an adjuvant of other antibiotics due to its good synergistic effect and the low rate of resistance [12].

Despite the use of oral fosfomycin for the treatment of urinary tract infections and, somewhat, for the management of CBP, which is common, only a few cases reported the efficacy of oral fosfomycin in the treatment of ABP sustained by diverse bacterial species: in two cases the microorganism responsible for the ABP and treated with fosfomycin was an ESBL producing *E. coli* [43][48], whilst *E. faecium* [49] has been reported only once.

With regards to ESBL *E. coli* cases, of note is the age difference between the two patients, the 30-year-old [48] and 73-year-old [43]. The younger patient was treated with oral fosfomycin for three weeks under a dose regimen of 3 g once daily for the first week, then switched to 3 g once every 48 h for the remaining two weeks [48]. The older patient received 3 g once daily of oral fosfomycin for 16 weeks [43]. In both cases, the regimen was set in response to the development of diarrhea when the clinicians tried to use a higher dose regimen of antibiotic. The pathogen eradication was reached in both the cases, revealing that the efficacy of fosfomycin seems to not be strictly related to the dosage due to its high concentration in the inflamed prostate.

The only ABP caused by a gram-positive bacterium and treated with fosfomycin reported in literature was sustained by an *E. faecium* resistant to ampicillin, chloramphenicol, vancomycin, gentamycin, and ciprofloxacin, but susceptible to nitrofurantoin and quinupristin-dalfopristin. To note, the strain had a high fosfomycin MIC of 64 mg/L, considered as an intermediate susceptibility by the researchers, which nowadays represents the cut-off of susceptibility for *E. faecalis* according to the clinical and laboratory standards institute (CLSI) [50]. Due to the 85-year-old patient's refusal of intravenous (IV) therapy and due to the scarce penetration of nitrofurantoin into the prostate, he was treated with a trial of prolonged and unconventional dosing of oral fosfomycin equal to 3 g every 3 days for 21 days. The patient's symptoms resolved after the second dose and the follow-up of two years demonstrated no recurrence of the infection [49].

According to other researchers, fosfomycin could be considered as an alternative therapy for quinolone-resistant ABP [51] or in combination with cefoxitin in its IV form for the treatment of ABP caused by fosfomycin susceptible *Enterobacterales*, paying attention to the heart and renal functionality [52].

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