Oral fosfomycin formulation for acute bacterial prostatitis; a new role for an old molecule: A case report and brief literature review

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Received May 12, 2022; Accepted June 14, 2022

DOI: 10.3892/wasj.2022.161

Abstract. Acute and chronic bacterial prostatitis are considered infections which are cumbersome to treat, due to the limited available selection of effective antibiotics and the pharmacologically poor distribution in prostatic tissue. Furthermore, the emergence of novel antimicrobial resistance patterns, such as extended spectrum β-lactamase (ESBL)-producing *Escherichia coli* (*E. coli*) along with increasing fluoroquinolone resistance poses major clinical concerns in selecting the appropriate therapy to treat and eradicate the infection, particularly considering the outpatient setting. The present study describes the case of a healthy male affected by a first acute bacterial prostatitis episode due to ESBL-producing *E. coli*. The patient was successfully treated with oral fosfomycin-trometamol administration, achieving clinical success with microbiological eradication. The case described in the present study, along with the literature review, encourage and suggest the use of oral fosfomycin for the treatment of both acute and chronic prostatitis, particularly for outpatients and for those subjects who cannot be administered other antibiotics.

Introduction

Overall, male urinary tract infections (UTIs) have an estimated prevalence between 1.5 and 9% (1).

Among these, acute bacterial prostatitis (ABP) and chronic bacterial prostatitis (CBP) are considered infections which are cumbersome to treat, due to the limited available selection of antibiotics and the poor drug distribution in prostatic tissue (2).

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Key words: acute bacterial prostatitis, fosfomycin-trometamol, *Escherichia coli* prostatitis

Escherichia coli (*E. coli*) represents the main causative agent of both ABP and CBP, being the most common agent of uncomplicated and complicated UTIs, although other infections from other organisms, including *Enterococcus* spp., *Klebsiella* spp. and *Proteus* spp. are increasing in prevalence (1-5).

Furthermore, the emergence of novel antimicrobial resistance patterns, such extended spectrum β-lactamase (ESBL)-producing *E. coli*, determining resistance to penicillins and cephalosporins, along with increasing fluoroquinolone resistance, poses major clinical concerns in the selection of the appropriate therapy to treat and eradicate the infection (2,6). Of note, some of the ESBL-producing *E. coli*, as well as *Klebsiella* spp., are developing increasing carbapenem resistance, thus rendering the treatment of acute and chronic prostatitis even more complex (6).

The oral fosfomycin-trometamol formulation has long been at the disposal of clinicians for the treatment of uncomplicated cystitis in women provoked by susceptible germs, due to the favorable capacity of fosfomycin to achieve high bladder concentrations, even after a single dose, and its capacity to not allow bacteria to develop cross-resistance (7,8).

Scientific literature have reported data on fosfomycin-trometamol treatment in patients with acute and chronic prostatitis owing to its advantageous safety along with its ability to achieve therapeutic concentrations in prostatic secretions and fluid (2).

The present study describes the case of a healthy 30-year-old male patient with ABP who achieved clinical success with microbiological eradication following treatment with the fosfomycin-trometamol oral formulation. Furthermore the present study focuses on the pharmacological characteristics of fosfomycin, discussing the findings from previous scientific studies on the oral formulation of this drug for the treatment of ABP.

Case report

A 30-year-old Italian male, whose medical history was relevant only for urolithiasis, was examined at ARNAS Garibaldi Hospital, Catania, Italy, due to 5 days of intense urinary symptoms, such as dysuria, pollakiuria, vesical tenesmus and

malaise, along with a fever (maximum temperature, 37.8˚C). Prior to symptom onset, he described urinary hesitancy during the last 15 days.

He did not take any medications, denying both smoking and drinking alcohol habits. The patient had a trimethoprim (TMP)-sulfamethoxazole (SMX) allergy. Furthermore, he denied any recent unprotected sexual intercourse. His clinical examination results were normal, apart from tenderness in the lower abdomen, under the navel. A digital rectal examination elicited pain and revealed an edematous and tender prostate.

His blood tests revealed a normal white blood cell count (8,600/mm^3, 64% neutrophils, 26% lymphocytes) with normal formula and high levels of inflammatory markers (erythrocyte sedimentation rate, 52 mm/h; C-reactive protein, 9.4 mg/dl); procalcitonin was negative. Renal and liver functions were also normal (creatinine levels were 0.8 mg/dl; the estimated glomerular filtration rate was calculated with a chronic kidney disease epidemiology collaboration of 120 ml/min; aspartate aminotransferase levels of 32 UI/l; alanine aminotransferase levels of 26 UI/l; and an international normalized ratio of 0.9). The results from HIV serology tests, as well as for hepatitis C virus and hepatitis B virus markers were negative. The total prostate-specific antigen (PSA) levels were 2.4 ng/ml, with normal levels of free PSA and PSA ratio (Table I).

A urine analysis revealed the presence of leukocyturia. The results of the urine culture test were negative, whereas those for the semen culture test were positive for ESBL-producing *E. coli* (>10^5 cfu/ml), resistant to fluoroquinolones and susceptible to carbapenems and fosfomycin (assessed using a MicroScan system; Beckman Coulter, Inc.). A transrectal prostate ultrasonography revealed an enlarged and homogeneous gland without abscesses or calcifications (ultrasonography images are unavailable since the patient only provided his clinical report). No genitourinary abnormalities were detected.

Based on the antibiogram and considering that the patient did not agree to hospital admission, preferring to be treated as an outpatient, oral fosfomycin-trometamol was administered using the following scheme: A 3 g-dose daily for 7 days followed by a 3 g-dose every 48 h for a further 14 days (overall, 14 doses of fosfomycin).

After the fourth dose, the patient reported aqueous diarrhea with abdominal discomfort; ahead of schedule, the dosage was switched to 1 dose every 48 h, thus achieving the complete gastrointestinal symptoms. Within 8 days, the urinary symptoms began to ameliorate, particularly vesical tenesmus and pollakiuria. He completed the full treatment without other adverse effects, as confirmed by blood tests performed after 7 days and at the end of treatment. A urine analysis did not reveal any abnormalities and semen culture results were negative in two different samples collected at the end of treatment and after 30 days. After 5 months, a urine examination along with a semen culture, without antibiotic treatments, did not reveal any recurrence of the UTI.

Discussion

Bacterial prostatitis, both ABP and CBP, are infections which are challenging to treat, due to the poor antibiotic penetration in prostatic tissue. CBP represents a complex setting to combat, due to the presence of prostatic calcifications, acting as bacterial sanctuary, along with bacterial biofilm formation, which lead to relapsing infections, persisting symptoms and treatment failure. Therefore, antibiotic treatment for CBP requires a longer duration (between 4 and 6 weeks) compared to acute forms, resulting in increased resistance selective pressure (2).

As opposed to CBP, ABP represents a clinically challenging setting, since intense urinary symptoms development along with a high risk of developing bacteremia and systemic sequelae (9). In addition, the emergence of bacterial strains resistant to commonly used antibiotic classes further hinders the clinical management of prostatitis due to the lack of treatment options, particularly for outpatients (6,10,11).

E. coli represents the most common pathogen causing bacterial prostatitis, accounting for 70-90% of cases, whereas other Enterobacterales, such as *Klebsiella* spp. and Enterococci constitute the remaining portion (2).

Despite the high frequency of allergies and intolerance, fluoroquinolones and TMP-SMX constitute the proper empiric choice against the majority of prostatitis-causing bacteria. Furthermore, prolonged fluoroquinolone treatment has been associated with severe adverse effects on muscles, tendons and joints, and can also lead to central nervous system impairment and cardiac involvement (QT prolongation).

Fosfomycin tromethamine, one of the smallest antibiotics in clinical use (the fosfomycin/trometamol molecular weight is 138.059/121.131 g/mol), is able to reach clinically relevant concentrations in the bladder as well in the prostatic gland. Its hydrophilicity together with negligible protein binding (<5%) and the overall PK/PD profile, allow the antibiotic to reach a bio-availability level of 33-50% within 2 h at concentrations of 20-30 mg/l and 2,000-2,500 mg/l in serum and in urine respectively, after a single dose of 3 g *per os* (12). Of note, as reported by European Committee on Antimicrobial Susceptibility Testing (EUCAST), fosfomycin epidemiological cut-off (ECOFF) values 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 *Staphylococcus aureus* (even lower for MRSA) (13), values lower than the antibiotic concentration in the urine even after 48 h following administration (100-700 mg/l) (12).

The reason behind the success of fosfomycin in the treatment of UTIs, as well as in the perioperative prophylaxis of prostate biopsy is due to its unaltered excretion in the urine and almost unaltered renal elimination (12). This poses an issue for the administration of fosfomycin to patients with compromised renal functions. Fosfomycin represents a reasonable choice for the treatment of bacterial prostatitis due to its high lipid solubility, a distribution volume of ~2 l/kg with almost no binding to proteins and a low molecular weight, which strongly support its penetration into the prostate lipid-rich parenchyma (14).

Oral fosfomycin treatment reaches elevated intraprostatic concentrations, even in uninflamed glands, being detectable within 17 h following a single 3-g dose, as previously reported in a prospective study on healthy volunteers (15) and in animal models of ABP, suggesting that fosfomycin can better achieve prostate distribution in inflamed conditions (16). These findings were confirmed in another prospective study, involving subjects with benign prostatic hyperplasia and treated with a parenteral single 4-g dose of fosfomycin (17).

Table I. Laboratory findings of the patient in the present case report.

Laboratory parameters (reference range)	Value
WBC, cells/mmc (4,000-10,000)	8,600
Neutrophils, % (40-75)	64
Lymphocytes, % (25-50)	26
ESR, mm/h (0-10)	52
CRP, mg/dl (0-0.5)	9.4
Procalcitonin, μg/l (<0,5)	0.03
Creatinine, mg/dl (0,8-1,2)	0.8
AST, UI/l (15-35)	32
ALT, UI/l (15-35)	26
INR, (0,8-1,1)	0.9
Total PSA, ng/ml (4-20)	1

WBC, white blood cell; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; PSA, prostate-specific antigen.

Fosfomycin has a bactericidal activity against numerous Gram- and Gram-negative bacteria, since its inhibition of bacterial cell wall synthesis along with antibiofilm activity (18). Considering the pharmacological characteristics, fosfomycin exhibits concentration-dependent mechanisms of action against susceptible bacteria, suggesting a dosing regimen optimization strategy in order to enhance the intraprostatic concentration over the minimum inhibitory concentration (MIC) value, allowing less frequent dosing administration (18,19).

Moreover, fosfomycin has other notable mechanisms of action, such as interfering with the initial steps of cell wall synthesis by inhibiting N-acetyl muramic acid formation through phosphoenolpyruvate synthetase involvement (20), and exhibiting a low grade of cross-resistance, a high synergistic effect rate with other antibiotic classes, and efficacy against several multidrug-resistant bacteria, including AmpC- and ESBL-producing Enterobacterales (21-23).

In addition, scientific literature has indicated that fosfomycin has favorable antimicrobial activity, even with difficult-to-treat Gram-positive bacteria, such as vancomycin-resistant Enterococci and methicillin-resistant Staphylococci (24). Moreover, the mechanisms of action of fosfomycin (25) suggest an additive or synergistic action in combination with other antibiotics. In fact, fosfomycin has been shown to exert notable synergistic effects with several other antibiotics, e.g. piperacillin/tazobactam, ceftazidime/avibactam, meropenem, colistin, daptomycin and linezolid (12,20,26-36). Considering the common UTI-causative organisms, the fosfomycin susceptibility rate of *E. coli* is usually higher than that for TMP-SMX and ciprofloxacin, namely between 86 and 100% (37-41).

Fosfomycin MIC distribution data reported by EUCAST emphasized that the majority of common uropathogens have low MIC values, which could be attained in the human prostate (15,17,42).

Some issues can arise in performing fosfomycin susceptibility testing as the gold standard method for Staphyilococci, Enterococci, Enterobacterales and *P. aeruginosa* in an agar dilution with the addition of glucose-6-phosphate in the medium. This methodology is time-consuming and demanding, and thus not suitable for every hospital setting. However, more effective and rapid antimicrobial susceptibility testing methods have been produced by different companies and several studies have been performed, demonstrating the validity of disk diffusion, gradient tests and automatized methods (43-48). The accuracy of the results is dependent on the selection of the most appropriate method for the isolation of species and on the strict adherence to the manufacturers' instructions, as reported by EUCAST (49).

Last but not least, when performing disk diffusion or gradient testing, it may be possible to visualize colonies within the inhibition zone. In accordance with the EUCAST recommendations, these colonies must be ignored. To date, no association has been found between their appearance and the onset of fosfomycin resistance, that remain very low (50,51).

To date, a small number of case reports have described oral fosfomycin administration for ABP, whereas there is a more notable availability of scientific literature on CBP (9,52-55). Grayson *et al* (56) reported two ABP cases due to ESBL-producing *E. coli* successfully treated with oral fosfomycin administration, in which plasma concentrations were periodically examined; in both cases, the germs were susceptible to fosfomycin (E-test method) and the subjects received oral fosfomycin for a total of 16 and 12 weeks, respectively at the dose of 3 g once daily, obtaining complete clinical success with microbiological eradication at 6 months of follow-up. Fosfomycin plasma concentrations always reported values above the MIC of the pathogen, achieving even better concentrations with 3 g twice daily doses; however, this regimen was associated with insufferable gastrointestinal side-effects (diarrhea) (56).

Shrestha *et al* (57) described the case of an 85-year-old patient with vancomycin-resistant *Enterococcus faecium* (VRE) ABP treated with 3 g oral fosfomycin every 72 h for 21 days, obtaining clinical success with microbiological eradication for 2 years. Recently, Bouiller *et al* (1) analyzed 16 male patients with UTIs due to MDR *Enterobacterales*, four of whom had acute UTIs, but without reporting ABP cases, and 12 patients with CBP, treated with oral fosfomycin-trometamol. Complete microbiological and clinical recovery was achieved for the acute UTI cases, whereas 7 of the 12 CBP patients had a relapse.

Although the patient described herein was young and healthy, and did not suffer from any previous episodes of UTIs, the therapeutic options were limited due to the *E. coli* antibiogram, the TMP-SMX allergy of the patient, and his decision to not to be admitted to hospital. After ruling out sexually transmitted diseases (58-61), and assessing the absence of intraprostatic lesions, such as abscesses or calcifications, the patient was successfully treated with 21 days of oral fosfomycin treatment, achieving clinical recovery and microbiological remission. Of note, although a rectal examination, particularly a prostatic massage, should be discouraged during ABP due to the risk of developing bacteremia and local sequelae, at the time of the examination, no blood test or imaging results were yet available. Furthermore, a rectal

examination assisted in obtaining the diagnosis of prostatitis, acting as a diagnostic tool.

Although some authors (56) have suggested not to outrun fosfomycin dose administrations due to reduction in plasma concentration levels, mild gastrointestinal events, which represent the most common adverse effects described during oral fosfomycin therapies, could be avoided or reduced by prolonging the frequency of fosfomycin administration to every 48 or 72 h (2). The evidence of the oral administration of fosfomycin in ABP is limited to case reports, since there is no explicit consensus yet available on the dosing regimen or treatment duration. Based on oral fosfomycin regimens for the treatment of CBP, it is possible to speculate that fosfomycin concentrations in ABP may be higher due to the prostate-inflamed status, thus allowing an increased drug penetration (2).

In conclusion, in the era of difficult-to-treat MDR infections, oral fosfomycin may represent a valid therapeutic option for male UTIs, particularly in prostatitis, due its favorable mechanisms of action and PK/PD properties. The case described in the present study, along with literature review, encourage and suggest the use of oral fosfomycin for the treatment of ABP, especially for outpatient and for those subjects who cannot be administered other antibiotics. However, the present study does not allow for any definitive conclusions to be drawn, since more valid data from randomized controlled trials and larger cohort studies are warranted to support routine treatment for this condition.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Authors' contributions

All authors (AM, SS, MC, AZ, GN and BC) contributed to the study conception and design. AM wrote the manuscript. SS and MC revised the literature and references. AZ provided clinical assistance to the patient. BC was responsible for the laboratory tests and pharmacological treatments. GN and BC revised the manuscript. AM and SS confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Written informed consent was obtained from the patient for the inclusion of his data in the present case report.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of the present case report.

Competing interests

The authors declare that they have no competing interests.

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