

Fosfomycin for Treatment of Prostatitis: New Tricks for Old Dogs

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(See the Editorial Commentary by Falagas and Rafailidis on pages 1144–6.)

Treatment options for prostatitis caused by multidrug-resistant gram-negative bacilli are limited. We report two cases cured with oral fosfomycin and provide a pharmacokinetic analysis of fosfomycin predose concentrations during treatment.

Keywords. fosfomycin; prostatitis; microbial drug resistance; pharmacology.

Prostatitis is a difficult infection to treat due to the poor penetration of many antimicrobials into prostatic tissue [1, 2]. Antimicrobial options are limited and prolonged courses of therapy (6–12 weeks) are required, with fluoroquinolones being cornerstones of therapy [3]. The increasing incidence of multidrug-resistant gram-negative bacilli (MDR-GNB) worldwide has had an impact on the microbial epidemiology of prostatitis [4, 5]. Fluoroquinolone resistance further limits oral treatment options for prostatitis and sometimes mandates long-term parenteral therapy with high rates of relapse in many patients [2].

Fosfomycin is an attractive alternative for the treatment of prostatitis because of its high oral bioavailability and ability to attain therapeutic levels in prostatic tissue [6, 7]. Although the use of fosfomycin for treatment of prostatitis has been reported previously, parenteral agents were frequently coadministered [1, 8–11], such that there is a paucity of information regarding the appropriate fosfomycin dosing regimen [12] and the drug's

tolerability and long-term outcomes. We report the successful treatment of 2 patients with MDR-GNB prostatitis with oral fosfomycin in whom detailed pharmacokinetic monitoring allowed identification of an effective fosfomycin treatment regimen.

PATIENTS AND METHODS

Patient 1

A 73-year-old diabetic man was transferred from an outside hospital for management after an initial failure of first-line therapy for extended-spectrum β -lactamase (ESBL) *Escherichia coli* acute prostatitis. He had a past history of recurrent urinary tract infections (UTIs) and 10 weeks prior had undergone a transrectal ultrasound (TRUS)-guided biopsy of the prostate to investigate an elevated prostate-specific antigen (PSA) level and possible prostatic malignancy. Soon after the biopsy he developed high fevers, dysuria, and frequency. Urine cultures grew ESBL-positive *E. coli* resistant to ciprofloxacin but susceptible to meropenem, ertapenem, and fosfomycin (minimum inhibitory concentration [MIC], 1 mg/L, Etest). His biopsy sample showed focal acute and chronic prostatitis but no malignancy. He was treated for prostatitis with meropenem 1 g intravenously every 8 hours for 2 weeks, followed by outpatient parenteral therapy with ertapenem 1 g daily for 4 weeks. Two weeks following completion of this 6-week course, the patient had a relapse with recurrence of his symptoms. ESBL *E. coli* with the same susceptibility pattern (fosfomycin MIC, 1 mg/L, Etest) was again isolated in the urine. He was transferred to our hospital and initially recommenced on meropenem 1 g every 8 hours, with an improvement in his symptoms and inflammatory markers and clearance of bacteriuria. Computed tomography and TRUS imaging of his prostate again demonstrated prostatomegaly but no intraprostatic collection, and his PSA level remained elevated (12.27 μ g/L [normal, <6.5 μ g/L]). After 2 weeks of therapy with meropenem, the patient was switched to oral fosfomycin 3 g once daily, with plasma fosfomycin concentrations assessed regularly (see "Results" section).

After 14 days of well-tolerated, clinically effective therapy, the patient's plasma fosfomycin concentrations were considered satisfactory (see "Results" section), but in an attempt to achieve concentrations substantially above the MIC of the pathogen, his fosfomycin was increased to 3 g twice daily. Within 36 hours of the increase in dose frequency, the patient developed prominent fecal urgency and diarrhea (2–3 bowel movements daily), which was repeatedly negative for diarrheal pathogens, including

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Clostridium difficile, and could not be controlled with loperamide. After 5 days of twice-daily therapy, the fosfomycin dose was reduced to 3 g once daily, with prompt resolution in the patient's symptoms.

The patient subsequently completed a total course of 16 weeks of oral fosfomycin (15 weeks, 2 days of 3 g once daily; 5 days of 3 g twice daily) without incident and was clinically and microbiologically cured 6 months after treatment completion.

Patient 2

An 80-year-old man was referred to our clinic for treatment of a UTI caused by MDR ESBL-positive *E. coli* that was resistant to ciprofloxacin but susceptible to fosfomycin (MIC, 1.0 mg/L, Etest). He had a past history of recurrent UTIs and urethral strictures requiring flexible cystoscopy and had recently traveled to Thailand.

He was initially treated with fosfomycin 3 g every 72 hours for 2 weeks [13]. Five days after cessation of therapy, he had a recurrence of dysuria, polyuria, and malodorous urine; repeat urine culture once again isolated ESBL *E. coli* with the same susceptibility profile. Computed tomography of the prostate showed prostatomegaly but no abscess. Acute prostatitis was clinically diagnosed, and he was recommenced on oral fosfomycin, this time at a dose of 3 g once daily. Predose (trough) plasma fosfomycin concentrations were measured periodically during therapy. The patient successfully completed 12 weeks of fosfomycin therapy with no significant adverse effects. He had no clinical or microbiologic evidence of recurrence at 6 months of follow-up.

Plasma fosfomycin levels were assessed on both patients using methods previously described [5]. The timing of plasma samples relative to each dose was recorded to allow a pharmaco-

kinetic analysis of dosing and especially to identify trough (0–3 hours predose) concentrations, as they were considered likely to represent steady-state intraprostatic levels [5].

RESULTS

After prolonged (6 months) follow-up, both patients with MDR prostatitis have been clinically and microbiologically cured with oral fosfomycin 3 g once daily.

For patient 1, 19 samples were collected (1 pretreatment; 13 trough samples after fosfomycin 3 g once daily; 2 were collected 15.8 and 16.8 hours after 3 g once daily; and 3 trough samples during therapy with 3 g twice daily). For patient 2, 10 trough samples were collected after 3 g once daily. Results for both patients are summarized in Figure 1 and Supplementary Table 1.

Mean trough plasma fosfomycin concentrations during therapy with 3 g once-daily and 3 g twice-daily dosing were 5.3 ± 1.3 $\mu\text{g}/\text{mL}$ (range, 2.3–7.6 $\mu\text{g}/\text{mL}$; median, 5.4 $\mu\text{g}/\text{mL}$) and 13.4 ± 3.0 $\mu\text{g}/\text{mL}$ (range, 10.9–16.7 $\mu\text{g}/\text{mL}$; median, 12.5 $\mu\text{g}/\text{mL}$), respectively. The twice-daily dosing regimen resulted in significantly higher mean trough concentrations ($P = .04$, t test), but was associated with intolerable gastrointestinal side effects.

DISCUSSION

This report is notable because it suggests that prolonged (12–16 weeks) monotherapy with oral fosfomycin 3 g once daily is effective in selected patients with MDR (but fosfomycin-susceptible) *E. coli* prostatitis. Furthermore, trough plasma fosfomycin concentrations were remarkably similar in both patients (overall mean \pm SD, 5.3 ± 1.3 $\mu\text{g}/\text{mL}$) when treated with a 3 g once-daily dosing regimen, which was well tolerated in both cases. Although it is hard to extrapolate the intraprostatic fosfomycin concentrations associated with this dosing regimen, it is likely that with prolonged therapy, steady-state concentrations that are similar to the observed trough plasma values are achieved [5]. We have previously found prostate fosfomycin levels of 6.5 ± 4.9 $\mu\text{g}/\text{g}$ (range, 0.7–22.1 $\mu\text{g}/\text{g}$) following administration of a single oral 3-g dose [5].

Although fosfomycin has few toxicities or drug interactions, we found the twice-daily dose to be poorly tolerated, in keeping with previous reports [14]. However, the twice-daily dose was associated with significantly higher trough plasma fosfomycin concentrations. In most previous case reports of successful fosfomycin treatment of prostatitis, combination regimens were used including doxycycline [1], ertapenem [9], and aztreonam [10]. Similar to others [1], we found the dose regimen routinely recommended for UTI (3 g every 72 hours [13]) to be ineffective. The single previous successful case report of fosfomycin monotherapy for prostatitis required parenteral administration [8]. Given that urologic procedures, in particular TRUS biopsy,

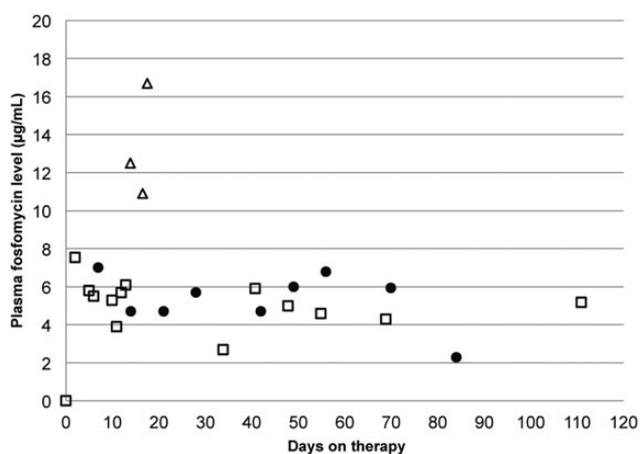


Figure 1. Trough plasma fosfomycin levels during therapy for prostatitis. Measurements were done on 23 samples from 2 patients for fosfomycin 3 g once daily (patient 1, open squares; patient 2, closed circles) and on 3 samples from 1 patient for fosfomycin 3 g twice daily (patient 1, open triangles).

are associated with a 2%–6% risk of UTI (with 30%–50% developing bacteremia) [14], the role of fosfomycin as prophylaxis [5] needs to be balanced against the risk of encouraging the emergence of fosfomycin resistance.

This study has some limitations. First, patient 1 received 2 weeks' initial treatment with meropenem prior to switching to fosfomycin; however, given that this patient had previously failed a 6-week course of carbapenem therapy, it is less likely that the short course of meropenem influenced the final outcome. Second, given that both our cases had infection due to *E. coli* strains with relatively low MICs (1 mg/L), we cannot be sure whether similar success would be achieved for less susceptible organisms, particularly if the MIC was substantially greater than the trough concentrations we observed. Finally, although patient 2 had clinical symptoms highly suggestive of prostatitis, he did not have biopsy confirmation (as in patient 1).

Despite these caveats, we believe our findings are encouraging and suggest that a prolonged course of fosfomycin, one of the “forgotten antibiotics,” at a dose of 3 g once daily, may be a safe and effective treatment option for selected cases of prostatitis where laboratory confirmation of susceptibility to fosfomycin has been confirmed.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (<http://cid.oxfordjournals.org>). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Potential conflicts of interest. All authors: No potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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