Fosfomycin for the Treatment of Prostate Infection

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Abstract

A 69-year-old man with diabetes mellitus was diagnosed with a prostate abscess. Although the pathogen was fluoroquinolone-resistant *Escherichia coli* and the oral administration of trimethoprim-sulfamethoxazole was initiated, the infection recurred after three months. The antibiotic therapy was subsequently changed to intravenous fosfomycin, and the patient’s condition promptly improved. Four weeks of fosfomycin therapy was successfully continued without any adverse events. In the era of antibiotic resistance, revival of forgotten drugs is an important issue for clinicians. Fosfomycin can be applied as an alternative option for prostate infections, considering the remaining susceptibility of multidrug-resistant pathogens to fosfomycin and the good pharmacokinetics of this drug in prostatic tissue.

Key words: chronic bacterial prostatitis, fluoroquinolone, fosfomycin, prostate abscess, revival of antibiotics


Introduction

Chronic bacterial prostatitis is an intractable disease that requires the prolonged administration of limited antibiotics. Due to the low penetration of antibiotics into prostatic tissue, prostate infections have a poor prognosis without appropriate treatment (1). The use of fluoroquinolones (FQs), following trimethoprim-sulfamethoxazole (TMP-SMX), is recommended in cases of refractory infection, whereas the application of beta-lactams is not endorsed due to the poor pharmacokinetics of these agents (2).

Resistance to FQs and TMP-SMX has been increasing worldwide (3), and the development of new antimicrobial agents is essential. However, in recent years, few new antibiotics have been manufactured (4). Against this background, it is necessary to consider reviving the use of old drugs to treat prostate infections. Fosfomycin remains susceptible to various pathogenic organisms (5) and exhibits potentially good penetration into prostatic tissues. We herein describe a case of a prostate abscess that was successfully treated with fosfomycin.

Case Report

A 69-year-old man with type 2 diabetes mellitus was admitted to our hospital for treatment of rhabdomyolysis. His blood glucose and hemoglobin A1c levels on admission were 116 mg/dL and 8.5%, respectively. Otherwise, the patient had no particular medical history, including urinary tract infections. Ten days later, systemic contrast-enhanced CT incidentally detected bilateral fluid retention inside the prostate, which was subsequently confirmed on contrast-enhanced magnetic resonance imaging (MRI) (Figure A, B). A urine culture was positive for FQ-resistant *Escherichia coli* (*E. coli*), and the oral administration of TMP-SMX (5 mg/kg/day of trimethoprim) was initiated under a diagnosis of bilateral prostate abscesses. Treatment with intravenous cefotaxime was combined for the first week. The patient’s clinical course was uneventful, and he was discharged under TMP-SMX treatment.

Although oral TMP-SMX administration was continued, the patient abruptly developed a high fever after three months and was readmitted. Upon admission, his vital signs...
were stable and there were no symptoms of residual urine or difficulty in urination; however, prostate tenderness was confirmed on a digital rectal examination. In addition, a laboratory examination demonstrated a state of elevated inflammation (C-reactive protein, 4.41 mg/dL), and contrast-enhanced MRI showed deterioration of the right prostate abscess (Figure C).

A urinary culture was positive for *E. coli* resistant to both FQs and TMP-SMX (Table). Considering its good penetration into prostatic tissues, fosfomycin was alternatively considered, and the administration of intravenous fosfomycin (12 g divided into three doses a day) was initiated. Informed consent for the use of high-dose fosfomycin was obtained prior to treatment, since prostate abscesses are not included as an indication on Japan’s package insert for intravenous fosfomycin, and the maximum dose of the drug is set to 4 g per day. Consequently, the patient’s serum C-reactive protein level greatly improved after one week (0.79 mg/dL), and transurethral resection of the prostate (TUR-P) was additionally performed for radical drainage. A sodium-restricted diet was prescribed, and 20 mg of furosemide and 25 mg of spirinolactone were orally administered, as the serum sodium level exhibited a gradual increase. During treatment, the patient’s serum sodium level ranged from 136 to 141 mEq/L.

The intravenous fosfomycin therapy was continued for four weeks without adverse events. Finally, although a low level of occult blood in the urine and slight leukocyturia remained, the bacteriuria disappeared and the serum inflammation completely resolved. The elimination of the prostate abscess was subsequently confirmed on follow-up contrast-enhanced MRI.

**Table. Results of Antibiotic Susceptibility Testing of E. coli**

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>MIC (µg/mL)</th>
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<tbody>
<tr>
<td>Ampicillin/sulbactam</td>
<td>&gt;16</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>≤2</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>≤4</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>≤0.5</td>
</tr>
<tr>
<td>Cefazidime</td>
<td>≤0.5</td>
</tr>
<tr>
<td>Cefepime</td>
<td>≤0.5</td>
</tr>
<tr>
<td>Cefmetazole</td>
<td>≤1</td>
</tr>
<tr>
<td>Meropenem</td>
<td>≤0.5</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>≤0.5</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>≤1</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>&gt;16</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>&gt;16</td>
</tr>
<tr>
<td>T osuloxacin</td>
<td>&gt;16</td>
</tr>
<tr>
<td>Minocycline</td>
<td>2</td>
</tr>
<tr>
<td>Fosfomycin</td>
<td>≤4</td>
</tr>
</tbody>
</table>

The causative organism was resistant to both fluoroquinolones and trimethoprim-sulfamethoxazole (TMP-SMX), while susceptible to fosfomycin. Susceptibility of fosfomycin was also confirmed by disk diffusion test; a diameter of inhibitory zone was more than 20 mm. Susceptibility testing for TMP-SMX was performed only by disk diffusion method.

Treating prostate infections is challenging due to the low penetration of antibiotics into prostatic tissues. Major factors determining the penetration of antimicrobial agents into the prostatic tissue have been reported to include a high level of lipid solubility, low degree of ionization, high dissociation constant, low protein binding and small molecular size (2, 6). FQs satisfy these conditions, and their use is recommended as optimal agents for the treatment of prostate infections (2).

The emergence of multidrug-resistant *Enterobacteriaceae* strains has become an increasing clinical problem worldwide. Due to the detection of strains resistant to FQs, there is a need to find other antimicrobials to treat prostate infections (2). One possible alternative is TMP-SMX; however, a long treatment course is required to achieve a satisfactory clinical outcome (7). Tetracycline and macrolides have also been reported to have good penetration into prostatic fluid and tissue. Minocycline appears to distribute well into prostatic tissue at a serum concentration of 40% to
susceptibility studies, including 2,205 clinical isolates of E. coli. The authors also reported that, limiting the findings to non-ESBL-producing E. coli, more than 90% of 70 strains were susceptible to fosfomycin. In addition, Falagas et al. summarized the results of 17 antimicrobial susceptibility studies, including 2,205 clinical isolates of multidrug-resistant E. coli, and concluded that nearly 90% of the isolates were susceptible to fosfomycin (5). Of the 17 studies, a Clinical and Laboratory Standards Institute breakpoint, in other words, the susceptibility defined as a minimum inhibitory concentration (MIC) of 64 mg/L or less, was primarily applied. Therefore, we consider that E. coli is usually sensitive to fosfomycin.

We confirmed that the pathogen in this case was susceptible to fosfomycin using both agar dilution and disk diffusion methods; the MIC was less than 4 μg/mL, and the diameter of the inhibitory zone was greater than 20 mm. Whether the breakpoint for urinary tract infection (an MIC of 64 mg/L or less) can be used for prostate infections is unknown. Hence, the particular breakpoint for prostate infection should be determined, and further investigation of this issue is necessary. In the absence of other superior antibiotics, we administered fosfomycin in the present case and obtained satisfactory therapeutic results.

To the best of our knowledge, the nationwide epidemiology of fosfomycin-resistant E. coli in Japan has not been addressed. A previous study of a Japanese medical facility showed 73% (1,46 of 200 strains) of extended-spectrum β-lactamase (ESBL)-producing E. coli to be susceptible to fosfomycin (9). The authors also reported that, limiting the findings to non-ESBL-producing E. coli, more than 90% of 70 strains were susceptible to fosfomycin (9). In addition, Falagas et al. summarized the results of 17 antimicrobial susceptibility studies, including 2,205 clinical isolates of multidrug-resistant E. coli, and concluded that nearly 90% of the isolates were susceptible to fosfomycin (5). Of the 17 studies, a Clinical and Laboratory Standards Institute breakpoint, in other words, the susceptibility defined as a minimum inhibitory concentration (MIC) of 64 mg/L or less, was primarily applied. Therefore, we consider that E. coli is usually sensitive to fosfomycin.

According to a previous study (10), the mean prostate and plasma concentrations after a single dose of 4 g of intravenous fosfomycin (within one hour) are 68.6±28.3 μg/g and 152.4±29.9 μg/mL, respectively, for a mean prostate to plasma ratio of approximately 0.45. The daily dose of intravenous fosfomycin ranges from 12 to 16 g on average, with a maximum allowed dose of up to 20 g per day in cases of life-threatening infection (11). Based on these facts, we assume that three doses of 4 g of intravenous fosfomycin per day can be used to achieve a therapeutic concentration. In the present study, the treatment inevitably burdened the patient with a large amount of sodium; 1 g of intravenous fosfomycin contains 0.33 g (14.4 mEq) of sodium. Therefore, his cardiac function was confirmed to be within the normal range prior to the administration of fosfomycin, and diuretics were combined in order to promote the excretion of excess sodium.

Oral fosfomycin is available in two formulations: fosfomycin-trometamol and fosfomycin-calcium. Fosfomycin-trometamol is preferred for oral administration, as its bioavailability is better than that of fosfomycin-calcium (40% vs. approximately 10%, respectively) (12). While fosfomycin-trometamol is approved for oral use in most European countries and the United State, it is unavailable in Japan. Although the administration of imported fosfomycin-trometamol was considered in this case, we decided against this option due to problems associated with cost, safety and time. Therefore, without access to useful oral antibiotics, we opted to administer intravenous fosfomycin under long-term hospitalization.

We conclude that the fosfomycin therapy for the prostate abscess was effective in this case. However, drainage therapy may have been the most important factor for achieving a cure. In order to conclusively determine the effectiveness of fosfomycin for treating prostate infections, the accumulation of cases treated with fosfomycin in the absence of surgical intervention is required.

In summary, we herein described a case of a prostate abscess that was successfully treated with a “forgotten antibiotic,” fosfomycin. Due to the continued susceptibility of multidrug-resistant pathogens to fosfomycin and the good pharmacokinetics of this drug, this agent is an alternative therapeutic option for refractory prostate infections.

The authors state that they have no Conflict of Interest (COI).

References