Case Report

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Successful treatment of lower urinary tract infections with oral fosfomycin: a report of three cases

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ABSTRACT

Infections due to multidrug-resistant organisms continue to increase, and therapeutic options remain scarce. Given this challenge, it has become necessary to use older antimicrobials for treatment of these pathogens. We report three patients with lower urinary tract infections caused by *Klebsiella pneumoniae* carbapenemase (KPC)-producing *Klebsiella pneumoniae* who were successfully treated with a seven-day course of oral fosfomycin monotherapy.

Keywords: Fosfomycin. Urinary tract infection treatment. KPC-producing *Klebsiella pneumoniae.*

INTRODUCTION

The emergence of multidrug-resistant (MDR), mainly carbapenem-resistant, *Klebsiella pneumoniae* has prompted re-evaluation of nontraditional antibiotics, such as fosfomycin, due to their efficacy for the treatment of both urinary and systemic infections. In particular, data regarding the use of fosfomycin for the treatment of infections caused by contemporary MDR gram-negative pathogens are warranted to further evaluate the optimal clinical use of this revived antimicrobial agent[1].

Studies supporting the use of this drug as monotherapy for these infections are limited. Here, we describe three patients with lower urinary tract infections (UTIs) caused by *Klebsiella pneumoniae* carbapenemase (KPC)-producing *K. pneumoniae* who were successfully treated with oral fosfomycin monotherapy.

CASE REPORT

The first case was a 70-year-old man who underwent coronary bypass surgery, without complications. Thirteen days after the surgery, the patient presented with dysuria and urgency without fever. A urinary tract infection was diagnosed. The urine analysis showed 750,000 leukocytes/mL, and the culture yielded KPC-producing *K. pneumoniae*.

The second case was a 48-year-old woman who underwent cardiac valve surgery owing to severe dysfunction of her existing metallic mitral valve. Because of surgical complications, she was admitted to the intensive care unit (ICU) with cardiogenic shock and severe ventricular dysfunction. She remained in the ICU for 35 days. Eight days post-discharge, the patient presented with dysuria and pelvic discomfort. The urine analysis showed 733,000 leukocytes/mL, and the culture yielded KPC-producing *K. pneumoniae.*

The third case was an 80-year-old man with chronic renal failure on peritoneal dialysis who was admitted to the hospital with a lower UTI. The urine analysis showed 265,000 leukocytes/mL, and the culture yielded KPC-producing *K. pneumoniae.*

A urinary catheter was not used by any of the three patients. Treatment for all patients included 3g oral fosfomycin every 12h for seven days, without adverse effects. Urine analyses were conducted, and cultures were collected at the end of the treatment and again one week later. No leukocyturia was evident, and all cultures remained negative.

Upon admission, the urine cultures of all three patients showed colony counts >100,000 CFU/mL (colony-forming units per milliliter), with growth of *K. pneumoniae* identified at >95% probability using the Vitek 2 Compact® (bioMerieux) automated system. The modified Hodge test and polymerase chain reaction for gene bla_{KPC} were positive for all isolates.

A disk diffusion test was performed using discs with 200µg fosfomycin trometamol supplemented with 50µg glucose-6-phosphate. The minimum inhibitory concentrations (MICs) were determined using the agar dilution method according to the Clinical and Laboratory Standards Institute (CLSI) recommendations. Briefly, Mueller-Hinton agar plates

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were supplemented with 100µL glucose-6-phosphate at a concentration of 5mg/mL. Fosfomycin concentrations ranged from 0.125µg/mL to 256µg/mL. A drug-free plate was used for growth control, and the standard strains *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 were used as quality controls. The results were within the expected ranges, for both methodologies. For agar dilution, the three isolates as well as the controls were used to prepare a solution with a turbidity of 0.5 McFarland (approximately 10^8 CFU/mL). This inoculum was diluted to 1:10 for a concentration of 10^7 CFU/mL. A 2-µL aliquot was inoculated on the plates to yield a final inoculum of 10^4 CFU/mL. The plates were incubated at 35°C and read after 18h.

As criteria to evaluate the susceptibility of *K. pneumoniae* to fosfomycin in the current CLSI guidelines were not available, the results were interpreted according to the breakpoints used for *E. coli* in UTIs: resistant, ≤12mm; intermediate, 13-15mm; susceptible: ≥16mm for disc diffusion and susceptible, MIC ≤64µg/mL; intermediate, MIC 128µg/mL; resistant, MIC ≥ 256µg/mL for agar dilution[2]. These breakpoints have been used previously in similar studies[1] [3] [4] [5] [6].

The susceptibility test results for fosfomycin are shown in **Table 1**. Only one minor error for the first isolate (agar dilution in the intermediate category and disk diffusion zone indicating susceptible, but near the intermediate zone) was found, reflecting good concordance between both methodologies. Other antimicrobial agents were also tested using Vitek 2 Compact®, and the MIC results are shown in **Table 2**. High levels of resistance to cephalosporins, quinolones, and piperacillin/tazobactam and susceptibility to aminoglycosides and colistin were found. MICs to carbapenems varied, although all isolates were carbapenemase producers.

TABLE 1 - Comparative results of disk diffusion and agar dilution for *three isolates.*

Strain	DD (mm)	MIC (µg/mL)
Patient 1	19 (S)	128 (I)
Patient 2	13(I)	128 (I)
Patient 3	22 (S)	8 (S)
Escherichia coli	23 (S)	1 (S)
Pseudomonas aeruginosa	-	4 (S)

DD: disk diffusion; **MIC:** minimum inhibitory concentration; **S:** susceptible; **I:** intermediate.

TABLE 2 - Minimum inhibitory concentration results for other antimicrobial agents using the Vitek 2 automated method.

	Patient 1	Patient 2	Patient 3
Amikacin	4 (S)	4 (S)	4 (S)
Cefepime	≥64 (R)	≥64 (R)	≥64 (R)
Cefotaxime	≥64 (R)	≥64 (R)	≥64 (R)
Ceftazidime	≥64 (R)	≥64 (R)	≥64 (R)
Ciprofloxacin	≥4 (R)	≥4 (R)	≥64 (R)
Colistin	≤0.5 (S)	≤0.5 (S)	≤0.5 (S)
Ertapenem	≥8 (R)	≥8 (R)	≥8 (R)
Gentamicin	≤1 (S)	≤1 (S)	≤1 (S)
Imipenem	4 (R)	≥16 (R)	≥16 (R)
Meropenem	1 (S)	≥16 (R)	2 (I)
Piperacillin-tazobactam	≥128 (R)	≥128 (R)	≥128 (R)

S: susceptible; **R:** resistant; **I:** intermediate.

DISCUSSION

Therapeutic options against infections caused by KPC-producing *K. pneumoniae* are often limited[5]. Thus, new therapeutic strategies against these isolates are urgently needed[7] [8]. Oral fosfomycin is an *old* antimicrobial drug marketed in Brazil, the United States, and other countries as a single dose for the treatment of uncomplicated UTIs. It shows potent bactericidal action against many gram-negative and gram-positive pathogens[6]. Unfortunately, the parenteral disodium salt of fosfomycin is not yet available in Brazil[7] [9].

Although fosfomycin tromethamine is only indicated for lower UTIs, it has been studied in both uncomplicated and complicated lower UTIs caused by MDR uropathogens because it shows synergistic action with other antimicrobial drugs[10] [11]. The parenteral formulation has been used in combination therapy to treat a wide range of infections including pneumonia and septicemia with cure rates >80%[12].

Given its low rates of resistance and the available evidence, fosfomycin may serve as a useful option for oral treatment of MDR uropathogens[1]. Surprisingly, data regarding *in vitro* and *in vivo* activity of fosfomycin against KPC-producing *K. pneumoniae* isolates have been lacking until recently. A better understanding of the most appropriate oral dosing regimen against MDR uropathogens that cause UTIs is needed[8].

Neuner et al. described the microbiological outcomes of treatment with oral fosfomycin monotherapy for UTIs caused by MDR pathogens, including 13 carbapenem-resistant *K. pneumoniae* isolates. Patients received an average of 2.9 ± 1.8 doses (each dose = 3g fosfomycin tromethamine) per course of therapy. A 92% *in vitro* fosfomycin susceptibility was observed with a corresponding microbiological cure of 46% (6/13 patients). Most patients who had treatment failure were immunosuppressed or had ureteral stents suggesting caution in using fosfomycin monotherapy in these types of patients[1].

In the present study, we analyzed the susceptibility of three samples using disk diffusion and agar dilution. Only the isolate from patient 3 was susceptible to fosfomycin by both methods. The other two isolates were in the intermediate category in one or both methodologies. Even so, all patients experienced a microbiological and clinical cure with the applied dose regimen.

The presence of a urinary catheter is considered a complicating factor that may be related with microbiological failure, probably due to the biofilm structure that gram-negative bacteria can produce. Thus, the absence of a catheter might have contributed to the successful treatment of these three patients. Furthermore, fosfomycin in combination with other antibiotics, e.g., colistin, gentamicin, or carbapenems, might be able to eradicate biofilms caused by gram-negative bacteria[1].

The incidence of KPC-related UTIs was very low in the hospital during the study period, with approximately 4.5% of urine cultures positive for KCP during the 1-year period. These three cases were the first three patients diagnosed with a KPC-related UTI and the only cases who were treated with fosfomycin during this period. The major therapeutic options for patients with a KPC-related UTI were polymyxins (polymyxin B or colistin) or aminoglycosides combined with carbapenems. We opted to treat these patients with fosfomycin because they had less severe UTIs and did not have a urinary indwelling catheter. Owing to the high probability of the development of resistance, we have not utilized fosfomycin as monotherapy for uncomplicated KPC-related UTIs in recent years.

In conclusion, fosfomycin demonstrated reasonable *in vitro* activity against contemporary KPC-producing *K. pneumoniae* isolates, representing a possible alternative to other antimicrobials.

Despite the small number of cases (three), our results demonstrated that oral fosfomycin is a possible therapeutic option for lower UTIs caused by KPC-producing *K. pneumoniae* isolates.

REFERENCES

1. Neuner EA, Sekeres J, Hall GS, van Duin D. Experience with fosfomycin for treatment of urinary tract infections due to multidrug-resistant organisms. Antimicrob Agents Chemother 2012; 56:5744-5748.
2. Wayne PA. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing. 21th informational supplement. CLSI document M100-S21. CLSI; 2011.
3. Falagas ME, Giannopoulou KP, Kokolakis GN, Rafailidis PI. Fosfomycin: use beyond urinary tract and gastrointestinal infections. Clin Infect Dis 2008; 46:1069-1077.
4. Falagas ME, Kastoris AC, Karageorgopoulos DE, Rafailidis PI. Fosfomycin for the treatment of infections caused by multidrug-resistant non-fermenting Gram-negative bacilli: a systematic review of microbiological, animal and clinical studies. Int J Antimicrob Agents 2009; 34**:**111-120.
5. Keating GM. Fosofomycin trometamol: a review of its use as a single-dose oral treatment for patients with acute lower urinary tract infections and pregnant women with asymptomatic bacteriuria. Drugs 2013; 73:1951-1966.
6. Maraki S, Samonis G, Rafailidis PI, Vouloumanou EK, Mavromanolakis E, Falagas ME. Susceptibility of urinary tract bacteria to fosfomycin. Antimicrob Agents Chemother 2009; 53:4508-4510.
7. Endimiani A, Patel G, Hujer KM, Swaminathan M, Perez F, Rice LB, et al**.** *In vitro* activity of fosfomycin against *bla*KPC-containing *Klebsiella pneumoniae* isolates, including those nonsusceptible to tigecycline and/or colistin. Antimicrob Agents Chemother 2010; 54:526-529.
8. de Cueto M, Lopez L, Hernandez JR, Morillo C, Pascual A. *In vitro* activity of fosfomycin against extended-spectrum-β-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*: comparison of susceptibility testing procedures. Antimicrob Agents Chemother 2006; 50**:**368-370.
9. Lopez-Cerero L, de Cueto M, Diaz-Guerrero MA, Morillo C, Pascual A. Evaluation of the Etest method for fosfomycin susceptibility of ESBL-producing *Klebsiella pneumoniae*. J Antimicrob Chemother 2007; 59:810-812.
10. Schito GC, Naber KG, Botto H, Palou J, Mazzei T, Gualco L, et al**.** The ARESC study: an international survey on the antimicrobial resistance of pathogens involved in uncomplicated urinary tract infections. Int J Antimicrob Agents 2009; 34**:**407-413.
11. Popovic M, Steinort D, Pillai S, Joukhadar C. Fosfomycin: an old, new friend? Eur J Clin Microbiol Infect Dis 2010; 29:127-142.
12. Roussos N, Karageorgopoulos DE, Samonis G, Falagas ME. Clinical significance of the pharmacokinetic and pharmacodynamic characteristics of fosfomycin for the treatment of patients with systemic infections. Int J Antimicrob Agents 2009; 34:506-515.