Fosfomycin Susceptibility in Urinary Tract Enterobacteriaceae

Bhargav Patel1, Kinjal Patel2, Anjali Shetty3, Rajeev Soman4, Camilla Rodrigues3

Abstract

Introduction: Antibiotic treatment of Urinary Tract Infections (UTI) is becoming increasingly difficult due to emergence of multi-drug resistant (ESBLs, AmpC, CRE) uropathogens. Fosfomycin is an old antibiotic that has evoked renewed interest with unique properties of not sharing any structural similarity and lack of cross-resistance with other antimicrobial agents. Our aim is to evaluate in-vitro activity of Fosfomycin against urinary tract Enterobacteriaceae.

Material and Methods: The study period was March 2014 to September 2015. All 72 isolates were identified using conventional biochemical tests. Antimicrobial susceptibility testing was performed using the automated broth microdilution system Vitek 2 (bio- Mérieux, Inc., Durham, NC). Fosfomycin susceptibility was determined by the E-test (bioMérieux, Inc., Durham, NC) method. Interpretive criteria from the Clinical and Laboratory Standards Institute (CLSI) for fosfomycin susceptibility are not available for the Enterobacteriaceae other than Escherichia coli. Therefore, results were interpreted according to criteria for E. coli (i.e., susceptible at a MIC of ≤ 64 μg/ml), as has been reported previously.

Results: Overall, 79.16% (57/72) isolates were susceptible to fosfomycin with 92.00% (23/25) susceptibility in ESBL producing enterobacteriaceae and 72.34% (34/47) in CRE. One CRE isolate has developed resistant while on treatment. There was not much difference in number of susceptible isolates CLSI:EUCAST = 57:53, but number of resistant isolates was more with EUCAST (CLSI:EUCAST = 10:19).

Conclusion: Study demonstrate that, a considerable proportion (79.16%) of the multidrug-resistant Enterobacteriaceae with diverse resistance mechanisms, including ESBL and CRE, found susceptible to fosfomycin. Consequently, fosfomycin may currently be considered a useful antibiotic agent in the treatment armamentarium of UTIs.

Table 1: CLSI and EUCAST interpretative criteria for fosfomycin

<table>
<thead>
<tr>
<th>Disc content</th>
<th>CLSI</th>
<th>EUCAST</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIC</td>
<td>S</td>
<td>I</td>
</tr>
<tr>
<td>Zone diameter</td>
<td>200 μg</td>
<td>≥ 16</td>
</tr>
</tbody>
</table>

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</thead>
<tbody>
<tr>
<td>MIC</td>
<td>–</td>
<td>≥ 64</td>
</tr>
</tbody>
</table>

Introduction

Antibiotic treatment of Urinary Tract Infections (UTI) is becoming increasingly difficult due to emergence of multi-drug resistant (ESBLs, AmpC, CRE) uropathogens. Fosfomycin is an old antibiotic that has evoked renewed interest with unique properties of not sharing any structural similarity and lack of cross-resistance with other antimicrobial agents. It inhibits cell wall formation by binding to enzyme UDP-N-acetylglucosamine and inhibits formation of the cell wall precursor N-acetylmuramic acid. It has broad antimicrobial spectrum against MDR pathogens, both Gram-negative and Gram-positive organisms. Recent reports show in vitro activity against carbapenem-resistant Klebsiella pneumoniae (CR-Kp), Pseudomonas aeruginosa, extended-spectrum β-lactamase (ESBL) producing bacteria, and vancomycin-resistant enterococci (VRE).2-5 IDSA and ESCMID recommends fosfomycin as one of the first line agent for uncomplicated cystitis and pyelonephritis.6 Susceptibility testing of this agent requires...
Table 2: Susceptibility to fosfomycin using CLSI

<table>
<thead>
<tr>
<th>Fosfomycin</th>
<th>E. coli</th>
<th>Klebsiella spps</th>
<th>Enterobacter spps</th>
<th>Proteus spps</th>
<th>Morganella spps</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susceptible</td>
<td>ESBL 17</td>
<td>CRE 11</td>
<td>ESBL 5</td>
<td>CRE 8</td>
<td>ESBL 1</td>
<td>CRE 10</td>
</tr>
<tr>
<td>Intermediate</td>
<td>ESBL -</td>
<td>CRE -</td>
<td>ESBL 1</td>
<td>CRE 1</td>
<td>ESBL -</td>
<td>CRE -</td>
</tr>
<tr>
<td>Resistant</td>
<td>ESBL 1</td>
<td>CRE 19</td>
<td>ESBL -</td>
<td>CRE -</td>
<td>ESBL -</td>
<td>CRE -</td>
</tr>
</tbody>
</table>

Table 3: Comparison of susceptibility using CLSI and EUCAST breakpoints

<table>
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<tr>
<th>Fosfomycin</th>
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<th>EUCAST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susceptible</td>
<td>57</td>
<td>53</td>
</tr>
<tr>
<td>Intermediate</td>
<td>05</td>
<td>-</td>
</tr>
<tr>
<td>Resistant</td>
<td>10</td>
<td>19</td>
</tr>
</tbody>
</table>

the incorporation of glucose-6-phosphate (G6PO₄) either in the media or disc/e-test strip to induce these transport systems and ensure adequate penetration of fosfomycin. The breakpoints proposed by CLSI and EUCAST for interpretation of fosfomycin susceptibility are different (Table 1). CLSI approves only disk diffusion and agar dilution method and that too only for urinary isolates of Escherichia coli and Enterococcus faecalis without broth microdilution criteria. EUCAST recommends both agar dilution and broth microdilution. Data from studies evaluating the role of fosfomycin in infections other than UTIs are also encouraging. Given its unlinked mechanism of resistance, its real value may be in the treatment of CRE, rather than as an alternative for ESBL producing organisms.

Aim and Objectives

We assessed the in vitro activity of fosfomycin against multidrug resistant urinary Enterobacteriaceae in admitted patients at our tertiary care centre.

Material and Methods

The study period was March 2014 to September 2015. Total 72 isolates were tested during the study period. All isolates were identified using conventional biochemical tests. Antimicrobial susceptibility testing was performed using the automated broth microdilution system Vitek 2 (bio- Mérieux, Inc., Durham, NC). We used CLSI guidelines to identify ESBL production. CRE were defined according to CDC definition used for infection control purpose. Fosfomycin susceptibility was determined by the E-test (bioMérieux, Inc., Durham, NC) method. Interpretive criteria from the Clinical and Laboratory Standards Institute (CLSI) for fosfomycin susceptibility are not available for the Enterobacteriaceae other than Escherichia coli. Therefore, results were interpreted according to criteria for E. coli (i.e., susceptible at a MIC of ≤ 64 µg/ml), as has been reported previously. Comparison of susceptibility using CLSI and EUCAST breakpoints was also made (Table 3).

Results

Overall, 79.16% (57/72) isolates were susceptible to fosfomycin (Table 2) with 92.00% (23/25) susceptibility in ESBL producing enterobacteriaceae and 72.34% (34/47) in CRE. One CRE isolate has developed resistant while on treatment.

Discussion

This study revealed good susceptibility against ESBL producing Enterobacteriaceae similar to earlier observations. Fosfomycin was found to be susceptible in 72.34% (34/47) of CRE isolates. These data are in concordance with others. Though only one susceptible isolate developed resistance while on treatment in our study, correlation between in-vitro susceptibility and microbiological cure is required. Neuner concluded that the rate of microbiological cure (59%) was lower than that of in-vitro susceptibility (86%).

Based on predictable urinary levels of fosfomycin, it would seem that EUCAST breakpoints are very stringent, while CLSI breakpoints would be more applicable, even to systemic infections. Chinnappan addressed the issues of interpretative criteria and methodology of susceptibility testing. Kaase compares susceptibility testing methods, like Etest and disk diffusion with agar dilution and found that Etest and disk diffusion showed poor agreement with fosfomycin agar dilution. Perdigao-Neto studied the activity of fosfomycin against MDR-Gram negative bacilli and demonstrated that with the high level of fosfomycin achievable in blood with intravenous infusion, the EUCAST breakpoint may be very stringent and the CLSI breakpoint may be applicable for systemic infections with MDR Gram negative bacilli and wide difference in susceptibility occurred between E-test and agar dilution method.

Conclusion

In conclusion, a considerable proportion (79.16%) of the multidrug resistant Enterobacteriaceae with diverse resistance mechanisms, including ESBL and CRE, found susceptible to fosfomycin. Consequently, fosfomycin may currently be considered a useful antibiotic agent in the treatment armamentarium of UTIs.
References


