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A Retrospective Study of Extended Spectrum Beta-Lactamases (ESBL) Urinary Tract Infections Treated with Fosfomycin and *in vitro* Susceptibility of 102 Isolates to Fosfomycin

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Authors' contributions

This work was carried out in collaboration between both authors. Author SJA designed the study and the work was carried out in collaboration with both authors. Author NA helped with the writing of the manuscript and literature searches and analysis of data. Both authors read and approved the final draft of the paper.

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Short Research Article

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ABSTRACT

The treatment of urinary tract infections (UTI) caused by extended-spectrum beta-lactamases [ESBL] pathogens has become an increasingly difficult problem due to the limited antibiotics available for therapy. Although fosfomycin has been available for over 40 years, it has not been extensively studied or used in the United States despite being well recognized for its efficacy in the treatment of uncomplicated cystitis. In this study, 102 isolates of ESBL were collected from three hospitals in the southwestern United States and studied for susceptibility to fosfomycin (MIC <16

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mm) and the clinical outcomes of 24 adult patients from age 18 years to 85 years of age with ESBL urinary tract infection were also evaluated. 95% of the 92 ESBL isolates studied were susceptible to fosfomycin. *Klebsiella* species was more likely than *E. coli* to be resistant to fosfomycin therapy. Despite the small number of patients in this study, the results are encouraging.

Keywords: Fosfomycin; UTI; ESBL.

1. INTRODUCTION

Several large in vitro surveys have looked at urinary tract infections and their causative organisms, such as *E. coli* [1,2]. It is clear now that *E. coli* has become increasingly resistant to most oral antibiotics including the fluoroquinolone class as well as to beta-lactam agents and trimethoprim-sulfamethoxazole [3,4,5].

ESBL producing uropathogens are a major source of infections in both hospitalized and community patients [4,5]. There have been very few studies in the United States that have looked at the rates of resistance to fosfomycin against multidrug resistant uropathogens. The majority of pathogens, in these studies in the US, Europe and Asia have reported a 90% susceptibility to fosfomycin [1,6-14].

2. MATERIALS AND METHODS

Urinary and wound ESBL isolates from the three hospitals in the southwestern United States were retrospectively collected between January 2015 and December 2015. ESBL was determined by screening and confirmation testing as per standard CLSI guidelines [CLSI 2009] and susceptibility testing results for each isolate were available from the clinical microbiology database. All isolates were tested for susceptibility to fosfomycin, which were determined by the use of disk diffusion and standard published breakpoints [fosfomycin MIC <16 mm for *E. coli*] [CLSI 2014]. Informed consent was obtained from all patients prior to the start of therapy. Samples were obtained from consenting adults between the ages of 18-85 years of age. Institutional review board (IRB) approval was obtained from the Las Palmas IRB for both the retrospective data collection and the use of fosfomycin.

3. RESULTS

A total of 102 ESBL isolates (92 urine and 10 wound) were tested for fosfomycin susceptibility rates. There were a total of 280 ESBL isolates at the time of the study, however only 102 of the isolates could be tested for susceptibility to fosfomycin. Pathogens such as *E. coli*, *Klebsiella*, *Pseudomonas* species, *Serratia, Morganelli, Citrobacter, Proteus* and *Enterobacter* species were evaluated. The overall susceptibility to fosfomycin for all the pathogens was 95 percent. Five percent of *E. coli* isolates were resistant to fosfomycin as compared to *Klebsiella* at 8%.

There was no difference in the resistance rates of ESBL to fosfomycin in urine or wound isolates. Among the 92 ESBL uropathogens, 74% were resistant to the two tested quinolones (ciprofloxacin and levofloxacin) and 62% were resistant to trimethoprim-sulfamethoxazole. Nitrofurantoin appeared to be the second most active agent with only 32% resistance (Fig. 1).

Twenty-four patients were treated for ESBL urinary tract infections with a one-time dose of 3 grams of fosfomycin. All patients had clinical evidence of active cystitis and symptomatic UTI. The majority of the pathogens were *E. coli* (92%) with the remaining being *Klebsiella, Proteus, Pseudomonas* species, *Serratia, Morganelli, Citrobacter,* and Enterobacter species. Seventeen of the twenty-four patients were treated in the outpatient setting with fosfomycin alone, and only one had a relapse with another pathogen. None of the patients had any intolerance or significant side effects to the medication. Seven of the patients had been admitted and given other antibiotics before susceptibility profiles were available and were switched to fosfomycin as soon as the pathogen was identified. None of the patients in the study had a complicated UTI nor had any concomitant bacteremia.

4. DISCUSSION

Urinary tract infections are among the most common causes of physician visits in the USA resulting in nearly 7 million office visits and 1 million emergency visits according to a National Ambulatory Medical Care Survey in 1997 [15]. The total estimated costs of these visits are over $1.6 billion dollars and are the most common cause of nosocomial-associated infections [15,16]. In addition, there has been a significant

increase in bacterial resistance of uropathological organisms with *E. coli* being the most common pathogen [17]. Recent data suggest that urinary *E. coli* antimicrobial resistance to be as high as 22.6% for trimethoprim-sulfamethoxazole (TMP/SMX), 6.8% for ciprofloxacin, and 1.4% for nitrofurantoin [17,18]. These authors also noted a clinically significant increase in resistance patterns in the two most common antimicrobials used for UTI treatment between the years 2000-2010 with ciprofloxacin which increased from 3% to 17.1% and TMP/SMX from 17.9% to 24.2% respectively [17].

Fosfomycin tromethamine is an oral phosphonic acid derivative that was first discovered in 1969 [4]. Although the drug has been available for over four decades, its use in the United States has been limited, however it has been extensively tested and used in European and Asian markets [1,8,9,11-14,19-21]. Fosfomycin has found its niche in treating UTI's due to its broad-spectrum activity against gram-positive and gram-negative uropathogens with therapeutic urinary concentrations lasting up to 48 hours with a single dose [1,7,22]. Susceptibilities of upwards of 80% have been published in the literature from numerous sources such as Elizabeth Hirsch and colleagues [7]. The study evaluated 323 urinary isolates and found that fosfomycin displayed significant activity against the majority of the pathogens with susceptibilities of 93.5% using the disk diffusion method. The majority of the *E. coli* isolates had low MIC's [less than 2 µg per ML] while those for *Klebsiella* species and other *Enterobacteriaceae* species were more widely distributed [1,2,7,23,24]. It was for this reason in 2010 the Infectious Diseases Society of America (IDSA) and the European Society for Microbiology and Infectious Diseases endorsed the use of fosfomycin tromethamine as a first-line treatment for uncomplicated urinary tract infections and cystitis [3,7]. However, because US physicians do not commonly use the drug there is little experience and confidence in it. Data has been sparse in the United States concerning the treatment of ESBL infections, especially with uncomplicated UTIs. However, recent studies by Linsenmyer et al. and Sastry el al have shown promising results with susceptibilities to fosfomycin at 96% and 100% respectively [1,25]. Fosfomycin has significant activity against vancomycin-resistant enterococci (VRE) with Sultan and colleagues reporting 98%-100% susceptibility against fosfomycin [26,27]. In this study, we noted susceptibility rates of 95% for almost all the pathogens. *Klebsiella* and *Proteus* had a varied susceptibility rates between 90-95%.

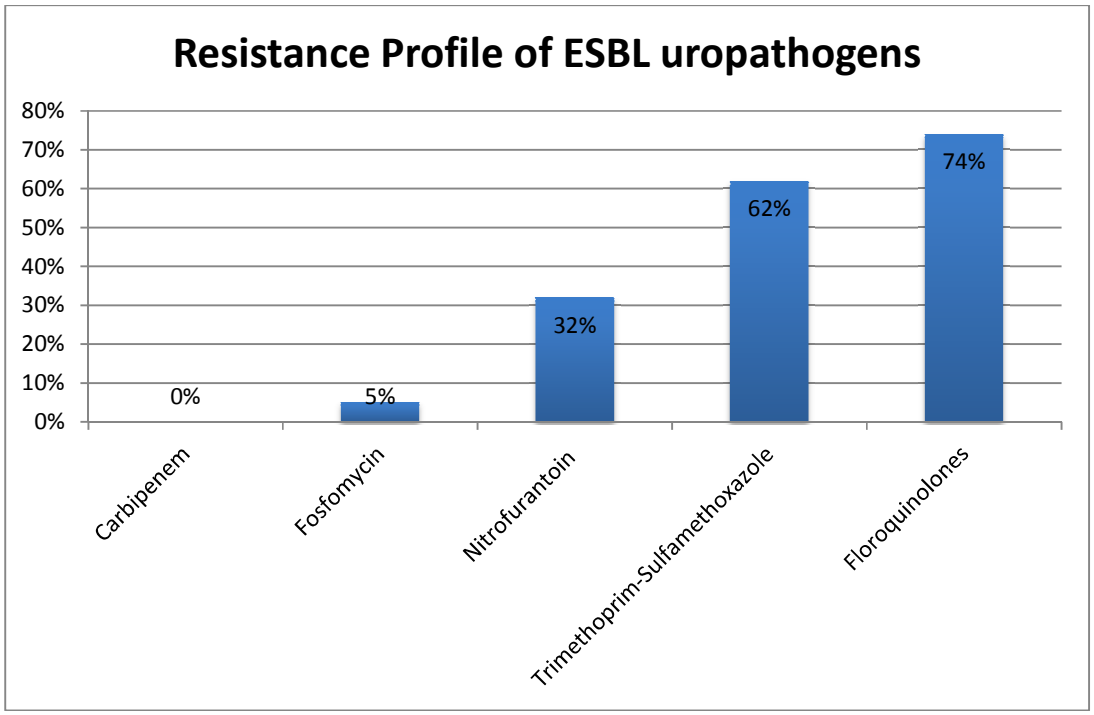

Fig. 1. Resistance profile of ESBL pathogens in the study

Although relatively low, fosfomycin resistance has been documented in the literature [1,7]. The mechanism of action is thought to be due to a mutation in the nutrient transport system gene of the glycerol-3-phosphate transporter (GlpT). As well, development of a fosfomycin-modifying enzyme (FosA) has been found in *Pseudomonas aeruginosa* species. Thus far, the fosfomycin resistant uropathogens have been primarily *Klebsiella* sp, *M. morganii*, *P. mirabilis* and *E. aerogenes*. Some prior studies have found resistance as low as 10% in *P. aeruginosa* [26]. The etiology is unclear regarding the reason the prevalence fosfomycin resistance is low however Nilsson el al. found slower growth rates of *E. coli* in fosfomycin strains that had resistant mutations [28]. They proposed that although the strains were resistant, the slowed growth and replication prevented their long-term establishment to the bladder [28]. As well, the concept of co-resistance between fosfomycin and other antimicrobials has been hypothesized, however no statistically significant data or patterns have been observed as yet [1,4].

Fosfomycin susceptibility data from the United States is not readily available. In a susceptibility study of 120 *E. coli* isolates collected in 2011 from 24 VA medical centers, fosfomycin was determined to be the most active oral active agent compared to the study's five alternatives [21]. Agar dilution is considered to be the standard method for fosfomycin susceptibility testing however it appeared that discrepancies were more common for the E test than for the disk diffusion in this particular study. Interestingly, no major errors were found using either method.

Despite the small number of patients in this retrospective study, it has been encouraging that the in vitro susceptibility rates seem to corroborate with the in vivo cure rates. The authors have continued to treat and collect treatment outcome data in patients with ESBL UTI's treated with fosfomycin.

5. LIMITATIONS

First, it is retrospective and has a relatively small number of samples and patients and therefore definite conclusions can be made. Second, disk diffusion was used to test for susceptibilities without the use of agar dilution as a confirmatory test.

6. CONCLUSIONS

This study suggests that fosfomycin, used as a first-line antimicrobial drug for UTI's such as ESBL *E. coli* has its place for UTI infections. ESBL urinary isolates have a 95% susceptibility to fosfomycin. In addition, no patients with concurrent bacteremia were studied to make adequate conclusions at this time. Fosfomycin's use in wound infections has yet to be determined.

ETHICAL APPROVAL

This study was approved the the Institutional Review Board of Las Palmas medical center, El Paso, Texas.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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