In Vitro Activity of Fosfomycin Against Extended Spectrum-β-Lactamase (ESBL) Producing Escherichia coli and Klebsiella pneumoniae Strains

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ABSTRACT

Escherichia coli and Klebsiella pneumoniae are the most commonly isolated microorganisms in cases of uncomplicated lower urinary tract infection (UTI). Because of the increased isolation of extended-spectrum β-lactamase (ESBL) producing E. coli and K. pneumoniae from the urine samples of uncomplicated UTI, it is important to find alternative oral drugs for the treatment of such infections. In this purpose fosfomycin may be a useful alternative for treatment because of its pharmaco-kinetic and microbiological properties. Therefore, this study aimed to test the in vitro susceptibility of 100 ESBL producing clinical urinary isolates, including 80 E. coli and 20 K. pneumoniae, to fosfomycin trometamol (FT) in comparison with amoxicillin/clavulanate (AMC), ciprofloxacin (CIP), carbapenem (IPM), and trimethoprim/sulphamethoxazole (SXT). In E. coli strains the highest resistance rate was observed in SXT 66.2%, followed by CIP 53.8%, and then AMC 18.8%. Similar to the percentages of resistance in K. pneumoniae strains were found to be 75% for SXT, 25% for CIP, 10% for AMC. Only ESBL producing one E. coli and one K. pneumoniae strain were found resistant to fosfomycin and imipenem. This data showed excellent activity of FT against ESBL producing E. coli and K. pneumoniae isolates and FT is being regarded as a new treatment alternative in the ESBL producing strains related lower urinary tract infection.


Key Word: Extended-spectrum β-lactamase (ESBL), Escherichia coli, Klebsiella pneumoniae, fosfomycin trometamol (FT), urinary tract infection (UTI)

INTRODUCTION

Extended-spectrum β-lactamases (ESBL), which are found predominantly in Escherichia coli and Klebsiella pneumoniae can hydrolyze all penicillins, cephalosporins, and monobactams, but not effective against cephamycins (e.g. cefoxitin or cefmetazole) or carbapenems (e.g. imipenem or meropenem). They may carry other drug-resistant genes for aminoglycosides, chloramphenicol, tetracyclines, and fluoroquinolones. In addition, some isolates of ESBL producers were susceptible to cephalosporins in vitro, but non-efficacious in vivo.

Extended spectrum β-lactamase (ESBL) producing E. coli and K. pneumoniae are growing problems in many parts of the world. The antibiotics of choice, carbapenems, usually require hospitalization and are associated with higher drug costs. So that it is important to find alternative oral drugs for the treatment of such infections.

Fosfomycin tromethamine (FT), which is derived from phosphonic acid and affects first step of cell wall synthesis by enolpyruvate transferase inhibition, and has a broad spectrum of antibacterial activity against most bacteria isolated from patients with lower urinary tract infections. It is rapidly metabolized and excreted in the urine unchanged. It
has the advantage of single dose administration and it is being regarded as a new treatment alternative. In previous reports it has been demonstrated that FT activity against ESBL producing isolates is similar to that observed against non-ESBL producing isolates. In this study we aimed to evaluate the effect of FT in the treatment of ESBL producing E. coli and K. pneumoniae strains which cause lower UTI.

MATERIALS AND METHODS

In this study ESBL producing 80 E. coli and 20 K. pneumoniae strains isolated from urine samples as pathogens over a period of 8 months (February-September) during 2007 from patients admitted to Afyon Kocatepe University Hospital, Afyonkarahisar, Turkey. Mid stream urine samples in sterile pots were inoculated on to 5% sheep blood agar and eosin methylene blue agar by using quantitative method. The bacterial identification was made by conventional methods. Duplicate isolates, which were obtained from the same patient, were not included in this study. Isolates were tested for the in vitro antimicrobial susceptibility by Kirby Bauer disk diffusion method according to the CLSI criteria. All E. coli and K. pneumoniae strains were tested as ESBL producers by the double-disc synergy test. A phenotypic confirmatory test for the ESBL production was performed according to the recommendation of the CLSI. The antimicrobial agents used in the susceptibility testing included amoxicillin-clavulanate (AMC), trimethoprim/ sulphamethoxazole (SXT), imipenem (IPM), ciprofloxacin (CIP), and FT (Oxoid, U.K). The reference strain E. coli ATCC 25922 and K. pneumoniae ATCC 700603 was used as the quality control strain for the susceptibility testing. The data were assessed using the SPSS 11.0 packet program.

RESULTS

Five antimicrobial agents including FT were tested for 80 E. coli and 20 K. pneumoniae strains isolated from urine samples. The results showed that IPM and FT had excellent activity against E. coli and K. pneumoniae isolates. Only ESBL producing one E. coli and one K. pneumoniae strain were found resistant to both FT and IPM. While the resistance rates of E. coli isolates detected were 66.2% (53/80) for SXT, 53.8% (43/80) for CIP, 18.8% (15/80) for AMC; the resistance rates of K. pneumoniae isolates were 75% (15/20) for SXT, 25% (5/20) for CIP, 10% (2/20) for AMC and these data are summarized in Table 1.

DISCUSSION

E. coli and K. pneumoniae are the most common etiological agent in either community-acquired or hospital-acquired UTI. Community- acquired ESBL producing strains are emerging as a problem. ESBL producing bacteria increase the risk of morbidity and mortality in hospital-acquired infections and are associated with high antibiotic costs. The antibiotic of choice in ESBL-producing E. coli or K. pneumoniae-related infections is generally carbapenems. High resistance rates for beta-lactams, SXT and CIP cause limitations for restrict empirical antibiotic use in ESBL-producing bacteria-related UTI. Due to the
fact that antibiotic resistance to this commonly used agents often exceeds 30-50% of strains.\textsuperscript{12,15}

FT, a bactericidal antibiotic, inhibits the first step of cell wall synthesis, and has a broad spectrum of antibacterial activity against most bacteria isolated from patients with lower UTI. It has been in use for a long time in European countries and our country in recent years. FT, despite many years of usage, continues to be characterized by an extremely low incidence of resistance (about 1%) in \textit{E. coli} strains worldwide.\textsuperscript{12,15} In a study which evaluated the in vitro activity of FT by three different methods against 428 ESBL producing strains and made up of 290 E. coli and 138 \textit{K. pneumoniae} isolates, 417 strains were found susceptible to fosfomycin.\textsuperscript{16} Tharavichitkul et al. tested the susceptibility of 37 ESBL (+) \textit{E. coli} and 43 ESBL (+) \textit{K. pneumoniae} isolates to FT and these ESBL producing strains were resistant to FT 3.7% and 12.6%, respectively.\textsuperscript{17}

FT resistance is also rare in UTI-related \textit{E. coli} strains in Turkey. Previous studies have reported a FT-resistance rate of 0.3% in 288 and no resistance in 100 \textit{E. coli} strains (14,18). FT resistance is very rare in ESBL producing \textit{E. coli} strains related to UTI too. Pullukcu et al. reported a resistance rate of 3.5% to FT in 344 ESBL producing \textit{E. coli} strains.\textsuperscript{19} Güdücüoğlu et al. reported FT resistance 4% and 1%, in ESBL producing 193 \textit{E. coli} and 75 \textit{K. pneumoniae} strains, respectively.\textsuperscript{20}

In our study, only one \textit{E. coli} and one \textit{K. pneumoniae} strain were found resistant to both FT and IPM. \textit{E. coli} strains were found resistant SXT, CIP, and AMC with rates of 66.2%, 53.8%, and 18.8% respectively. Similarly \textit{K. pneumoniae} strains were found resistant SXT, CIP, and AMC with rates 75%, 25%, and 10%, respectively.

This data shows excellent activity of FT against \textit{E. coli} and \textit{K. pneumoniae} isolates including ESBL producing strains and FT may be an effective alternative in the treatment of ESBL producing \textit{E. coli} and \textit{K. pneumoniae}-related lower UTI.

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**REFERENCES**


