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ScienceDirect
Diagnostic Microbiology and Infectious Disease 58 (2007) 111–115
DIAGNOSTIC MICROBIOLOGY AND INFECTIOUS DISEASE
www.elsevier.com/locate/diagmicrobio

In vitro activity of fosfomycin against ciprofloxacin-resistant or extended-spectrum β-lactamase–producing *Escherichia coli* isolated from urine and blood

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Received 19 July 2006; accepted 17 November 2006

Abstract

In this study, we evaluated the in vitro activity of fosfomycin and 7 other comparator agents against 307 *Escherichia coli* isolates including ciprofloxacin-resistant or extended-spectrum β-lactamase (ESBL)–producing isolates. Bacterial isolates were collected from urine and blood from patients at a Korean tertiary-care hospital. Among 307 *E. coli* isolates, 30.3% were resistant to ciprofloxacin (MIC_{90}, >32 mg/L) and 7.8% produced ESBLs. The highest resistance rate was observed in ampicillin (69.7%), followed by trimethoprim–sulfamethoxazole (43.0%), and then amoxicillin–clavulanate (32.2%). All isolates were susceptible to imipenem (MIC_{90}, 0.125 mg/L). All but 1 isolate was susceptible to fosfomycin (MIC_{90}, 16 mg/L), regardless of the collected sources, ciprofloxacin resistance, and ESBL production. The data showed excellent activity of fosfomycin against *E. coli* isolates including fluoroquinolone-resistant strains. The clinical usefulness of fosfomycin, as a 1st-line therapy for urinary tract infection, should be evaluated further, especially in regions where ciprofloxacin resistance rates are high.

Keywords: Fosfomycin; Urinary tract infection; *Escherichia coli*; Ciprofloxacin resistance; Extended-spectrum β-lactamase (ESBL)

1. Introduction

Resistance to antibiotic treatment in patients with urinary tract infections (UTIs) is a representative example of the increasing problem of antimicrobial resistance. *Escherichia coli* accounts for most uncomplicated UTIs (Hoepelman et al., 2003; Marchese et al., 2003). Although trimethoprim–sulfamethoxazole has been used successfully to treat UTIs previously, fluoroquinolones are currently being used more frequently as 1st-line treatment because of the increasing occurrence of resistance to trimethoprim–sulfamethoxazole among uropathogens (Hooton, 2003). In addition, the frequency of ciprofloxacin resistance to *E. coli* has also been rapidly increasing worldwide, including in Korea (Karlowsky et al., 2004; Oteo et al., 2005; Lee et al., 2004).

Increasing trends of antimicrobial resistance to *E. coli* from UTIs require the use of other treatment options. Fosfomycin is a phosphonic acid antibiotic agent with excellent in vitro activity against most uropathogens including *Citrobacter*, *Enterobacter*, *Klebsiella*, *Serratia*, and *Enterococcus faecium* as well as *E. coli*. There appears to be little cross-resistance between fosfomycin and other antibiotics; this is possibly due to the fact that it differs from other antibiotics in its general chemical structure and site of action. Fosfomycin has been extensively used in several European countries for the treatment of uncomplicated UTIs since 1988. Despite many years of treatment use, fosfomycin continues to be characterized by an extremely low incidence of resistant *E. coli* strains (about 1%) worldwide. However, the in vitro activity of fosfomycin against *E. coli* isolates has not yet been evaluated in Korea. Given the high

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doi:10.1016/j.diagmicrobio.2006.11.015

Table 1
Antimicrobial resistances among 307 *E. coli* isolates[a]

Antimicrobials	*I* (%)	*R* (%)	MIC (mg/L)	
			MIC_{50} (mg/L)	MIC_{90} (mg/L)
Fosfomycin	0	0.3	4	16
Ciprofloxacin	1.3	30.3	0.0625	>32
Ampicillin	3.9	69.7	>64	>64
Amoxicillin–clavulanate	32.6	32.2	16/8	32/16
Imipenem	0	0	0.125	0.125
Gentamicin	10.4	22.8	4	>64
Trimethoprim–sulfamethoxazole	–	43.0	0.5/9.5	>64/1216
Amikacin	9.4	2.6	8	32

I = intermediate; *R* = resistance.

[a] Interpretive criteria for susceptibility were those developed by CLSI (2005): for fosfomycin, $I = 128$ mg/L and $R \geq 256$ mg/L; for ciprofloxacin, $I = 2$ mg/L and $R \geq 4$ mg/L; for ampicillin, $I = 16$ mg/L and $R \geq 32$ mg/L; for amoxicillin–clavulanate, $I = 16/8$ mg/L and $R \geq 32/16$ mg/L; for imipenem, $I = 8$ mg/L and $R \geq 16$ mg/L; for gentamicin, $I = 8$ mg/L and $R \geq 16$ mg/L; for trimethoprim–sulfamethoxazole, $R \geq 4/76$ mg/L; for amikacin, $I = 32$ mg/L and $R \geq 64$ mg/L. The same criteria were applied to Tables 2 to 4.

prevalence of antimicrobial resistance in Korea, the evaluation of the antimicrobial activity of fosfomycin against *E. coli* to determine antimicrobial resistance is warranted. A comprehensive investigation of in vitro activity of fosfomycin against *E. coli* could provide important information on new therapeutic options for treatment of UTIs.

In this article, we present the in vitro activity of fosfomycin and other comparators against *E. coli* isolates from urine and blood of patients in Korea.

2. Materials and methods

2.1. Bacterial isolates

A total of 307 clinical isolates of *E. coli* were collected from a tertiary-care hospital in Korea (Samsung Medical Center, Seoul) over a period of 5 months (May–September) during 2005. Of these 307 isolates, 267 (87.0%) were from urine and 40 (13.0%) were from blood. Duplicate isolates, which were obtained from the same patient, were not included in this study.

2.2. In vitro susceptibility testing

In vitro activities of fosfomycin and 7 other comparator agents were tested: ciprofloxacin, amoxicillin–clavulanate, ampicillin, imipenem, gentamicin, trimethoprim–sulfamethoxazole, and amikacin. In vitro susceptibility testing was performed according to the Clinical and Laboratory Standards Institute (CLSI, 2005). The agar dilution method was used for fosfomycin, and the broth microdilution method was applied for the other antimicrobial agents. Interpretive criteria for susceptibility were those developed by the CLSI (2005). Extended-spectrum β-lactamase (ESBL)–producing isolates were detected by the clavulanate double-disk synergy method using a BBL Sensi-Disc Antimicrobial Susceptibility Test Disc (Becton, Dickinson and Company, Sparks, MD). Polymerase chain reaction (PCR) method was used to identify the gene responsible for the ESBL phenotype in ESBL producers. PCRs for bla_{TEM}, bla_{SHV}, and $bla_{CTX\text{-}M}$ were performed using PCR primers and conditions as previously described (Kim et al., 2005). Quality control was performed using *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *Pseudomonas aeruginosa* ATCC 27853, *E. coli* ATCC 25922, *E. coli* ATCC 35218, and *Klebsiella pneumoniae* ATCC 700603. The χ^2 test and Fisher's exact *t* test were used to determine the significance of differences in resistance where appropriate.

3. Results

Eight antimicrobial agents including fosfomycin were tested for 307 *E. coli* isolates from urine or blood; these data are summarized in Table 1. The results showed that imipenem and fosfomycin had excellent activity against *E. coli* isolates. All *E. coli* isolates tested, in this study, were susceptible to imipenem, and only 1 isolate from a voided urine was resistant to fosfomycin (MIC, 512 mg/L). This fosfomycin-resistant *E. coli* isolate was susceptible to the other antimicrobials tested in this study. The MIC_{50} and MIC_{90} of fosfomycin, for all *E. coli* isolates, were 4 and 16 mg/L, respectively. By contrast, more than 30% of the *E. coli* isolates were resistant to ciprofloxacin; this is much higher than previously reported in Korea (15.2%) (Lee et al., 2004). The resistance rates for the other antimicrobials were

Table 2
Comparison of antimicrobial resistances in *E. coli* between blood and urine

Antimicrobials	Blood ($n = 40$)		Urine ($n = 267$)		*P*	
	R (%)	MIC_{90} (mg/L)	*R* (%)	MIC_{90} (mg/L)	χ^2	Fisher
Fosfomycin	–	16	0.4	32	.698	1.000
Ciprofloxacin	25.0	>32	31.5	>32	.408	.466
Ampicillin	77.5	>64	68.5	>64	.250	.275
Amoxicillin–clvaulanate	37.5	64/32	31.5	32/16	.446	.471
Imipenem	0	0.125	0	0.25	NA	NA
Gentamicin	20.0	>64	23.2	>64	.651	.840
Trimethoprim–sulfamethoxazole	32.5	>64/1216	44.6	>64/1216	.150	.173
Amikacin	0	32	3.0	32	.267	.603

Table 3
Antimicrobial resistance in *E. coli* isolates with respect to ciprofloxacin resistance[a]

Antimicrobials	CIP-S (n = 210)		CIP-NS (n = 97)		P	
	R (%)	MIC_{90} (mg/L)	R (%)	MIC_{90} (mg/L)	χ^2	Fisher
Fosfomycin[b]	0.5	32	0	16	.497	1.000
Ampicillin	61.4	>64	87.6	>64	<.001	<.001
Amoxicillin–clavulanate	31.0	32/16	35.1	64/32	.311	.323
Imipenem	0	0.125	0	0.25	NA	NA
Gentamicin	11.4	32	47.4	>64	<.001	<.001
Trimethoprim–sulfamethoxazole	31.0	>64/1216	68.1	>64/1216	<.001	<.001
Amikacin	0.5	16	7.2	32	.007	.013

CIP-S = ciprofloxacin-susceptible (MIC, ≤1 mg/L); CIP-NS = ciprofloxacin-resistant or intermediate (MIC, ≥2 mg/L).
[a] In this analysis, we included *E. coli* isolates both from blood and urine except for fosfomycin.
[b] Antimicrobial resistance rates of fosfomycin were estimated for only *E. coli* isolates from urine (CIP-S, 180 isolates; CIP-R, 83 isolates).

as follows: ampicillin (69.7%), trimethoprim–sulfamethoxazole (43.0%), and amoxicillin–clavulanate (32.2%). Gentamicin showed a moderate in vitro activity, but its MIC_{90} reached >64 mg/L. For amikacin, 2.6% and 9.4% of *E. coli* isolates were resistant and intermediate.

Table 2 shows a comparison of the antimicrobial resistance observed between *E. coli* isolates from urine (267 isolates) and those from blood (40 isolates). For all antimicrobial agents including fosfomycin, the resistance rates between these 2 groups were not significantly different. Although the trimethoprim–sulfamethoxazole resistance rate in *E. coli* isolates from urine (44.6%) was higher than that from isolates of blood (32.5%), this difference was not significant (P = .150).

The resistance rates of ampicillin, gentamicin, trimethoprim–sulfamethoxazole, and amikacin were significantly higher in ciprofloxacin-resistant *E. coli* isolates (Table 3). However, fosfomycin also showed good activity against ciprofloxacin non-susceptible *E. coli* isolates. That is, of 97 ciprofloxacin-non-susceptible isolates, none were resistant to fosfomycin. Although the resistance rates of amoxicillin–clavulanate and imipenem were not significantly different in comparisons between ciprofloxacin-susceptible and ciprofloxacin-resistant isolates, the MIC_{90}'s of both antimicrobials increased. However, the MIC_{90}'s for fosfomycin (16 mg/L) decreased.

In this study, 24 *E. coli* isolates (7.8%) produced ESBLs. Only 2 ESBL-producing *E. coli* isolates were from blood (2/40, 5.0%); the others were from urine (22/247, 8.9%). Based on PCR analysis, 14 *E. coli* isolates (58.3%) produced both TEM and CTX-M enzymes, and 7 isolates produced only CTX-M–type ESBLs. The other 3 *E. coli* isolates produced only SHV, only TEM, and both SHV and CTX-M enzymes, respectively. As a whole, 22 *E. coli* isolates produced CTX-M–type ESBLs, 15 isolates did TEM-type ESBLs, and 2 isolates did SHV-type ESBLs. ESBL-producing *E. coli* isolates showed significantly higher resistance rates than the ESBL-negative isolates for most antimicrobial agents except for fosfomycin and imipenem (Table 4). All 24 ESBL-producing *E. coli* isolates showed susceptibility to fosfomycin and imipenem. Antimicrobial resistance rates were not significantly different with respect to the kind of ESBLs.

4. Discussion

UTIs are one of the most frequently encountered conditions in clinical medical practice requiring antimicrobial therapeutic intervention. To date, *E. coli* has been the most common isolated pathogen causing UTIs, and trimethoprim–sulfamethoxazole has been successfully used for treatment (Warren et al., 1999). However, the prevalence of resistance to trimethoprim–sulfamethoxazole among *E. coli* isolates has been increasing; this has been shown in prior studies as well as in the present study (resistance rates, 38.7% to 43.0%) (Lee et al., 2004; Table 1). Due to the reduced activity of trimethoprim–sulfamethoxazole against *E. coli* isolates, fluoroquinolones such as ciprofloxacin are being used frequently as 1st-line treatment of UTIs; β-lactams and fosfomycin are being used as 2nd-line antimicrobial agents.

Table 4
Antimicrobial resistance in *E. coli* with respect to ESBL production

Antimicrobials	ESBL negative (n = 283)		ESBL positive (n = 24)		P	
	R (%)	MIC_{90} (mg/L)	R (%)	MIC_{90} (mg/L)	χ^2	Fisher
Fosfomycin	0.4	16	0	32	.771	1.000
Ciprofloxacin	25.8	>32	83.3	>32	<.001	<.001
Ampicillin	67.1	>64	100	>64	.001	<.001
Amoxicillin–clavulanate	29.3	32/16	66.7	64/32	<.001	<.001
Imipenem	0	0.125	0	0.25	NA	NA
Gentamicin	19.1	4	66.7	>64	<.001	<.001
Trimethoprim–sulfamethoxazole	40.6	>64/1216	79.2	>64/1216	.004	.005
Amikacin	1.4	16	16.7	>64	<.001	.002

However, ciprofloxacin resistance, among *E. coli* isolates, is also increasing worldwide (Livermore, 2005). In Europe, ciprofloxacin resistance in *E. coli* isolates causing uncomplicated UTIs has been found to be variable in different countries and has been reported to range from 0% to 14.7% (Kahlmeter, 2003). In the United States, 18.9% *E. coli* isolates from fecal samples showed reduced susceptibility to fluoroquinolones in a study (Lautenbach et al., 2006). The increasing fluoroquinolone resistance in *E. coli* is of great concern because fluoroquinolone resistance is associated with mortality (Lautenbach et al., 2005). Korea has one of the highest resistance rates to ciprofloxacin (Lee et al., 2004). The results of this study confirmed reduced activity of ciprofloxacin against *E. coli* isolates in Korea. This finding suggests probable limitation of the use of fluoroquinolones for the treatment of *E. coli* infections as a 1st-line choice. Thus, other antimicrobial agents should be considered as therapeutic options for the treatment of *E. coli* infections in Korea.

ESBL-producing *E. coli* isolates have also become a serious problem in the clinical setting (Bradford, 2001). In this study, 7.8% of *E. coli* isolates produced ESBLs; prior studies have reported that about 10% of clinical isolates were ESBL producers in Korea (Jeong et al., 2004; Kim et al., 2005; Ryoo et al., 2005). Although the prevalence of ESBL-producing *E. coli* isolates in Korea was found to be lower than in some Asian countries such as China, Hong Kong, and Singapore, it was higher than in Taiwan, the Philippines, Japan, South Africa, and Australia (Hirakata et al., 2005). As expected, most ESBL-producing *E. coli* isolates were resistant to ciprofloxacin, ampicillin, amoxicillin–clavulanate, gentamicin, and trimethoprim–sulfamethoxazole. The amikacin resistance rate also increased up to 16.7% in ESBL-producing *E. coli* isolates (Table 4).

In this study, we evaluated the in vitro susceptibility of *E. coli* isolates to fosfomycin, including ciprofloxacin-resistant or ESBL-producing isolates, which were obtained from urine or blood. As shown in Tables 1–4, fosfomycin showed excellent activity against *E. coli* isolates, regardless of source, ciprofloxacin resistance, and ESBL production. Only 1 isolate was resistant to fosfomycin. This fosfomycin-resistant isolate, which was from a voided urine, showed no resistance against the other antimicrobial agents. MICs of ciprofloxacin, amoxicillin–clavulanate, gentamicin, trimethoprim–sulfamethoxazole, ampicillin, imipenem, and amikacin of this strain were ≤0.03125, 8/4, 2, 0.25/4.75, 4, 0.125, and 16 mg/L, respectively. This finding suggests that fosfomycin might have no cross-resistance with other antimicrobial agents. The extremely low resistance rate of fosfomycin in *E. coli* has been reported in other parts of the world (Chomarat, 2000; Kahlmeter, 2003; Marchese et al., 2003). Marchese et al. (2003) proposed that exceedingly low resistance rates worldwide results from defects in the fosfomycin-resistant strains; they showed that the overall fosfomycin-resistant strains were impaired so that they were unable to express the potential to maintain or initiate infections because of biologic cost such as reduced growth rate or adherence to uroepithelial cells (Nilsson et al., 2003). Moreover, these modifications of bacterial properties caused a change in their pathogenicity, resulting in loss of virulence (Marchese et al., 2003; Schito, 2003). This may partly explain that fosfomycin maintains its potent antimicrobial activity against uropathogens. In addition to the measured MIC values of fosfomycin, its high urinary concentrations estimated as a pharmacokinetic parameter (urinary C_{max}, 4415 mg/L) (Mazzei et al., 2006) guarantee its effectiveness in the treatment of uncomplicated UTIs (De Cueto et al., 2006; Lautenbach et al., 2004).

In conclusion, our data suggest that fosfomycin may be an alternative for treatment of UTIs caused by *E. coli* as a 1st-line antimicrobial agent in regions where ciprofloxacin resistance rates are high. Further clinical verification is required to assess the clinical efficacy of fosfomycin for the treatment of UTIs caused by ciprofloxacin-resistant or ESBL-producing *E. coli* isolates.

Acknowledgment

This study was supported partly by Ildong Pharmaceutical (Seoul, Korea) and the Asian Pacific Research Foundation for Infectious Diseases (ARFID) (Seoul, Korea).

References

Bradford PA (2001) Extended-spectrum β-lactamases in the 21st century: characterization, epidemiology, and detection of this important resistance threat. *Clin Microbiol Rev* 14:933–951.

Chomarat M (2000) Resistance of bacteria in urinary tract infections. *Int J Antimicrob Agents* 16:484–487.

Clinical and Laboratory Standards Institute (CLSI) (2005) Performance Standards for Antimicrobial Susceptibility Testing; Fifteenth Informational Supplement. CLSI/NCCLS Document M100-S15. Wayne, PA: CLSI.

de Cueto M, López L, Hernández JR, Morillo C, Pascual A (2006) In vitro activity of fosfomycin against extended-spectrum-β-lactamase–producing *Escherichia coli* and *Klebsiella pneumoniae*: comparison of susceptibility testing procedures. *Antimicrob Agents Chemother* 50:368–370.

Hirakata Y, Matsuda J, Miyazaki Y, Kamihira S, Kawakami S, Miyazawa Y, Ono Y, Nakazaki N, Inoue M, Trunidge JD, Bell JM, Jones RN, Kohno S, the SENTRY Asia-Pacific participants (2005) Regional variation in the prevalence of extended-spectrum β-lactamase–producing clinical isolates in the Asia-Pacific region (SENTRY 1998–2002). *Diagn Microbiol Infect Dis* 52:323–329.

Hoepelman AIM, Meilland R, Geerlings SE (2003) Pathogenesis and management of bacterial urinary tract infections in adult patients with diabetes mellitus. *Int J Antimicrob Agents* 22(Suppl 2):S35–S43.

Hooton TM (2003) Fluoroquinolones and resistance in the treatment of uncomplicated urinary tract infection. *Int J Antimicrob Agents* (Suppl 2):S65–S72.

Jeong SH, Bae IK, Lee JH, Sohn SG, Kang GH, Jeon GJ, Kim YH, Jeong BC, Lee SH (2004) Molecular characterization of extended-spectrum beta-lactamases produced by clinical isolates of *Klebsiella pneumoniae* and *Escherichia coli* from a Korean nationwide survey. *J Clin Microbiol* 42:2902–2906.

Kahlmeter G (2003) An international survey of the antimicrobial susceptibility of pathogens from uncomplicated urinary tract infections: the ECO.SENS Project. *J Antimicrob Agents* 51:69–76.

Karlowsky JA, Jones ME, Draghi DC, Thornsberry C, Sahm DF, Volturo GA (2004) Prevalence and antimicrobial susceptibilities of bacteria isolated from blood cultures of hospitalized patients in the United States in 2002. *Ann Clin Microbiol Antimicrobiol* 3:7–14.

Kim J, Lim YM, Rheem I, Lee Y, Lee JC, Seol SY, Lee YC, Cho DT (2005) CTX-M and SHV-12 β-lactamases are the most common extended-spectrum enzymes in clinical isolates of *Escherichia coli* and *Klebsiella pneumoniae* collected from 3 university hospitals within Korea. *FEMS Microbiol Lett* 245:93–98.

Lautenbach E, Strom BL, Nachamkin I, et al (2004) Longitudinal trends in fluoroquinolone resistance among Enterobacteriaceae isolates from inpatients and outpatients, 1989–2000: differences in the emergence and epidemiology of resistance across organisms. *Clin Infect Dis* 38:655–662.

Lautenbach E, Metlay JP, Bilker WB, Edelstein PH, Fishman NO (2005) Association between fluoroquinolone resistance and mortality in *Escherichia coli* and *Klebsiella pneumoniae* infections: the role of inadequate empirical antimicrobial therapy. *Clin Infect Dis* 41:923–929.

Lautenbach E, Fishman NO, Metlay JP, Mao X, Bilker WB, Tolomeo P, Nachamkin I (2006) Phenotypic and genotypic characterization of fecal *Escherichia coli* isolates with decreased susceptibility to fluoroquinolones: results from a large hospital-based surveillance initiative. *J Infect Dis* 194:79–85.

Lee SJ, Lee SD, Cho IR, Sim BS, Lee JG, Kim CS, Kim ME, Cho YH, Woo YN (2004) Antimicrobial susceptibility of uropathogens causing acute uncomplicated cystitis in female outpatients in South Korea: a multicentre study in 2002. *Int J Antimicrob Agents* 24S:S61–S64.

Livermore DM (2005) Minimizing antibiotic resistance. *Lancet Infect Dis* 5:450–459.

Marchese A, Gualco L, Debbia EA, Schito GC, Schito AM (2003) In vitro activity of fosfomycin against gram-negative urinary pathogens and the biological cost of fosfomycin resistance. *Int J Antimicrob Agents* 22(Suppl 2):S53–S59.

Mazzei T, Cassetta MI, Fallani S, Arrigucci S, Novelli A (2006) Pharmacokinetic and pharmacodynamic aspects of antimicrobial agents for the treatment of uncomplicated urinary tract infections. *Int J Antimicrob Agents* 28(Suppl 1):S35–S41.

Nilsson AI, Berg OG, Aspevall O, Kahlmeter G, Andersson DI (2003) Biological costs and mechanisms for fosfomycin resistance in *Escherichia coli*. *Antimicrob Agents Chemother* 47:2850–2858.

Oteo J, Lazaro E, de Abajo FJ, Baquero F, Campos J, Spanish members of EARSS (2005) Antimicrobial-resistant invasive *Escherichia coli*, Spain. *Emerg Infect Dis* 11:546–553.

Ryoo NH, Kim EC, Hong SG, Park YJ, Lee K, Bae IK, Song EH, Jeong SH (2005) Dissemination of SHV-12 and CTX-M–type extended-spectrum β-lactamases among clinical isolates of *Escherichia coli* and *Klebsiella pneumoniae* and emergence of GES-3 in Korea. *J Antimicrob Chemother* 56:698–702.

Schito GC (2003) Why fosfomycin trometamol as first line therapy for uncomplicated UTI? *Int J Antimicrob Agents* 22(Suppl 2):S79–S83.

Warren JW, Abrutyn E, Hebel JR, Johnson JR, Schaeffer AJ, Stamm WE (1999) Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. *Clin Infect Dis* 29:745–758.