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BRIEF COMMUNICATION

Changes in minimum inhibitory concentration of levofloxacin for *Escherichia coli* strains isolated from urine samples in mainland China, 2004 to 2014

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Abstract *Eschrichia coli* urinary isolates were collected from 20 Chinese hospitals during five 1-year periods from 2004 to 2014. The susceptibility of *E. coli* to levofloxacin has remained stable during the past 11 years, and 90% of strains had minimum inhibitory concentrations of ≤32 mg/L. The urine-specific susceptibility breakpoints for levofloxacin should be reset based on more relevant clinical studies and the current pharmacokinetic/pharmacodynamic considerations in this field.

Introduction

Urinary tract infections (UTIs) are the most frequently occurring bacterial infections, both in the community and in hospitals. *Escherichia coli* is the most commonly encountered uropathogen. Several international guidelines recommend levofloxacin as the drug of choice for empirical treatment of UTIs, including catheter-associated UTIs.[1,2] However, the widespread use of levofloxacin for complicated or catheter-associated UTIs might result in reduced susceptibility of *E. coli* to levofloxacin.[3]

The aim of this study was to evaluate and compare the susceptibility pattern of *E. coli* urinary isolates to levofloxacin in mainland China during five 1-year periods from 2004 to 2014.

Materials and methods

Isolates

Overall, a total of 1127 nonreplicate clinical *E. coli* urinary isolates were collected from 20 widely dispersed tertiary

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hospitals in China during five 1-year periods (October 2004—September 2005, January 2007—December 2007, July 2009—June 2010, July 2011—June 2012, and July 2013—June 2014). All isolates were sent to the Institute of Clinical Pharmacology, Peking University First Hospital, where they were stored at −80°C until further analysis.

Antimicrobial susceptibility testing

Susceptibility to antimicrobial agents was determined using the agar dilution method established by the Clinical and Laboratory Standards Institute. Extended-spectrum beta-lactamase (ESBL)-producing isolates were detected using previously described methods.[4] The control strain was ATCC 25922. The breakpoint for resistance to levofloxacin for *E. coli* was ≥8 mg/L, and sensitivity was defined as a minimum inhibitory concentration (MIC) of ≤2 mg/L.[4]

Statistical analyses

Statistical tests were performed using SPSS for Windows, version 14.0 (SPSS Inc., Chicago, IL, USA). Enumeration data were expressed as percentages. Differences in susceptibility between the groups were compared using the chi-square test or Fisher's exact test. Differences were considered statistically significant at a two-sided p value of <0.05. The Bonferroni method was used to adjust the significance levels (0.05/10 = 0.005) in multiple comparisons between any two levels of the susceptibility outcome.

Results and discussion

Less than 33% of the isolates were susceptible to levofloxacin, and more than 90% of strains had MICs of ≤32 mg/L. The ESBL positivity rate was 41.7% during October 2004—September 2005 and increased to 58.7% during January 2007—December 2007, to 66.0% during July 2009—June 2010, to 60.9% during July 2011—June 2012, and to 69.4% during July 2013—June 2014 ($p < 0.001$). However, the levofloxacin susceptibility rate (about 30%) remained stable throughout the study period ($p = 0.579$; Table 1).

Levofloxacin showed 13.2% to 23.7% activity against ESBL-producing strains of *E. coli* with 37.8% to 56.7% activity against non-ESBL-producing strains in different years (MIC ≤ 2.0 mg/L). Non-ESBL-producing *E. coli* isolates showed significantly higher levofloxacin susceptibility rates than did ESBL-producing isolates. The MIC_{50} of levofloxacin for ESBL-producing and non-ESBL-producing isolates was 16 and 4 mg/L, respectively. The MIC_{90} was 32 mg/L for all isolates (Table 1).

Levofloxacin and cephalosporins have been widely used in the management of UTIs in China for a long time. We observed a decline in the susceptibility to cefuroxime, cefotaxime, and cefepime from 2004 to 2012 in China,[5] but the susceptibility of *E. coli* to levofloxacin remained stable at about 30%; this was lower than the susceptibility in the United States (65.2%).[6] The increased use of fluoroquinolones has resulted in the rapid emergence of fluoroquinolone-resistant *E. coli* and other uropathogens, raising concerns about whether fluoroquinolones should remain the drugs of choice for UTIs.[7] In a current consensus review from the Asia Pacific region, fluoroquinolones (ciprofloxacin and levofloxacin) were not recommended as the drugs of choice for the treatment of UTIs if the rate of resistance of urinary *E. coli* isolates to fluoroquinolones was greater than 20%.[8] In our clinical practice, the symptoms of many patients with lower UTIs resolved in 7 days after treatment with levofloxacin at 500 mg daily, but the urine culture revealed levofloxacin-resistant *E. coli*. The Clinical and Laboratory Standards Institute provided a urine-specific breakpoint for Enterobacteriaceae for some fluoroquinolones (lomefloxacin, ofloxacin, and norfloxacin), but not for levofloxacin. Although most clinical microbiology laboratories determine the susceptibilities of urinary isolates of Enterobacteriaceae to levofloxacin by

Table 1 Susceptibility of *Escherichia coli* to levofloxacin, 2004—2014.

Year	All strains						ESBL positive					ESBL negative				
	No.	ESBL (%)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	S (%)	R (%)	No.	MIC_{50} (mg/L)	MIC_{90} (mg/L)	S (%)	R (%)	No.	MIC_{50} (mg/L)	MIC_{90} (mg/L)	S (%)	R (%)
October 2004—September 2005	168	41.7	8	32	31.0	62.5	70	16	64	21.4	71.5	98	8	32	37.8	56.1
January 2007—December 2007	271	58.7*	16	32	28.0	66.7	159	16	32	13.2	83.0	112	4	32	49.1	43.8
July 2009—June 2010	262	66.0*	8	32	28.2	64.9	173	16	32	17.3	76.3	89	4	32	49.4	42.7
July 2011—June 2012	207	60.9*	8	32	32.4	61.3	126	16	32	19.8	76.2	81	1	32	51.9	38.3
July 2013—June 2014	219	69.4*	8	32	33.8	61.2	152	8	64	23.7	71.7	67	1	16	56.7	37.3
October 2004—June 2014	1127	58.1	8	32	30.4	64.2	680	16	32	18.7	76.3	447	4	32	48.3	44.3
p		<0.001			0.579					0.177					0.150	

* Compared with October 2004—September 2005, $p \leq 0.001$.

ESBL = extended-spectrum beta-lactamase; I = intermediate; MIC = minimum inhibitory concentration; R = resistant; S = sensitive.

applying nonurine-specific MIC breakpoints, this does not mean that levofloxacin is not a suitable treatment for UTIs caused by pathogens with "*in vitro* resistance" to the agent.[8] Previous studies have clearly demonstrated that the mean peak urinary concentration of levofloxacin (0.0—1.5 hours) was 347 mg/L at a dose of 500 mg. Levofloxacin exhibited early (0.0- to 1.5-hour period) bactericidal activity of virtually all participants against study isolates with MICs of $\leq$32 mg/L.[9]

The urine-specific susceptibility breakpoints for levofloxacin should be reset based on more relevant clinical studies, especially in regions with a high prevalence of UTIs caused by multidrug-resistant uropathogens. This is especially prudent given the current pharmacokinetic/pharmacodynamic considerations in this field. Fluoroquinolone resistance within society should also be meticulously investigated.[7]

Conflicts of interest

The authors declare that they have no financial or nonfinancial conflicts of interest related to the subject matter of materials discussed in the manuscript.

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