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ORIGINAL ARTICLE

Correlation between levofloxacin consumption and the incidence of nosocomial infections due to fluoroquinolone-resistant *Escherichia coli*

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Background/purpose: The relationship between fluoroquinolone resistance in *Escherichia coli* isolates causing nosocomial infection and hospital antibiotic consumption were investigated. Restriction of levofloxacin use was implemented to control the incidence of fluoroquinolone-resistant *E coli* in the hospital.
Methods: The study was conducted from January 2004 to December 2010. Antimicrobial agent consumption was obtained from the pharmacy computer system and presented as the defined daily doses per 1000 patient-days every 6 months. The incidence of fluoroquinolone-resistant *E coli* isolates causing nosocomial infections was obtained from the Department of Infection Control every 6 months. An antimicrobial stewardship program, restricting levofloxacain use, was implemented in July 2007.
Results: The incidence of fluoroquinolone-resistant *E coli* causing nosocomial infections was significantly correlated with fluoroquinolone usage ($p = 0.005$), but not with the use of third- or fourth-generation cephalosporins, piperacillin-tazobactam, or carbapenems. Parenteral ($p = 0.002$), oral ($p = 0.018$), and total levofloxacin ($p = 0.001$) use were significantly

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correlated with the extent of fluoroquinolone resistance. With a reduction of levofloxacin use, a decrease of the incidence of fluoroquinolone resistance in *E coli* isolates was observed.
Conclusion: There is a significant correlation between levofloxacin use and the incidence of nosocomial fluoroquinolone-resistant *E coli* isolates. The incidence of fluoroquinolone-resistant *E coli* could be reduced by limiting levofloxacin consumption.

Introduction

Escherichia coli is a common infection pathogen associated with both community acquired and nosocomial infections. Antibiotic resistance among *E coli* isolates continues to increase, limiting the choices of antibiotics available for treating urinary tract infections.[1] A high ratio, >20%, of fluoroquinolone resistance among *E coli* uropathogens has been reported in several countries.[2] The frequency of extended-spectrum-beta-lactamase (ESBL)-producing *E coli* bacteremia has increased worldwide; thus the use of carbapenems has increased.[3] The emergence of carbapenemases, *Klebsiella pneumoniae* carbapenemases (KPC) and New Delhi metallo-beta-lactamase-1 (NDM-1), has also been reported. The NDM-1-producing gene was identified in *Enterobacteriaceae*, mainly in *E coli* and *K pneumoniae*.[4] NDM-1-producing bacteria exhibited a high resistance rate to other classes of antimicrobial agents, such as fluoroquinolones or aminoglycosides.[5]

Fluoroquinolones were introduced as an antibiotic group in the 1980s.[6] Because of their broad antimicrobial spectrum, excellent oral and parenteral bioavailability, and low toxicity, fluoroquinolones have been widely prescribed to patients with bacterial infections.[7] Fluoroquinolone use in hospitals is reportedly associated with the emergence of resistance in a variety of bacteria, including *Staphylococcus aureus, Pseudomonas aeruginosa*, and *E coli*.[8] Antibiotic use is considered to be the main factor contributing to the emergence of resistance.[6] In this study, we investigated whether the incidence of nosocomial fluoroquinolone-resistant *E coli* can be reduced by controlling fluoroquinolone use in the hospital.

Methods

Hospital setting

Taipei Medical University Hospital (TMUH) is a private, tertiary care, university-affiliated, teaching hospital in Taipei, Taiwan. Medical, surgical, neonatal, and pediatric intensive care units and an emergency room are available at this hospital. The number of beds available was 350 in 2004, 560 in 2008, and 702 in 2010. The study period was from January 1, 2004 to December 31, 2010.

Bacterial isolates and susceptibility testing

The broth microdilution method (Phoenix; Becton Dickinson, Sparks, MD, USA) was used to determine the antimicrobial susceptibility of *E coli* isolates. Antimicrobial susceptibility tests were performed according to the Clinical and Laboratory Standards Institute (CLSI) guidelines.[9] Moxifloxacin susceptibility data were not available during the study period. Only the first *E coli* isolate from each patient was included. Fluoroquinolone-resistant *E coli* was defined as an *E coli* isolate exhibiting either intermediate resistance or resistance to either ciprofloxacin or levofloxacin. According to the CLSI criteria,[9] susceptibility breakpoints for ciprofloxacin and levofloxacin for *E coli* used in this study were ≤1 mg/L and ≤2 mg/L, respectively. Susceptibility data for *E coli* isolates causing nosocomial infections were collected from the Infection Control Department; these data were obtained every 6 months.

Antibiotic consumption

Fluoroquinolones (ciprofloxacin, levofloxacin, or moxifloxacin), third-generation cephalosporins (ceftriaxone, cefotaxime, flomoxef, ceftazidime, or cefoperazone), fourth-generation cephalosporins (cefepime or cefpirome), piperacillin-tazobactam, and carbapenems (ertapenem, imipenem, or meropenem) can be prescribed to treat nosocomial *E coli* infections at TMUH. Parenteral ciprofloxacin, oral ciprofloxacin, and oral levofloxacin were available throughout the study period. Parenteral levofloxacin was available after January 2005, and parenteral moxifloxacin between January 2004 and June 2005. Oral and parenteral moxifloxacin were listed in pharmacy formulation from January 2007. In patients with normal renal function, parenteral ciprofloxacin dose was 400 mg every 12 hours, whereas the oral dose was 500 mg every 12 hours. Before 2007, the suggested levofloxacain dose was 500 mg once daily parenterally and orally. After 2007, the suggested levofloxacin dose was 750 mg once daily parenterally and orally. The suggested moxifloxacin dose was 400 mg once daily parenterally and orally. Antibiotic utilization was expressed as the defined daily doses per 1000 patient-days (DDD/1000PD) every 6 months.

The Department of Infection Control at TMUH led the antimicrobial stewardship program, which has restricted the use of levofloxacin since July 2007. Thus, the period from January 2004 to June 2007 was the preintervention period, and July 2007 to December 2010 was the post-intervention period.

Statistical analysis

Least-squares linear regression was used to examine the univariate relationship between antibiotic use and the incidence of fluoroquinolone-resistant *E coli* isolates