Infection/Inflammation

Prevalence of and Risk Factors for Levofloxacin-Resistant E. coli Isolated from Outpatients with Urinary Tract Infection

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Purpose: Levofloxacin has been widely used because of its broad spectrum and excellent penetration of the prostate. But levofloxacin-resistant Escherichia coli (E.coli) has been reported all over the world. We analyzed the annual levofloxacin resistance of E. coli and its risk factors.

Materials and Methods: From 2005 to 2009, we retrospectively analyzed patients who had undergone a urine analysis and a urine culture at the Outpatient Section of the Department of Urology of Kwangju Christian Hospital. Among them, we chose 509 patients infected by E. coli and evaluated the resistance rate to levofloxacin and its risk factors.

Results: The annual rates of levofloxacin resistance of E. coli were 29.49% in 2005, 26.51% in 2006, 40.21% in 2007, 43.20% in 2008, and 31.75% in 2009. A close correlation with the resistance rate was shown in cases that had underlying neurogenic bladder (p=0.002, odds ratio [OR]=4.236), a history of ciprofloxacin (p<0.001, OR=3.753) and levofloxacin (p<0.001, OR=2.996) administration for at least 48 hours in the past year, urolithiasis (p=0.003, OR=3.317), and older age (p<0.001, OR=1.027).

Conclusions: This study from 2005 to 2009 showed that the levofloxacin resistance rates of E. coli were high at over 25%. The risk factors that affected the levofloxacin resistance rates of E. coli were underlying neurogenic bladder, ciprofloxacin administration history, urolithiasis, levofloxacin administration history, and older age. Levofloxacin should be prescribed cautiously in patients with these risk factors until the pathogen is identified.

Key Words: Drug resistance; Fluoroquinolones; Risk factors

INTRODUCTION

Cephalosporin and penicillin antibiotics were used to be the primary prescriptions for infections in the past. After the increase in resistant strains against these antibiotics, quinolone-class antibiotics emerged. According to IMS Health statistics, sales of quinolones reached approximately 151.3 billion won in the fourth quarter of 2010 in South Korea [1]. Sales of ciprofloxacin in the fourth quarter of 2010 increased by 75% to about 64.5 billion won over the same period in 2004, whereas sales of levofloxacin increased by 195% to about 62.1 billion won (Fig. 1) [1]. The rapid increase in sales of levofloxacin is attributed to its broader antimicrobial spectrum compared with that of ciprofloxacin. Levofloxacin has been widely used worldwide, while reports of levofloxacin-resistant Escherichia coli (E. coli) have surfaced. Domestic studies on ciprofloxacin resistance have been reported several times, but there have been few studies on resistance to levofloxacin amid the recent increase in its usage. Therefore, we performed this study to support the choice of antibiotics before the identification of the pathogen in treating urinary tract infection (UTI). We studied outpatients whose urine culture results had been identified with E. coli, the most common causative pathogen of UTI, within the past 5 years and analyzed the annual levofloxacin resistance of E. coli and...
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its risk factors.

MATERIALS AND METHODS

1. Inclusion and exclusion criteria

E. coli was isolated from 701 of the 8,063 patients who had visited the Outpatient Section of the Department of Urology of Kwangju Christian Hospital and had undergone a urine culture test from January 2005 to December 2009. Patients who had repeatedly undergone urine culture tests in the same year were excluded. E. coli was determined as the causative pathogen if the amount of the isolated E. coli colony was over 10^5 counts per ml of voided urine or was over 10^3 counts per ml of catheterized urine. The subjects of this study were 509 patients who met the aforementioned inclusion and exclusion criteria. The patients’ mean age was 55.1±17.3 years. The ratio of males to females was 1.0 to 5.8.

2. Methods of urine collection and urine test

Urine sample collection was performed by the following methods. For patients with a urinary catheter, urine was collected by using a sterilized syringe after the tip of the catheter was washed with a boric sponge. For patients without a urinary catheter and who could self-urinate, their midstream urine was collected after the opening of their urethra and its surroundings were washed with a boric sponge. For pediatric patients who could not control their urination, urine was collected after the opening of their urethra and its surroundings were washed with a boric sponge and a feeding tube was inserted through the urethra to the bladder.

The collected urine samples were gram-stained for microscopic observation, and 0.001 ml of each sample was inoculated on a serum agar medium and a MacConkey agar medium for culture at 37°C for 24 to 48 hours. Pathogen identification was conducted by using MicroScan® of Siemens, and the antibiotic sensitivities were determined by using the minimum inhibitory concentration.

3. Various risk factors

Retrospective analyses were performed for the sex and age of the patients, their antibiotic sensitivity against E. coli, and various clinical factors. The patients were categorized according to age: under 10, 10 to 19, 20 to 29, 30 to 39, 40 to 49, 50 to 59, 60 to 69, 70 to 79, and over 79 years. The clinical factors included underlying diseases, medical histories, and status of the urinary catheterization of the patients at the time of their hospital visit. The underlying diseases were diabetes mellitus, hypertension, urinary incontinence, benign prostatic hyperplasia, urolithiasis, neurogenic bladder, digestive diseases, cerebrovascular diseases, and arthritis. The checked medical histories involved levofloxacin, ciprofloxacin, and antibiotics except for quinolone administration for at least 2 days in the past 12 months, regardless of the disease, hospitalization, experience of urological surgery and surgery besides urological surgery, and UTI. Also, the insertion of a Foley catheter, the insertion of a percutaneous nephrostomy (PCN) tube, and the use of clean intermittent catheterization (CIC) were checked at the time of the patient’s hospital visit.

4. Statistical analysis

To examine the annual variations in resistance of E. coli to levofloxacin in the outpatients, the mean values in the levofloxacin-resistant cases were compared among those who had been identified as having E. coli in their urine culture test each year from 2005 to 2009 via ANOVA. In addition, to explore the correlation of the levofloxacin resistance of E. coli with various risk factors, the risk factors and the levofloxacin-resistant or levofloxacin-susceptible pathogens were cross-tabulated against E. coli (the chi-square method). Logistic regression analysis was used to determine whether there was a significant correlation between the factors that showed differences in the cross-tabulation with the levofloxacin resistance of E. coli. SPSS ver. 12.0 (SPSS Inc., Chicago, IL, USA) was used as the statistical analysis program, and a p-value of less than 0.05 was considered statistically significant.

RESULTS

Levofloxacin-resistant E. coli was identified in the antibiotic susceptibility test in 178 of the 509 patients (34.97%). E. coli was identified in the urine culture test in 75 male patients from among the 509 patients (14.70%); of these 75 males, levofloxacin-resistant E. coli was identified in 32 males (42.70%). E. coli was identified in the urine culture test in 434 female patients from among the 509 patients (85.30%); of these 434 females, levofloxacin-resistant E. coli was identified in 146 females (33.60%). The annual rates of resistance of E. coli to levofloxacin were 23 among 78 patients (29.49%) in 2005, 22 among 83 patients (26.51%) in 2006, 39 among 97 patients (40.21%) in 2007, 2008, 2009, and 2010...
54 among 125 patients (43.20%) in 2008, and 40 among 126 patients (31.75%) in 2009. These figures did not increase with statistical significance given the set 0.05 significance level (p=0.058), but all the resistance rates were over 25%, which was high (Table 1). In the older patients, the resistance rates were high (Table 2). The levofloxacin resistance rates of E. coli according to other various risk factors were calculated (Table 3). Statistically significant differences were shown in the following via cross-tabulation: older age; cases with levofloxacin and ciprofloxacin administration history; hospital visit rates; maintenance of a Foley catheter, PCN tube, cystostomy tube, or CIC at the time of hospitalization; and underlying diseases such as diabetes mellitus, hypertension, urolithiasis, neurogenic bladder, and cerebrovascular diseases. Via logistic regression analysis, a close correlation with levofloxacin-resistant E. coli was shown in the cases that had underlying neurogenic bladder (p<0.002, odds ratio [OR]=4.236), a history of ciprofloxacin (p<0.001, OR=3.753) and levofloxacin (p<0.001, OR=2.996) administration for at least 48 hours in the past year, urolithiasis (p=0.003, OR=3.317), and older age (p<0.001, OR=1.027) (Table 4). In the cases of underlying neurogenic bladder, the odds ratio was 4.236, which showed the highest statistical correlation with levofloxacin-resistant E. coli.

The reasons for the high rates of levofloxacin-resistant E. coli in 2007 and 2008 were analyzed. A close correlation with the occurrence of levofloxacin-resistant E. coli was anticipated in the analysis of the patients with neurogenic bladder and ciprofloxacin and levofloxacin administration history. The hospital visit rates of the patients with neurogenic bladder from 2005 to 2009 were 2.56%, 8.43%, 9.28%, 9.60%, and 7.14%, respectively, and were especially high in 2007 and 2008. In the patients who had taken levofloxacin, the hospital visit rates were 11.54%, 15.66%, 20.62%, 21.60%, and 19.84% from 2005 to 2009, respectively. In the patients who had taken ciprofloxacin, the hospital visit rates were 7.69%, 7.23%, 16.49%, 19.20%, and 13.49% from 2005 to 2009, respectively, with high rates seen in the patients with risk factors in 2007 and 2008.

### Table 1. Annual levofloxacin resistance rate of E. coli

| Years | 2005 | 2006 | 2007 | 2008 | 2009 |
|-------|------|------|------|------|------|
| No. of total patients | 78 | 83 | 97 | 125 | 126 |
| No. of patients with levofloxacin-resistant E. coli | 23 | 22 | 39 | 54 | 40 |
| Resistance rate (%) | 29.49 | 26.51 | 40.21 | 43.20 | 31.75 |

### Table 2. Levofloxacin resistance rate of E. coli according to age

| Age (yr) | No. of patients | Resistance rate (%) |
|---------|----------------|---------------------|
| 0-10    | 10             | 0.00                |
| 10-19   | 5              | 20.00               |
| 20-29   | 27             | 25.93               |
| 30-39   | 62             | 14.52               |
| 40-49   | 63             | 28.57               |
| 50-59   | 113            | 34.51               |
| 60-69   | 115            | 42.61               |
| 70-79   | 90             | 43.33               |
| 80-     | 24             | 66.67               |
| Total   | 509            | 34.97               |

### Table 3. Levofloxacin resistance rate of E. coli according to various risk factors

| Various risk factors          | Resistance rate (%) |
|-------------------------------|---------------------|
| Medical history               |                     |
| Levofloxacin administration   | 65.96 (27.95)       |
| Ciprofloxacin administration  | 68.12 (29.77)       |
| Other antibiotics administration | 40.65 (32.49)     |
| Hospitalization               | 45.71 (32.18)       |
| Urological surgery            | 42.86 (34.39)       |
| Other surgery                 | 37.89 (33.62)       |
| Urinary tract infection       | 42.11 (33.33)       |
| Underlying disease            |                     |
| Diabetes mellitus             | 48.44 (33.03)       |
| Hypertension                  | 43.90 (32.12)       |
| Urinary incontinence          | 46.30 (33.63)       |
| Benign prostatic hyperplasia  | 48.78 (33.76)       |
| Urolithiasis                  | 65.79 (32.48)       |
| Neurogenic bladder            | 79.49 (31.28)       |
| Digestive disease             | 33.33 (35.34)       |
| Cerebrovascular disease       | 60.87 (32.40)       |
| Arthritis                     | 45.83 (34.43)       |
| Status of urinary catheterization |                 |
| Catheter                      | 84.21 (33.06)       |
| CIC                           | 81.82 (33.94)       |

Catheter: state of Foley catheterization, percutaneous nephrostomy (PCN), or cystostomy; CIC: clean intermittent catheterization

### Table 4. Logistic regression analysis of risk factors for levofloxacin resistance of E. coli

| Variables                       | OR (95% CI) | p-value |
|---------------------------------|-------------|---------|
| Aging                           | 1.027 (1.012-1.042) | <0.001  |
| Levofloxacin administration history | 2.996 (1.704-5.266) | <0.001  |
| Ciprofloxacin administration history | 3.753 (1.991-7.075) | <0.001  |
| Admission history               | 0.809 (0.463-1.412)  | 0.456   |
| Catheter                        | 2.715 (0.658-11.206) | 0.167   |
| CIC                             | 1.205 (0.208-6.977)  | 0.835   |
| Diabetes mellitus               | 1.216 (0.637-2.319)  | 0.553   |
| Hypertension                    | 0.920 (0.538-1.572)  | 0.759   |
| Urolithiasis                    | 3.317 (1.520-7.238)  | 0.003   |
| Neurogenic bladder              | 4.236 (1.667-10.767) | 0.002   |
| Cerebrovascular diseases        | 1.665 (0.780-3.555)  | 0.187   |

Catheter: state of Foley catheterization, percutaneous nephrostomy (PCN), or cystostomy; CIC: clean intermittent catheterization

Korean J Urol 2011;52:554-559
The resistance rates of *E. coli* to antibiotics other than levofloxacin were also analyzed (Table 5). The annual resistance rates to ciprofloxacin from 2005 to 2009 were 28.2%, 22.9%, 42.3%, 44.8%, and 34.1%, respectively; for moxifloxacin, they were 29.5%, 37.4%, 39.6%, 40.0%, and 32.8%, respectively. They were all above 20%. Ampicillin and ampicillin/sulbactam had the highest resistance rate of over 60%. Trimethoprim/sulfamethoxazole (TMP-SMX) showed resistance rates of 41.0%, 30.1%, 38.5%, 43.2%, and 31.8%, respectively; cefazolin, a first-generation cephalosporin, had a relatively higher resistance rate than the third-generation cephalosporins. Gentamicin showed resistance rates of 26.9%, 30.1%, 33.0%, 27.2%, and 27.0%, respectively; tobramycin, 29.5%, 30.1%, 37.5%, 25.6%, and 27.0%, respectively; and amikacin, 9.0%, 6.0%, 6.3%, 4.8%, and 3.2%, respectively. Among the carbapenem-class antibiotics, aztreonam had resistance rates of 11.5%, 14.5%, 21.7%, 22.4%, and 10.3%, respectively; imipenem, 1.3%, 4.8%, 3.1%, 4.0%, and 1.6%, respectively; and meropenem, 28.2%, 14.5%, 3.1%, 2.4%, and 1.6%, respectively. The antibiotics with *E. coli* resistance rates that were lower than 20% from 2007 to 2009 were cefotetan, ceftriaxone, ceftazidime, cefotaxime, ceftazidime, amikacin, Piperacillin/Tazobactam, imipenem, and meropenem (Table 5).

**DISCUSSION**

*E. coli*, the most prevalent pathogen of UTI, had been susceptible to ampicillin and amoxicillin, but the widespread use of these β-lactam antibiotics is associated with the emergence of resistant strains. Resistance to these agents is usually mediated by the production of β-lactamases, which inactivate these antibiotics [2]. According to a domestic report, ampicillin resistance rates of *E. coli* were 70% in 2005 and 71% in 2006 among outpatients [3].

TMP-SMX, which has been used to treat UTI, competitively inhibits folate synthetic enzymes. TMP-SMX-resistant *E. coli* bypasses the inhibition by generating insensitive targets [4]. The resistance rate of TMP-SMX had already reached a serious level in the United States, and, thus, alternatives are essential for at least certain areas. Lee et al reported in 2003 that the domestic resistance rate to TMP-SMX was 38.7%, which means that TMP-SMX can no longer be used for first-line treatment of uncomplicated UTI [5].

Since empirical first-line therapy with TMP-SMX became more difficult due to the increase in the resistant pathogens of UTI, the Infectious Disease Society of America (IDSA) suggested guidelines [6]. According to the IDSA guidelines, fluoroquinolone should be the empirical first-line choice for the treatment of uncomplicated UTI if the resistance rate of *E. coli* to TMP-SMX exceeds 20% in a territory. Thus, fluoroquinolones are suggested as alternatives for the empirical first-line treatment of uncomplicated UTI, and they are commonly prescribed worldwide. Despite the disadvantages of fluoroquinolone, such as their high price and contraindication in pediatric patients, they have been used for first-line treatment of UTI because gram-negative pathogens are very susceptible to them and fewer pathogens are resistant to them compared with other drugs. Fluoroquinolone, which inhibits DNA gyrase (topoisomerase II) to interrupt the DNA

**TABLE 5. Variations in resistance rates of *E. coli* to antibiotics**

| Antibiotic                        | Resistance Rate (%) |
|-----------------------------------|---------------------|
| **2005**                          | **2006**            | **2007** | **2008** | **2009** |
| Amoxicillin                       | 66.67               | 62.65    | 74.23    | 71.20    | 65.08    |
| Amoxicillin/Sulbactam             | 62.82               | 61.45    | 70.83    | 65.60    | 62.70    |
| Cefazolin                         | 23.08               | 22.89    | 37.50    | 33.60    | 19.05    |
| Cefuroxime                        | 14.10               | 16.87    | 27.08    | 25.60    | 14.29    |
| Cefotetan                         | 3.85                | 8.43     | 12.50    | 8.00     | 4.76     |
| Ceftriaxone                       | 7.69                | 4.82     | 18.56    | 16.00    | 9.52     |
| Ceftazidime                       | 3.85                | 3.61     | 15.63    | 16.80    | 9.52     |
| Cefotaxime                        | 7.69                | 3.61     | 17.53    | 16.80    | 9.52     |
| Cefepine                          |                     | 7.69     | 6.02     | 13.54    | 16.00    | 7.94     |
| Trimethoprim/Sulfamethoxazole     | 41.03               | 30.12    | 38.54    | 43.20    | 31.75    |
| Ciprofloxacin                     | 28.21               | 22.89    | 42.27    | 44.80    | 34.13    |
| Levofloxacin                      | 29.49               | 26.51    | 40.21    | 43.20    | 31.75    |
| Moxifloxacin                      | 29.49               | 37.35    | 39.58    | 40.00    | 32.79    |
| Gentamicin                        | 26.92               | 30.12    | 32.99    | 27.20    | 26.98    |
| Amikacin                          | 8.97                | 6.02     | 6.25     | 4.80     | 3.17     |
| Tobramycin                        | 29.49               | 30.12    | 37.50    | 25.60    | 26.98    |
| Aztreonam                         | 11.54               | 14.46    | 21.65    | 22.40    | 10.32    |
| Imipenem                          | 1.28                | 4.82     | 3.09     | 4.00     | 1.59     |
| Meropenem                         | 28.21               | 14.46    | 3.13     | 2.40     | 1.59     |
| Piperacillin/Tazobactam           | 11.54               | 22.89    | 13.54    | 16.80    | 7.94     |
| Ticarcillin/K clavulanate         | 21.79               | 12.05    | 28.13    | 21.60    | 16.67    |
synthesis of bacteria, has been known to be associated with very rare resistance cases that developed by natural mutation in vitro. The issue has surfaced, however, because of the recent increase in E. coli resistance to ciprofloxacin [7]. The decrease in fluoroquinolone susceptibility is known to have developed via the mutation of parC and gyrA, which code topoisomerase enzymes, which affects the cell efflux mechanism to primarily lower the intracellular drug accumulation [8].

According to statistical data from IMS Health, a specialized consulting firm for the health care and pharmaceutical sectors, domestic sales of quinolones reached 151.352 billion won in the fourth quarter of 2010, with ciprofloxacin and levofloxacin accounting for approximately 84% at 64.451 billion won and 62.098 billion won, respectively [1]. Among fluoroquinolones, ciprofloxacin has been prescribed most frequently so far; but the ciprofloxacin resistance rate of E. coli has been reported as 20% in Brazil, 20% in Spain, and 26% in Europe [9-11]. In South Korea, ciprofloxacin has been widely prescribed for the treatment of UTI, and the resistance rate due to its increased use and abuse has increased. Ko et al reported that the susceptibility of Gram-negative bacteria to ciprofloxacin was 87.8% in 1994 and 78.8% in 1998 [12]. Song and Kim reported that E. coli had been identified in 46.4% of 584 hospitalized patients and 305 outpatients with UTI, whereas the ciprofloxacin resistance rate was 19.8% and 18.8%, respectively, in 2003 [13]. Ryu et al also reported that the ciprofloxacin resistance rate of E. coli had increased from 46.8% to 52.5% among hospitalized patients and from 27.2% to 34.9% among outpatients in 2000 and 2005, respectively [14]. The ciprofloxacin resistance rate has already reached a serious level.

Levofloxacin has been reported to have excellent antimicrobial activity and to be effective for both Gram-positive bacteria and anaerobes, compared to ciprofloxacin [15,16]. Thus, it has recently been used to treat H. pylori infection and pneumonia and to prevent infections in hepatobiliary surgeries [17-19]. Especially in urology, with the emerging importance of Gram-positive bacteria such as Enterococcus faecalis and Staphylococcus epidermidis, as well as of Gram-negative enterobacteria including E. coli, which is the causative pathogen of bacterial prostatitis, levofloxacin has become the standard therapy in the treatment of chronic bacterial prostatitis [20,21]. In the United States, between 1998 and 2005, however, as prescriptions of levofloxacin increased from 3.1 to 12.7 prescriptions per 1000 outpatient visits, the rate of levofloxacin-resistant E. coli increased from 1% to 9%. The switch to levofloxacin for the initial management of outpatient UTI was followed by the rapid emergence of levofloxacin-resistant E. coli [22]. According to a Japanese report in 2008, four sepsis cases caused by levofloxacin-resistant E. coli had been reported among 665 patients upon ultrasound-guided transrectal prostate biopsy from July 2002 to December 2006. The authors suggested that fluoroquinolone-resistant E. coli infection after ultrasound-guided transrectal prostate biopsy might be increasing due to the widespread use of fluoroquinolones in both humans and food animals [23].

In South Korea, the levofloxacin resistance rate may be increasing as the use of levofloxacin has increased. Excluding 2007 and 2008, in which the percentage of patients with significant risk factors in this study was high, the levofloxacin resistance rate of E. coli increased through the years. The outcome of this study does not exactly represent the levofloxacin resistance rate of E. coli in South Korea, however, because this study was conducted at a single hospital in only one community from 2005 to 2009. To confirm the levofloxacin resistance rate of E. coli in South Korea, combined data from multiple community health center sites are required.

CONCLUSIONS

Although ciprofloxacin resistance of E. coli has been reported, reports on the levofloxacin resistance rate for over 5 years and its correlation to risk factors are rare. Thus, we studied the resistance of E. coli to levofloxacin, the chemical structure of which is unlike that of ciprofloxacin, even though they belong to the same class of fluoroquinolones. In addition, various factors related to the levofloxacin resistance rate of E. coli were investigated by using statistical analysis. The levofloxacin resistance rates of E. coli were high at over 25% from 2005 to 2009. The results of the regression analysis showed that the factors that affected the resistance rate were an underlying neurogenic bladder, ciprofloxacin administration history, urolithiasis, levofloxacin administration history, and older age. For patients who have risk factors for levofloxacin resistance, as analyzed in this study, levofloxacin should be cautiously prescribed until the pathogen is identified. In such cases, prescription of other antibiotics that have lower resistance rates should be considered.

Conflicts of Interest
The authors have nothing to disclose.

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