The assessment of susceptibility of gram-negative strains to fluoroquinolones and their consumption in the oncological urology department in 2005–2007

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KEY WORDS

urinary tract infection ◗ gram-negative rods ◗ DDD/100 patient-days ◗ fluoroquinolones

ABSTRACT

Introduction. Fluoroquinolones are used, among other drugs, in perioperative prophylaxis and therapy of urinary tract infections.
The aim of the study was to analyze the susceptibility of Gram-negative rods to fluoroquinolones with reference to their consumption in the Urology Department.
Material and methods. The rods of the *Enterobacteriaceae* family and of the *Pseudomonas* and *Acinetobacter* genera, that in overall were 60 isolates, were subjected to microbiological analysis. The analyzed Gram-negative rods were cultured from urine of 57 urological patients in years 2005-2007. The consumption of fluoroquinolones in years 2005-2007 was 46.6, 48.1, and 14.0 DDD/100 patient-days, respectively.
Results. Among 60 tested Gram-negative rods, *in vitro* resistance to ciprofloxacin and norfloxacin was found in 31 (51.7%) and 30 (50%) isolates, respectively.
Conclusions. Gram-negative rods resistant to fluoroquinolones were frequent in the study material.

INTRODUCTION

Urinary tract infections are second in order of frequency of hospital infections and account for 40% of all cases. Anatomical malformations and functional defects such as e.g. prostatic hypertrophy, neurogenic-muscular urinary bladder dysfunctions, ureterostenosis and calculi in the urinary tract, tumors, arterial hypertension, diabetes mellitus, hepatic failure and AIDS create favorable conditions for urinary tract infections to arise. Operations on the urinary tract, such as bladder drainage, prostatectomy, cystectomy, and nephrectomy, as well as chemotherapy and radiotherapy can lead to urinary tract infections [1].

Fluoroquinolones, among other drugs, are used in the prophylaxis and treatment of urinary tract infections, due to their broad antibacterial spectrum and pharmacokinetic properties [2, 3, 4]. However, an increase in resistance to this group of drugs has been observed among Gram-negative rods, which is caused by various mechanisms. The genes determining resistance to fluoroquinolones are located in the bacterial chromosome. Point mutations in *gyrA* and *gyrB* genes cause defects of gyrase enzyme (topoisomerase II) and loss of the main target locus for fluoroquinolones. The mutations are spontaneous and occur with 1 x 10^{-5} incidence in *Pseudomonas aeruginosa* and 1 x 10^{-8} in *Escherichia coli*. The resulting resistance is low grade and develops when the concentration of the chemotherapeutic in the kidneys or urine is close to the MIC (minimal inhibitory concentration) [3, 4, 5]. It was found that two mutations in the *gyrA* gene and one in the *parC* gene determine a high grade of drug resistance. Additional mutations, also in *acrR* and *marR* genes produce a higher grade of resistance to fluoroquinolones. These mutations occur with a significantly lower incidence. The occurrence of point mutations in *parC* and *parE* genes leads to topoisomerase IV dysfunction [4, 6, 7]. Point mutations in *acrR* and *marR* genes cause excessive elimination of fluoroquinolones from the cytoplasm by an RND-type (resistance-nodulation-division family) pump, i.e. AcrAB-TolC, which is found in *Escherichia coli, Enterobacter cloacae* and *Proteus mirabilis*. The resistance of Gram-negative rods is also influenced by the availability of OMP (outer membrane protein) channels, through which the chemotherapeutic enters the cell. This type of resistance is exemplified by OmpF protein, which excessive expression reduces the ability of fluoroquinolones to penetrate the cell. Tran and Jacoby in 2002 discovered the *qnr* gene, which protects gyrase against the cidal effect of fluoroquinolones [6, 7, 8].

MATERIAL AND METHODS

Rods of the *Enterobacteriaceae* family (n = 53) and of *Pseudomonas* (n = 5) and *Acinetobacter* (n = 2) genera, totalling 60 isolates, were subjected to microbiological assessment. The analyzed Gram-negative rods were cultured from urine of 57 patients of the Urology Department in the years 2005-2007. One isolate was obtained from each patient. Table 1 presents the analyzed bacteria. Identification and drug susceptibility tests of the organisms were carried out according to the instructions, which are in force in the Microbiology Unit, Oncology Center in Bydgoszcz. Reference strains from the American Type Culture Collection (ATCC), namely *E.coli* ATCC 25922, *E.coli* ATCC 35218, *K.pneumoniae* ATCC 700603 and *P.aeruginosa* ATCC 27853 were used for control of the susceptibility determinations.

Fluoroquinolone consumption is expressed in DDD/100 patient-days (DDD – accepted mean daily drug dose). The consumption of fluoroquinolones in the first and second halves of 2005 was 16.1 and 30.5 DDD/100 patient-days, respectively; in 2006 it was 34.0 and 14.1 DDD/100 patient-days, respectively; and in 2007 it was 7.2 and 6.8 DDD/100 patient-days, respectively. Figure 1 shows the occurrence of strains resistant to fluoroquinolones and consumption of that group of drugs.

RESULTS

Resistance to fluoroquinolones was found in 30 (50%) out of 60 tested isolates. Out of 27 *Escherichia coli* strains, 18 (66.7%) were resistant to fluoroquinolones. *In vitro* ineffectiveness of ciprofloxacin and norfloxacin was found in three (30%) out of 10 *Proteus mirabilis* strains. In the study period, multiresistant *Enterobacter cloacae* strains were isolated, including

five strains (62.5%) resistant to fluoroquinolones out of eight strains tested. One *Providencia rettgeri* strain demonstrated resistance to both quinolones. Out of seven non-glucose-fermenting strains, two *Pseudomonas aeruginosa* strains (40%) and one *Acinetobacter baumanni-calcoaceticus complex* strain were resistant to fluoroquinolones.

In the first half of 2005 no fluoroquinolone-resistant strain was found, in the second half year the percentage of resistant strains was 6.7%. The percentages of fluoroquinolone-resistant strains in the first and second halves of 2006 were 16.7% and 5% ,while those in 2007 were 10% and 11.7%, respectively.

DISCUSSION

An increasing incidence of Gram-negative rods resistance to fluoroquinolones was observed in years 2005-2007 in our center. In the second half of 2005, strains resistant to ciprofloxacin and norfloxacin were cultured, which coincided with the period of increased consumption of these drugs. The highest percentage of strains resistant to fluoroquinolones was found in the first half of 2006, which corresponded to high consumption of the drug group mentioned above. In 2007 the percentage of resistant strains decreased but despite the significant reduction of fluoroquinolone consumption, it exceeded 10%.

In years 1997-1998 in the USA and Canada the *in vitro* susceptibility of Gram-negative rods to ciprofloxacin was almost two times higher in comparison to our data, i.e. 89.6% [9]. A high *in vitro* efficacy of ciprofloxacin – from 88.6% against *P.aeruginosa* to 93.1% against *Enterobacteriaceae* rods was also achieved by D.J. Farrell et al. (1999-2000); these results were representative for eight centers in England [10]. In the USA, the drug susceptibility of about 7,000 *P.aeruginosa* and *Enterobacteriaceae* strains isolated in years 1999-2001 was assessed as part of the MYSTIC (Meropenem Yearly Susceptibility Test Information Collection) program. An increase in resistance to ciprofloxacin in *P.aeruginosa* was observed up to 22.1% and in other Gram-negative rods to 6.8%, but these values were still lower when compared to our results. The authors also found a correlation between the increase of resistance to ciprofloxacin and its consumption, i.e. 3.1 DDD/100 patient-days in 1999 and 6.4 DDD/100 patient-days in 2001 [11]. A similar tendency was disclosed in our study.

In Poland in 2003, rods were already isolated demonstrating susceptibility to fluoroquinolones that did not exceed 70% (*Enterobacteriaceae*) and 50% *(Pseudomonadaceae*) [12]. The problem of increasing resistance of rods to new quinolones was also noticed in urology departments in two other Polish hospitals, which was in concordance with our observations [13, 14]. Unfortunately, no information is available on fluoroquinolone consumption. The susceptibility of *E.coli, E.cloacae* and *Klebsiella* rods isolated from urine samples of patients hospitalized in a Warsaw hospital in 2003 was higher than that in our center, not exceeding, however, 80% [15].

Table 1. The analyzed *Enterobacteriaceae* rods and non-glucose-fermenting rods.

Enterobacteriaceae	Number of isolates (n = 53)	Non-glucose-fermenting rods	Number of isolates (n = 7)
Escherichia coli	n = 27	*Pseudomonas aeruginosa*	n = 5
Proteus mirabilis	n =10	*Acinetobacter baumannii-calcoaceticus complex*	n = 2
Enterobacter cloacae	n = 8		
Citrobacter freundii	n = 2		
Klebsiella pneumoniae	n = 2		
Klebsiella oxytoca	n = 1		
Providencia rettgeri	n = 1		
Morganella morganii	n = 1		
Serratia marcescens	n = 1		

According to EARSS (European Antimicrobial Resistance Surveillance System) data from 2001-2006, an increase in resistance to fluoroquinolones among *Enterobacteriaceae* rods and *P.aeruginosa* was also observed in other European countries, which resulted from excessive use of these chemotherapeutics both in long-term prophylaxis and in treatment [16, 17].

The use of antibacterials, including fluoroquinolones, for a longer time can cause development of drug resistance in microorganisms. Many controversies have been aroused by the use of perioperative prophylaxis, which can lead to the selection of resistant strains. In urology departments in Poland, first generation cephalosporins, aminoglycosides and fluoroquinolones are administered as part of prophylaxis [2]. Since 2007, in the Urology Department, Oncology Center, the administration of fluoroquinolones for perioperative prophylaxis has been abandoned. In spite of significant reduction of consumption of fluoroquinolones, in 2007 in the Urology Department strains resistant to these chemotherapeutics were still isolated. Elimination of multiresistant strains, including those resistant to fluoroquinolones, is difficult due to their transmission between departments of the same hospital and other hospitals. Bacteria living in patients, staff and in inanimate environments form a niche specific to a given department, which sometimes can last for years, despite strenuous efforts of the staff and the team for control of hospital infections. In the Oncology Center, after the information on increasing resistance to quinolones had been obtained, the decision was taken about changes in the antibiotic policy. In summary, in view of increasing drug resistance of microorganisms, during selection of drugs, it is important to take into account the results of bacteriological investigations and drug resistance of the organisms specific to a given department, which requires constant surveillance. An assessment of the efficacy of activities undertaken to reduce microbial resistance to fluoroquinolones should be carried out over a longer time period.

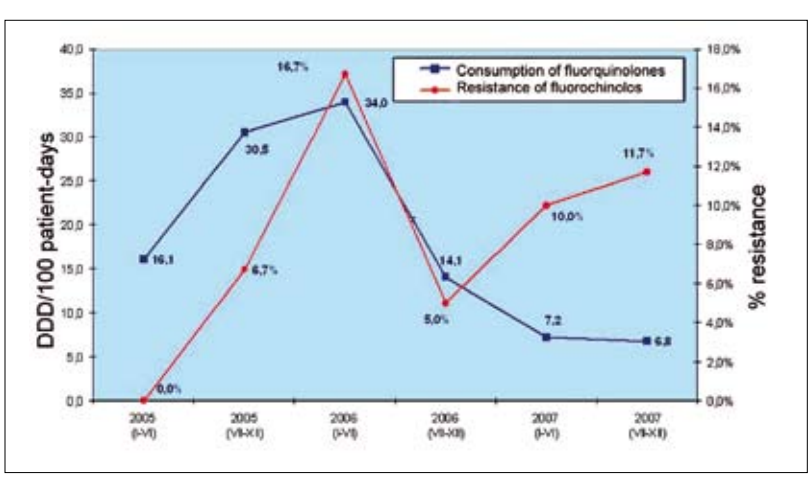

Fig. 1. Occurence of fluoroquinolone resistant Gram-negative rods versus fluoroquinolone usage in The Urology Department during 2005-2007.

CONCLUSIONS

1. The resistance to fluoroquinolones among Gram-negative rods isolated from urine was frequent and increased to 10.8%.
2. The wide use of quinolones in inpatient and outpatient services can be one of the factors increasing resistance to these drugs.
3. In case of observed increasing resistance to quinolones, the antibiotic policy of the hospital should be modified.

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