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IMIPENEM CONSUMPTION AND GRAM-NEGATIVE PATHOGEN RESISTANCE TO IMIPENEM AT SESTRE MILOSRDNICE UNIVERSITY HOSPITAL

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SUMMARY - The study was performed to determine the consumption of imipenem and resistance of gram-negative pathogens (*Pseudomonas aeruginosa, Acinetobacter* sp., *Klebsiella* sp., *Escherichia coli*, *Proteus mirabilis, Serratia marcescens, Enterobacter* sp.) to imipenem. Gram-negative pathogens were isolated at the Sestre milosrdnice University Hospital from Zagreb in 1999 and 2000. The imipenem sensitivity testing was performed by disk diffusion and E-test methods. The consumption of imipenem was expressed in DDD/100 hospital days in the same periods. Imipenem resistance of *Acinetobacter* sp. decreased significantly in the year 2000 (p=0.0052), especially in the first six months (p=0.021) when the lowest consumption of imipenem was recorded. Imipenem resistance of other gram-negative pathogens did not decrease significantly. Results suggest that the consumption of imipenem might lead to changes in resistance to imipenem among *Acinetobacter* strains.

Key words: *Gram-negative bacterial infections; Cross infections; Drug resistance; Imipenem, therapeutic use; Imipenem, pharmacology*

Introduction

The carbapenem antibiotic imipenem is a beta-lactam antibiotic characterized by its ultrabroad spectrum of activity against clinically important aerobic gram-positive and gram-negative species as well as anaerobes[1]. Its wide antibacterial spectrum and great beta-lactamase stability make imipenem an option for monotherapy in serious bacterial infections such as intra-abdominal infections, lower respiratory infections, gynecologic infections, septicemia, genitourinary tract infections, bone and joint infections, skin and soft tissue infections, and endocarditis[2,3]. Its attributes make it ideally suited as first-line empiric monotherapy for serious bacterial infections in hospitalized patients, especially in intensive care units or in febrile neutropenic patients, where the causative organism is unknown or resistance may be suspected[4]. Imipenem is also a useful agent when cephalosporin-resistant or difficult-to-treat organisms have been identified[4,5].

It is often kept in reserve, and its use is commonly restricted for fear of emergence of resistance through overuse by clinicians. Imipenem is in clinical use for over 15 years, and development of bacterial resistance to imipenem has been reported for *Acinetobacter* sp.[6,7], *Pseudomonas aeruginosa*, and *Enterobacter* sp.[7,8] Imipenem-resistant strains occur after increased use of imipenem[6,7]. Bacterial resistance to imipenem arises from the production of carbapenemases capable of hydrolyzing the carbapenem nucleus, and from alteration in the porin channels in the bacterial cell walls, thereby reducing the permeability of the drug[5,9-12]. *Stenotrophomonas* (*Xanthomonas*) maltophilia is intrinsically resistant to imipenem, as are *Enterococcus faecium* and methicillin-resistant staphylococci[4].

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Emergence of resistance to imipenem during treatment has also been seen, mainly in *Pseudomonas aeruginosa* isolated from lower respiratory tract infections[13]. Emergence of quinolone-imipenem cross-resistance in *Pseudomonas aeruginosa* after fluoroquinolone therapy has also been documented[14]. In general, the emergence of resistance to imipenem among gram-negative pathogens has become an evolving, ongoing potential problem in the hospitals that must be monitored.

The aim of the study was to determine the consumption of imipenem and imipenem resistance of gram-negative pathogens.

Material and Methods

Resistance to imipenem was determined in 1999 and 2000 in the following gram-negative pathogens: *Pseudomonas aeruginosa, Acinetobacter* sp., *Klebsiella* sp., *Escherichia (E.) coli, Proteus mirabilis, Serratia marcescens* and *Enterobacter* sp. These microorganisms were isolated from different clinical specimens of hospitalized patients at Sestre milosrdnice University Hospital. Duplicate or multiple isolates of the selected pathogens were excluded from the study.

All microorganisms were identified according to colonial morphology, Gram stain, and biochemical tests[5]. Imipenem sensitivity testing was performed by the disk diffusion method according to the National Committee for Clinical Laboratory Standard procedures[15], and E-test imipenem method. The consumption of imipenem was determined in the same periods and expressed in defined daily doses of imipenem *per* 100 hospital days (DDD/100 hospital days). DDD was always 2 g of imipenem. The consumption of imipenem for each ward was calculated as follows: number of DDD : number of hospital days x 100. The consumption of imipenem was observed at the following hospital wards: Department of Surgery with intensive care unit (ICU), Department of Medicine, Divison of Hematology, and Department of Pediatrics.

Results

The consumption of imipenem expressed in DDD/100 hospital days is shown in Table 1. The highest consumption of imipenem in the Hospital was recorded at the Department of Surgery with ICU. There was an obvious decrease in the consumption of imipenem from 1998 (1.57 DDD/100 hospital days) to 2000 (0.48 DDD/100 hospital days). The decrease in the consumption of imipenem was more pronounced in the first six months of 2000 than in the year 2000 as a whole. The first six months of 2000 was the period when the consumption of imipenem at Department of Surgery with ICU was lowest.

Department of Medicine showed a lower consumption of imipenem, however, with a moderate increase from 1998 (0.085 DDD/100 hospital days) to 2000 (0.19 DDD/100 hospital days). At the Division of Hematology of the Department of Medicine, imipenem was not used at all.

Table 1. Imipenem consumption in DDD/100 hospital days

	1998	1999	Jan - Jun 2000	Jan - Dec 2000
Department of Surgery with ICU	1.57	1.34	0.20	0.48
Department of Medicine	0.085	0.123	0.19	0.19
Division of Hematology	–	–	–	–
Department of Pediatrics	0.00932	0.036	0.055	0.042

DDD/100 hospital days= defined daily doses of imipenem *per* 100 hospital days; ICU=intensive care unit

Department of Pediatrics had a low consumption of imipenem, however, a moderate increase from 1998 (0.00932 DDD/100 hospital days) to 2000 (0.042 DDD/100 hospital days) was recorded.

Table 2 shows percentage of resistance to imipenem of different gram-negative pathogens throughout the year 1999, in the first six months of 2000, and throughout the year 2000. Imipenem resistance of *Pseudomonas aeruginosa* was 13.5% in 1999, and decreased to 10.44% in 2000. Imipenem resistance of *Pseudomonas aeruginosa* in the first six months of 2000, when the consumption of imipenem at Department of Surgery with ICU was lowest, decreased to 8.8%.

Imipenem resistance of *Acinetobacter* sp. was 12.6% in 1999, decreased to 4.9% in 2000, and even to 3.6% in the first six months of 2000, when the consumption of imi-

penem at Department of Surgery with ICU was lowest. Almost all resistant *Acinetobacter* and *Pseudomonas* strains were isolated at Department of Surgery with ICU.

E. coli, Klebsiella sp., and *Proteus mirabilis* were the species for which no imipenem resistance was recorded. Imipenem resistance of *Serratia marcescens* was 2.7% in 1999 and 2000. Imipenem resistance of *Enterobacter* sp. was 1.39% in 2000.

Table 2. Resistance of gram-negative pathogens to imipenem

	1999		Jan-Jun 2000			Jan - Dec 2000		
	n	%	n	%	p	n	%	p
Pseudomonas aeruginosa	406	13.5	170	8.8	NS	412	10.44	NS
Acinetobacter sp.	191	12.6	84	3.6	p=0.021	224	4.9	p=0.0052
Klebsiella sp.	439	0	154	0	–	325	0	–
Escherichia coli	1101	0	515	0	–	1100	0	–
Proteus mirabilis	329	0	162	0	–	303	0	–
Serratia marcescens	37	2.7	8	0	NS	38	2.63	NS
Enterobacter sp.	28	0	12	0	NS	72	1.39	NS

%=percent of resistance to imipenem; n=number of strains tested for imipenem resistance; NS=non-significant

The test of difference between proportions was performed, and level of significance was calculated (Table 2). Significant differences (with alpha level of 0.05) were only found for *Acinetobacter* sp., for both study periods.

Discussion

In recent years, several reports have emphasized the development of resistance to imipenem among gram-negative pathogens, especially *Pseudomonas aeruginosa, Acinetobacter sp*., and *Enterobacter sp*. Gaynes et al., in a study of resistance to imipenem among selected gram-negative bacilli in the United States, found 11.1% of 3316 *Pseudomonas aeruginosa* tested to be resistant to imipenem, especially those isolated from respiratory tract. Imipenem resistance among *Enterobacter* sp. was 1.3%[8]. In a surveillance study of the incidence of multi-resistance in gram-negative bacterial isolates from ICUs in Belgium, Verbist found 15% of *Pseudomonas aeruginosa*, 7% of *Acinetobacter* sp., 3% of *Enterobacter* sp., 2% of E. coli and 3% of *Klebsiella* sp. to be resistant to imipenem[16]. In a study of the prevalence of antibiotic resistance among gram-negative bacteria in ICUs, Elhag *et al.* found 2% of *Pseudomonas aeruginosa*, and none of *E. coli* and *Klebsiella* sp. to be resistant to imipenem[17]. Our data on imipenem resistance of different gram-negative pathogens are mostly consistent with literature reports. In our study, a high rate of imipenem resistance was recorded in 1999 for *Acinetobacter* sp. (12.6%) and *Pseudomonas aeruginosa* strains (13.5%). Imipenem resistance of *Acinetobacter* sp. decreased significantly in the year 2000 (p=0.0052), especially in the first six months (p=0.021), when the lowest consumption of imipenem was recorded at the Department of Surgery with ICU. Imipenem resistance of *Pseudomonas aeruginosa* did not decrease significantly in 2000, although a decreasing trend was observed. The significant decrease in imipenem resistance of *Acinetobacter* sp. in the period characterized by the lowest consumption of imipenem at the Department of Surgery with ICU suggests that imipenem usage might lead to changes in imipenem resistance among *Acinetobacter* strains.

The emergence of resistance to carbapenems of *Acinetobacter* sp. and *Pseudomonas aeruginosa* poses a serious concern. The prolonged use of carbapenems in the treatment of nosocomial infections can favor the development of resistance to these antimicrobial agents. Urban *et al.* report on an outbreak of infections due to *Acinetobacter baumannii* resistant to carbapenems, which occurred after an increased use of imipenem[7]. The spread of these

strains within the hospital environment is a serious problem that could contribute to poor patient outcome.

Heavy and widespread use of antibiotics in hospital does not only force the emergence of antibiotic resistance, but also promotes selection of drug-resistant organisms in the hospital environment. In case of imipenem, these are: *Stenotrophomonas maltophilia*, imipenem resistant strains of *Acinetobacter* sp., *Pseudomonas aeruginosa, Serratia* sp., *Enterobacter* sp., and methicillin resistant staphylococci. Overuse of imipenem appears to continue, not without a risk. The development of imipenem resistance during the treatment of *Pseudomonas* infections has been reported[13]. Imipenem has the highest induction potential of class 1 chromosomal beta-lactamases, leading to high resistance to cephalosporins and penicillins[18]. Overuse of fluoroquinolones has also been associated with the development of resistance to imipenem in *Pseudomonas aeruginosa*. Cross--resistance of ciprofloxacin and imipenem has been reported to occur after the treatment with fluoroquinolones[14,19]. In conclusion, imipenem should be kept in reserve, and its use should be controlled. Controlled use together with an effective infection control program to prevent horizontal transfer of imipenem resistant bacteria will provide a relatively resistance-free future. An imipenem resistance surveillance program with registration of its consumption is necessary to promote an optimal use of imipenem and to encourage its rational prescribing.

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Sažetak

POTROŠNJA IMIPENEMA I OTPORNOST GRAM NEGATIVNIH UZROČNIKA NA IMIPENEM U KLINIČKOJ BOLNICI "SESTRE MILOSRDNICE"

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Cilj istraživanja bio je odrediti potrošnju imipenema, kao i otpornost gram negativnih uzročnika (*Pseudomonas aeruginosa*, *Acinetobacter* sp., *Klebsiella* sp., *E. coli, Proteus mirabilis, Serratia marcescens, Enterobacter* sp.) na imipenem. Gram negativni uzročnici izolirani su u Kliničkoj bolnici "Sestre milosrdnice" 1999. i 2000. godine. Testiranje osjetljivosti na imipenem provedeno je metodom disk difuzije i E-testom. Potrošnja imipenema je izražena u DDD/100 bolničkih dana u istim vremenskim razdobljima. Otpornost na imipenem u *Acinetobacter* sp. je statistički značajno pala 2000. godine (p=0,0052), a poglavito u prvih šest mjeseci (p=0,021) kada je potrošnja imipenema bila najniža. Otpornost ostalih gram negativnih uzročnika na imipenem nije statistički značajno pala. Rezultati ukazuju na to da bi potrošnja imipenema mogla utjecati na promjene u otpornosti *Acinetobacter* sp. na imipenem.

Ključne riječi: *Gram-negativne bakterijske infekcije; Križne infekcije; Otpornost na lijekove; Imipenem, terapijska primjena; Imipenem, farmakologija*