

***In vitro* Activity of Imipenem, Aztreonam, Amoxicillin-clavulanic Acid and Ciprofloxacin Against Multiresistant *Klebsiella pneumoniae*.**

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Abstract

Thirty strains of *Klebsiella pneumoniae* resistant to aminoglycosides and third generation cephalosporins were tested for susceptibility of imipenem, aztreonam, amoxicillin-clavulanic acid and ciprofloxacin by the agar dilution method. Ciprofloxacin and imipenem were the most active agents with MIC₉₀ of 0.25 and 0.5 mg/L respectively. Organisms were more resistant to amoxicillin-clavulanic acid (MIC₉₀ = 16 mg of amoxicillin/L). Most of the organisms were resistant to aztreonam (MIC₉₀ = 256 mg/L).

This study suggests that ciprofloxacin and imipenem might be useful for treatment of multiresistant *K. pneumoniae* infections. (*J Infect Dis Antimicrob Agents* 1993; 10:9-11.)

Key words : Imipenem, *Klebsiella pneumoniae*

เรื่องย่อ

ความไวของเชื้อ *Klebsiellapneumoniae* ที่ดื้อต่อยาปฏิชีวนะหลายชนิดต่อยา imipenem, aztreonam, amoxicillin-clavulanic acid, และ ciprofloxacin

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ศึกษาความไวของเชื้อ *Klebsiella pneumoniae* ที่ดื้อต่อยาปฏิชีวนะในกลุ่ม aminoglycosides และ cephalosporins รุ่นที่ 3 จำนวน 30 สายพันธุ์ ต่อยา imipenem, aztreonam, amoxicillin-clavulanic acid และ ciprofloxacin โดยหาค่าความเข้มข้นต่ำสุดที่สามารถยับยั้งการเจริญเติบโตของเชื้อได้ (MIC) โดยวิธีเจือจางยาในอาหารรุ้น ผลพบว่าเชื้อทุกตัวยังไวต่อยา ciprofloxacin และ imipenem โดยมีค่าความเข้มข้นต่ำสุดที่สามารถยับยั้งการเจริญเติบโตของเชื้อได้ร้อยละ 90 (MIC₉₀) เท่ากับ 0.25 และ 0.5 มล./ล. ตามลำดับ. ในขณะที่ MIC₉₀ ของยา amoxicillin-clavulanic acid = 16 มล. ของ amoxicillin/ล. เชื้อส่วนใหญ่ดื้อต่อยา aztreonam โดยมีค่า MIC₉₀ = 256 มล./ล.

จากผลการศึกษานี้ ciprofloxacin และ imipenem น่าจะเป็นยาที่ใช้รักษาการติดเชื้อที่เกิดจากเชื้อ *K. pneumoniae* ที่ดื้อต่อยาหลายชนิดได้ (*วารสารโรคติดเชื้อและยาต้านจุลชีพ* 2536; 10:9-11.)

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INTRODUCTION

At present, multiresistant *Klebsiella pneumoniae* which are resistant to aminoglycosides (gentamicin, netilmicin, amikacin), third generation cephalosporins (cefotaxime, ceftriaxone, ceftazidime), penicillins (ticarcillin, piperacillin), cotrimoxazole and chloramphenicol have become a major nosocomial problem in many countries including Thailand.

Several in vitro and in vivo studies had shown that imipenem, aztreonam, amoxicillin-clavulanic acid and ciprofloxacin are active against many gram negative organism (1-13). In this study we examined the in vitro activity of these antibiotics against multiresistant *K. pneumoniae*.

MATERIALS AND METHODS

Microorganisms

Thirty strains of multiresistant *K. pneumoniae* characterized by resistance to amikacin (Bristol Myers) and ceftazidime (Glaxo) by 30 mcg disc susceptibility test (zone diameter \leq 14 mm) were studied. Identification of the species was carried out by using standard diagnostic microbiology techniques. The majority of isolates were from patients with nosocomial infections seen at Songklanagarind Hospital from 1989-1990.

Antimicrobial agents

Standard antibiotic powders used were: imipenem (Merck Sharp and Dohme BV, USA), aztreonam (Squibb), amoxicillin-clavulanic acid (Beecham Re-

search Laboratories) and ciprofloxacin (Bayer AG, Germany).

Susceptibility studies

Susceptibility testing was performed in Mueller-Hinton agar by a two fold serial dilution method, using a multiple inoculating apparatus (15,16) The inoculum was approximately 10^4 CFU per spot. Growth reactions were recorded after 18 hours of incubation at 35°C. The MICs were the lowest concentrations preventing visible bacterial growth on agar. *Escherichia coli* ATCC 25922 was used as a quality control.

RESULT

The distribution of the MICs against multiresistant *K. pneumoniae* is shown in Table 1. All strains were susceptible to ciprofloxacin and imipenem with MIC₉₀ of 0.25 and 0.5 mg/L respectively. Eighty-three percent of the organisms were susceptible to amoxicillin-clavulanic acid but MIC₉₀s were much higher (MIC₉₀ = 16 mg of amoxicillin/L). Eighty-three percent of the organisms were resistant to aztreonam.

DISCUSSION

This study shows that ciprofloxacin and imipenem were active agents for multiresistant *K. pneumoniae* in vitro. The MICs of the drugs were lower than achievable blood levels (17) and clinical trials of the drugs have shown them to be generally well tolerated and effective for the treatment of infections in various body systems (1-10). Since quinolone compounds are not approved for children and adolescents, imipenem

Table 1 Minimal Inhibitory Concentrations (MIC) of antibiotics against 30 strains of multiresistant *K. pneumoniae*

Antibiotics	Cumulative percent susceptibility MIC (mg/L)											MIC (mg/L) break point ref. 1,10,12,14	Resistant	Sensitive	Common peak serum concen- tration of anti- biotics, mg/L (IV dosage-gm) ref. 17			
	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64					128	256	
Imipenem	0	50	77	100	-	-	-	-	-	-	-	-	-	-	≥ 16	≤ 4	43 (0.5)	
Ciprofloxacin	83	87	90	93	100	-	-	-	-	-	-	-	-	-	≥ 4	≤ 1	3.8 (0.2)	
*																		
Amoxicillin- clavulanic acid	0	0	0	0	10	17	67	83	100	-	-	-	-	-	≥ 32	≤ 8	40 (1)	
Aztreonam	17	-	-	-	-	-	-	-	-	-	57	87	100	-	≥ 32	≤ 8	54 (0.5)	

*Concentration of amoxicillin in the drug formulation (ratio of amoxicillin: clavulanic acid = 2:1 w/w).

should be the alternative drug in pediatric and young adult patients. Ciprofloxacin has been used to treat severe multiple resistant gram negative bacilli infection in twenty-one adult patients at our hospital, eighteen of whom were infected with *K. pneumoniae*. The overall clinical improvement and bacteriologic eradication were 85 and 90 percent, respectively (18). In the same period, imipenem-cilastatin has been used to treat severe multiresistant *Klebsiella pneumoniae* infections in nine pediatric patients. Seven of the nine had clinical improvement and 8/9 had bacteriological eradication after 48-72 hours of therapy (19).

Since the MICs of amoxicillin-clavulanic acid were variable and most of the strains were resistant to aztreonam, these drugs should be used in severe multiple resistant *K. pneumoniae* infection only after the results of susceptibility tests are known.

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