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A comparative study of the in-vitro activity of Cefepime and other cephalosporins

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Abstract

Cefepime is a new cephalosporin antibiotic which is highly active against both Gram-positive and Gram-negative organisms. The purpose of this study was to establish the *in-vitro* activity of cefepime and three other cephalosporins against recent clinical isolates from patients at the General Hospital Kuala Lumpur. A total of 334 strains comprising Enterobacteriaceae, non-fermentative Gram-negative bacilli and *Staphylococcus aureus* were tested for their sensitivity to cefepime, cefotaxime, ceftriaxone and ceftazidime. Minimum inhibitory concentrations of the antibiotics were established using an agar dilution method. With the exception of some strains of *Flavobacterium meningosepticum, Xanthomonas maltophilia* and other non-fermentative Gram-negative bacilli, cefepime was found to be active against a wide range of Gram-negative organisms. Cefepime was as or more active than the other cephalosporins against *Acinetobacter,* Enterobacteriaceae and methicillin-sensitive *Staphylococcus aureus.* Strains of *Klebsiella* and *Salmonella* that were resistant to the third generation cephalosporins were sensitive to cefepime. Cefepime could be a valuable alternative for the treatment of nosocomial infections due to multiply resistant organisms.

Key words: Cefepime, cephalosporin.

INTRODUCTION

Cefepime is a a new semi-synthetic cephalosporin which bears a quarternary N-methyl pyrollidine side-chain at the 3 position of an aminothiazole cephalosporin (Fig. l).' Cefepime has been shown to possess high *in-vitro* activity against a wide range of Gram-negative organisms as well as staphylococci.[2,3] The purpose of this study was to assess the *in-vitro* activity of cefepime against clinical isolates obtained from the General Hospital Kuala Lumpur as well as to compare its activity with three other currently used cephalosporins, namely cefotaxime, ceftriaxone and ceftazidime.

MATERIALS AND METHODS

A total of 334 clinical isolates comprising Enterobacteriaceae, *Acinetobacter, Pseudomonas aeruginosa, Xanthomonas maltophilia,* other non-fermentative Gram-negative bacilli and *Staphylococcus aureus* were obtained from the General Hospital Kuala Lumpur between April to September 1992. Repeated isolates from the same patient were excluded but no attempts were made to type the strains; thus the possibility of the same strain from different patients being tested cannot be excluded. The routine antibiograms were not used to try to differentiate between strains since only a limited number of

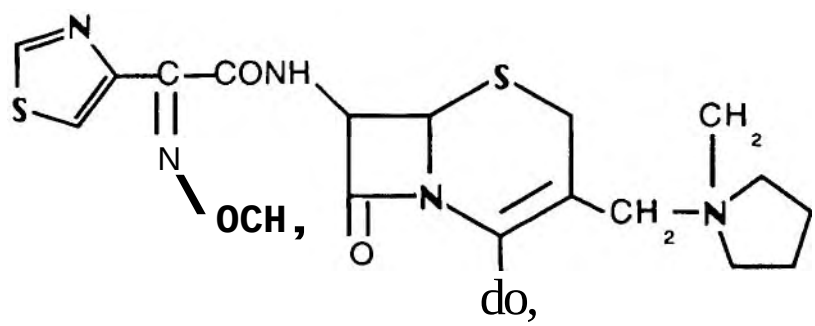

FIG. 1: Chemical structure of cefepime (7 a – (2–Aminothiazol–4–y1) – a – (z) – methoxyiminoacetamido)–3–(l–methylpyrollidinio) methy–3–cephem–4–carboxylate.

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antibiotics were tested for. The *Flavobacterium meningosepticum* isolates were from the laboratory's collection and were strains isolated from patients over the last 12 years. The Enterobacteriaceae strains were identified by routine biochemical tests incuding colonial morphology, the IMViC tests, urease, motility and a short set of sugars. The non-fermenters were identified using the API 20NE (API System S.A., Montalieu Vercieu, France). The numbers of each species or genus tested are shown in Table 1. An agar dilution method was used to determine the minimum inhibitory concentrations of these isolates to four cephalos-

TABLE 1: *In-vitro* activity of four cephalosporins against 334 clinical isolates

Organism (no. of strains)	Antibiotic	MIC_{50}	MIC_{90}	Range
E. coli (40 strains)	Cefepime	0.03	0.5	0.015-2.0
	Cefotaxime	0.06	0.12	0.03-16.0
	Ceftriaxone	0.06	0.12	0.03-8.0
	Ceftazidime	0.25	1.0	0.12-128.0
Klebsiella sp (40 strains)	Cefepime	0.015	2.0	0.015-16.0
	Cefotaxime	0.06	16.0	0.03-64.0
	Ceftriaxone	0.06	16.0	0.03-128.0
	Ceftazidime	0.25	256.0	0.12->256.0
Enterobacter sp (37 strains)	Cefepime	0.06	4.0	0.015-64.0
	Cefotaxime	0.25	16.0	0.06->256.0
	Ceftriaxone	0.12	16.00	0.015->256.0
	Ceftazidime	0.5	8.0	0.25->256.0
Proteus sp (40 strains)	Cefepime	0.06	0.25	0.015-4.0
	Cefotaxime	0.03	0.25	0.015-128.0
	Ceftriaxone	0.015	0.5	0.015-256.0
	Ceftazidime	0.06	0.25	0.015-16.0
Salmonella sp (40 strains)	Cefepime	0.06	4.0	0.03-16.0
	Cefotaxime	0.25	32.0	0.06-64.0
	Ceftriaxone	0.12	16.0	0.06-128.0
	Ceftazidime	0.5	16.0	0.25-256.0
P. aeruginosa (40 strains)	Cefepime	4.0	8.0	0.25-16.0
	Cefotaxime	16.0	64.0	0.5-128.0
	Ceftriaxone	16.0	128.0	1.0-256.0
	Ceftazidime	2.0	4.0	1.0-8.0
X. maltophilia (10 strains)	Cefepime	32.0	128.0	1.0-128.0
	Cefotaxime	128.0	>256.0	8.0->256.0
	Ceftnaxone	256.0	>256.0	4.0->256.0
	Ceftazidime	16.0	32.0	2.0-64.0
A. calcoaceticus (40 strains)	Cefepime	2.0	16.0	0.03-128.0
	Cefotaxime	8.0	64.0	0.12->256.0
	Ceftnaxone	8.0	64.0	0.12->256.0
	Ceftazidime	4.0	16.0	0.25->256.0
F. meningosepticum (12 strains)	Cefepime	8.0	>256.0	0.03->256.0
	Cefotaxime	64.0	>256.0	0.015->256.0
	Ceftriaxone	64.0	>256.0	0.03->256.0
	Ceftazidime	32.0	>256.0	0.12-256.0
Methicillin-sensitive *S. aureus* (22 strains)	Cefepime	2.0	2.0	1.0-2.0
	Cefotaxime	2.0	2.0	1.0-2.0
	Ceftriaxone	4.0	8.0	1.0-16.0
	Ceftazidime	16.0	16.0	8.0-16.0
Methicillin-resistant *S. aureus* (18 strains)	Cefepime	256.0	256.0	–
	Cefotaxime	>256.0	>256.0	64.0->256.0
	Ceftriaxone	256.0	>256.0	256.0->256.0
	Ceftazidime	256.0	>256.0	128.0->256.0

porins, namely, cefepime, cefotaxime, ceftriaxone and ceftazidime. The antibiotic powders were gifts from the respective manufacturers, namely, Bristol-Myers Squibb (cefepime, potency 825 mcg/mg). Roche (ceftriaxone, potency 831 mcg/mg), Glaxo (ceftazidime, therapeutic injectable preparation) and Hoechst (cefotaxime, therapeutic injectable preparation). The test medium used was Diagnostic Sensitivity Test Agar (Oxoid) for all strains except for ***P. aeruginosa*** where Mueller-Hinton agar (BBL) was used. Overnight broth cultures of the test organisms were diluted a hundred-fold to serve as the inocula and plates were inoculated using a Denley multipoint inoculator. Each inoculating pin delivered approximately 1.5 microlitres of the inoculum or approximately 10^4 colony-forming units. The control organisms used were ***E. coli*** NCTC 10418, ***P. aeruginosa*** NCTC 10662 and ***S. aureus*** NCTC 6571. After inoculation the plates were incubated at 37°C for 18 hours before being read. The minimum inhibitory concentration (MTC) was defined as the concentration of antibiotic that inhibited all visible growth on the plate.

RESULTS

The results were expressed as the MIC range. MIC, and MIC_{90} (Table 1). The MIC_{50} and MIC, are the concentrations of the antibiotic that inhibited 50% and 90% of the strains tested respectively. Cefepime was the most active cephalosporin against *Klebsiella* sp, ***Enterohacter*** sp and ***Salmonella*** sp and was as active as the other cephalosporins against ***E. coli*** and ***Proteus sp***. Ceftazidime was the most active agent against ***P. aeruginosa*** and *X*. ***maltophilia*** followed by cefepime. Cefepime was almost four times as active as the other cephalosporins against ***A. calcoaceticus.*** The activity of the cephalosporins against F. *meningosepticum* was variable with MICs ranging from as low as 0.015 mg/l to >256 mg/l. Cefepime also had the highest activity against methicillin-sensitive S. ***aureus.*** The methicillin-resistant ***S. aureus*** strains were ***re***sistant to all the cephalosporins.

Fig. 2 shows the percentage of the strains of selected organisms with MICs of less than 32 mg/l and could therefore be deemed sensitive. All strains of ***E. coli, Klebsiella*** sp, ***Salmonella*** sp, ***Proteus*** sp and ***P. aeruginosa*** were sensitive to cefepime.

DISCUSSION

The ***in-vitro*** activity of a cephalosporin is dependent on three main factors: (i) its ability to

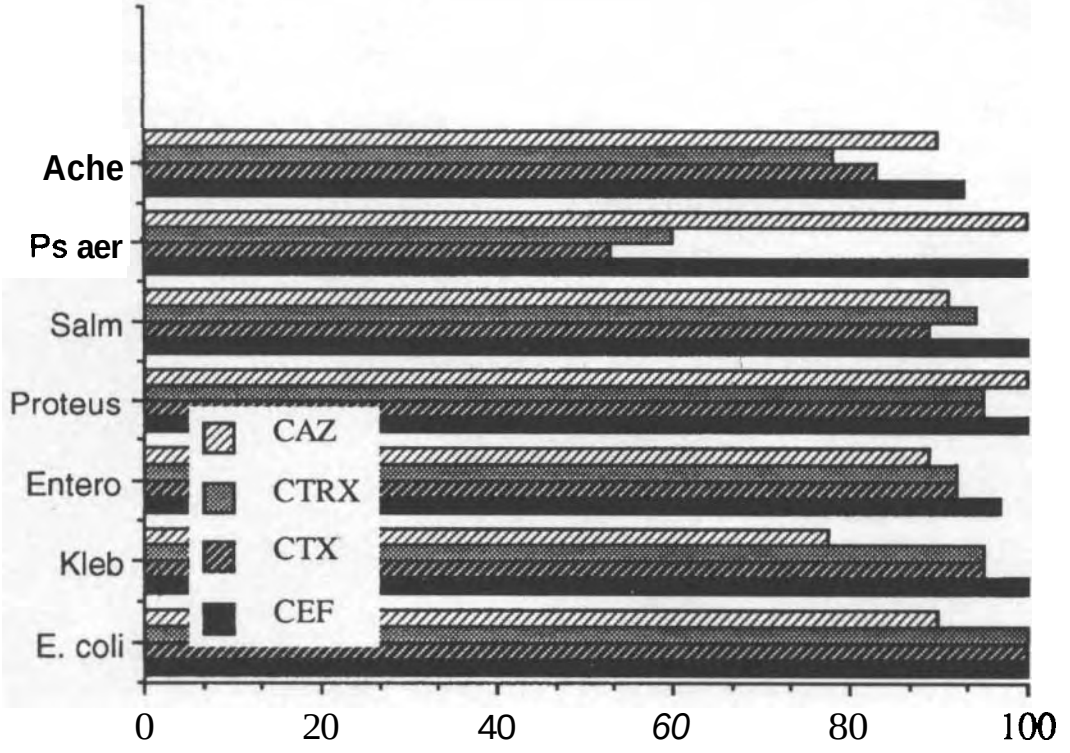

FIG. 2: Percentage susceptability of selected organisms to four cephalosporins. Note: **CAZ** = Ceftazidirne. CTRX = Ceftriaxone, CTX = Cefotaxime, CEF = Cefipime, Acine = Acinetobacter, **Ps** aer = P. aeruginosa. Salm = Salmonella. Entero = Enterobacter, Kleb = Klebsiella.

penetrate the bacterial cell wall (ii) its stability to betalactamases and (iii) its affinity for the penicillin binding proteins (PBPs). Cefepime owes its good antibacterial activity to a combination of all three factors. Cefepime has been shown to have an outer membrane permeation rate in Enterobacter that is 5 to 20 fold higher than ceftriaxone and cefotaxime.[4] Nikaido *et al* concluded that cefepime would penetrate intact bacterial cells 2 to 10 times more rapidly than will anionic compounds like cefotaxime or ceftazidime.[5] Cefepime has also been shown to be more stable towards the extended spectrum betalactamases that are capable of hydrolysing the third generation cephalosporins.[6] Cefepime has been shown to display some advantages in PBP binding for PBP 2 and PBP 3 when compared to cefpirome, another new cephalsporin.[7]

Although many studies of the *in vitro* activity of cefepime have been published in the United States and Europe, we believe this to be the first report of its activity on strains isolated in Malaysia. The *in-vitro* activity of cefepime against organisms isolated in our hospital were generally not very different from those that have already been reported from the United States and Europe but the MIC, (2.0 mg/l) for our isolates of *Klebsiella* sp was however much higher.[2,3] This was probably due to the presence of an endemic multiply resistant strain in our hospital which is resistant to the aminoglycosides as well as the third generation cephalosporins. The mechanism of resistance in this *Klebsiella* strain is unclear but preliminary studies suggest it is due in part to the production of a plasmid-mediated extended spectrum bectalactamase.[8] Nonetheless the MICs of these strains of *Klebsiella* sp to cefepime remained at 16 mg/1 or less (MIC, = 2.0 mg/l). Methicillin-resistant S. *aureus*, as expected, were resistant to all cephalosporins tested. The MICs of our methicillin-resistant strains were noted to be higher than that reported elsewhere.[2,3,9] Cefepime also showed very good *in-vitro* activity against *A. calcoaceticus* which is increasingly being isolated as a nosocomial pathogen in our hospital. The activity of cefepime against F. *meningosepticum* was variable ranging from 0.015 to >256 mg/l. Since there are only a very limited number of antibiotics that are effective in the treatment of *Flavobacterium* infection it may be worthwhile including cefepime when testing for antibiotic sensitivities for such infections. However its clinical efficacy in these situations needs to be properly assessed.

Cefepime has been shown to possess good *in-vitro* activity against many clinical isolates in our hospital. Since multiply resistant Gram-negative bacilli have become increasingly common in our hospital in recent years, cefepime would be a welcome alternative in the treatment of infections caused by these organisms.

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