

# *In vitro* Activity of Cefepime, an Extended-spectrum Parenteral Cephalosporin in Comparison with other Cephalosporins\*

Surapee Pruksachatvuthi, M.Sc.\*\*

Nalinee Aswapokee, M.D., M.M.Sc.\*\*

Busaba Charoensook, Cert (Med Tech).\*\*\*

## Abstract

Cefepime, an extended spectrum cephalosporin, was tested *in vitro* against bacterial isolates in a Southeast-Asian country where prevalence of bacterial resistance is high. Cefepime had excellent activity, against Streptococci and Enterobacteriaceae. *E. coli*, *K. pneumoniae*, *P. mirabilis* were highly susceptible with the MIC<sub>90</sub> of 0.125-0.5 mg/L. *Enterobacter* sp., the cephalosporinase producer, was also susceptible (MIC<sub>90</sub> of 2 mg/L). *P. aeruginosa* was moderately susceptible (MIC<sub>90</sub> of 16 mg/L), while *A. anitratus* was marginally susceptible (MIC<sub>90</sub> of 32 mg/L). Among gram-positive bacteria, *S. aureus* was susceptible (MIC<sub>90</sub> of 4 mg/L), *Streptococcus* sp. was highly susceptible (MIC<sub>90</sub> of 0.1-0.5 mg/L). However *Enterococcus* sp. was resistant to the agent (MIC<sub>90</sub> of > 32 mg/L). When compared to cefotaxime, ceftriaxone and ceftazidime, cefepime was more active against Enterobacteriaceae especially *Enterobacter* sp., which was resistant to other agents. Cefepime was less active than ceftazidime only for *P. aeruginosa*. Cefepime was as active as cefotaxime for *S. aureus* and was more active than ceftazidime. This result indicated that cefepime had an extended-spectrum against many important gram-positive and gram-negative bacteria including those producing cephalosporinases. Cefepime had broader spectrum than other third generation cephalosporins. The susceptibility pattern of cefepime for local isolates in Thailand did not differ from those reported from Western countries. (*J Infect Dis Antimicrob Agents* 1994; 11:103-6.)

**Key word :** Cefepime

## เรื่องย่อ

ความไวในหลอดทดลองของ cefepime, เซฟาโลสปอรินรุ่นสุดท้าย, เปรียบเทียบกับเซฟาโลสปอรินตัวอื่น

สุรณี พฤษชาติวุฒิ, วท.ม.\*\* นลินี อัครโกที, พ.บ.\*\* บุษบา เจริญสุข, ปกศ\*\*\* (จุฬาลงกรณ์มหาวิทยาลัย)

\*\*ภาควิชาอายุรศาสตร์, \*\*\*ภาควิชาเวชศาสตร์ป้องกันและสังคม คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล

Cefepime เป็นเซฟาโลสปอรินรุ่นสุดท้ายชนิดฉีดที่มีฤทธิ์ต่อเชื้อแบคทีเรียแกรมลบ โดยเฉพาะที่ผลิตเอ็นซัยม์ chromosomal cephalosporinase และขณะเดียวกันยังคงมีฤทธิ์ต่อเชื้อแบคทีเรียแกรมบวกอยู่. คณะผู้ศึกษาได้ทดสอบความไวในหลอดทดลองของยาต่อเชื้อแบคทีเรียที่สำคัญทางคลินิก จำนวน 730 ตัว โดยเปรียบเทียบกับยาอื่นคือ ceftazidime, ceftriaxone และ cefotaxime ด้วยวิธี agar dilution มาตรฐาน. พบว่า

Reprint request : Associate Professor Nalinee Aswapokee, M.D., Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

\*Presented at the 3rd Western Pacific Congress on Chemotherapy and Infectious Diseases, December 6-9, 1992, Bali, Indonesia.

\*\*Departments of Medicine, and \*\*\*Preventive and Social Medicine Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

Received for publication : April 2, 1994

cefepime มีฤทธิ์ดีมากที่สุดต่อเชื้อกลุ่ม Enterobacteriaceae. เชื้อ *E. coli*, *K. pneumoniae*, *P. mirabilis* และ *Salmonella* มี  $MIC_{90} \leq 0.5$  มก/มล. *Enterobacter* sp. ซึ่งมักคือต่อเซฟาโลสปอรินรุ่นที่ 3 มี  $MIC_{90}$  เป็นเพียง 2 มก/มล. เชื้อ *P. aeruginosa* ไวต่อยานี้ด้วย. ส่วน *A. anitratus* ไวปานกลางถึงคือต่อยา. สำหรับเชื้อแบคทีเรียแกรมบวก cefepime มีฤทธิ์ต่อ *S. aureus* และ *S. pyogenes*. ส่วน *Enterococcus* sp. ไม่ไวต่อยา เช่นเดียวกับเซฟาโลสปอรินตัวอื่น. เมื่อเปรียบเทียบกับยาอื่นพบว่า cefepime มีฤทธิ์ต่อ Enterobacteriaceae ใกล้เคียงหรือดีกว่าเล็กน้อย. แต่ cefepime เป็นยาตัวเดียวที่มีฤทธิ์ต่อ *Enterobacter* sp. และเป็นยาที่มีระดับ MIC ต่ำสุดต่อ *A. anitratus*. Ceftazidime เป็นยาที่มีฤทธิ์ดีที่สุดต่อเชื้อ *P. aeruginosa* และมีฤทธิ์ด้อยที่สุดต่อเชื้อ *S. aureus*. ไม่พบว่าแบบแผนความไวดังกล่าวแล้วต่างไปจากที่มีรายงานในต่างประเทศ. (วารสารโรคติดเชื้อและยาต้านจุลชีพ 2537 ; 11 : 103-6.)

Cefepime (BMY-28142), a new methoxyimino cephalosporin, exerts good activity against both gram-positive and gram-negative bacteria (1,2). This agent is, therefore, classified as an extended spectrum cephalosporin. The structural modification at position 3 as having a quarternized ammonium group (Fig. 1) renders this compound a zwitterionic property which enhances entry through outer membrane protein of gram-negative bacilli (3). This property was proposed to be one of the major determinant of the activity of this compound against bacteria hyperproducing cephalosporinase (4). As there is increase in prevalence of infections caused by mutants with cephalosporinase hyperproduction, agents such as cefepime, cefpirome and other extended-spectrum cephalosporins would be promising agents for treating those infections, since there was no such cephalosporins available in clinical use at the present. We undertook susceptibility testing of cefepime against local bacterial isolates in Bangkok, Thailand, in comparison to third generation cephalosporins.

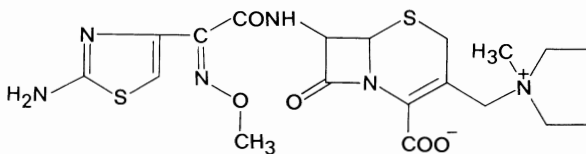


Figure 1. Structure of cefepime.

## MATERIALS AND METHODS

### Antimicrobial agent

Cefepime was provided by Bristol Myer Squibb, U.S.A. The compound had a potency of 870 mcg/mg of free acid and was processed according to the

manufacturer's direction. Ceftazidime, ceftriaxone and cefotaxime were generous gifts from Glaxo, Roche and Hoechst AG, respectively.

### Bacteria

A total of 730 gram-positive and gram-negative bacteria were obtained from patients hospitalized at Siriraj Hospital, Bangkok, Thailand. These were recent isolates and were obtained singly either as community-acquired or nosocomial in origins.

### Susceptibility testing

Susceptibility testing was performed by standard agar dilution technic using Mueller-Hinton agar (BBL) (5). The final inocula of approximately  $10^5$  cfu/ml were used. These were inoculated onto agar plates using a replicator. These were then incubated at  $35^\circ\text{C}$  for 18 hours. The minimum inhibitory concentrations ( $MIC_5$ ) were the concentrations completely inhibited visible growth. Control strains of *S. aureus* ATCC 25923, *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 were used.

## RESULTS

Cefepime had excellent activity against most Enterobacteriaceae with the  $MIC_{90}$  of  $\leq 2$  mg/L. *E. coli*, *K. pneumoniae*, *P. mirabilis* and *Salmonella* sp. were highly susceptible ( $MIC_{90}$  of 0.062-0.5 mg/L). *Enterobacter* sp. was very susceptible ( $MIC_{90}$  of 2 mg/L). *P. aeruginosa* and *A. anitratus* were, however, only moderately susceptible. Among gram-positive species, *S. aureus* and *S. pyogenes* were susceptible while *Enterococcus* sp. were resistant.

Comparing to third generation cephalosporins namely ceftazidime, ceftriaxone and cefotaxime, cefepime had similar activity against Enterobacteriaceae except

for *Enterobacter* sp., against which cefepime was the only agent which was active for this genus, while all the comparative agents were not active. All agents had similar activities against *A. anitratus*, while ceftazidime was the most active agent for *P. aeruginosa*. Cefepime and cefotaxime were the most active compounds against *S. aureus* where as ceftazidime was the least active agent. All agents were very active against *S. pyogenes* and all agents were not active for *Enterococcus* sp. Table 1 and 2 summarize the activity of cefepime, comparing to third generation cephalosporins against gram-negative and gram-positive bacteria, respectively.

## DISCUSSION

In this study, cefepime shows good to excellent activities against Enterobacteriaceae and *P. aeruginosa*. This agent was also active against *S. aureus* which was not the feature of antipseudomonal third generation cephalosporins. The pattern of local bacterial susceptibility to cefepime does not differ from other studies (1,2,6-8). Of note, only cefepime exerted good activity against *Enterobacter* sp., the genera known to produce cephalosporinase. Phelp et al found that the activity of this compound against this species was correlated with

**Table 1. Susceptibility of gram-negative bacteria to cefepime in comparison with other cephalosporins.**

Bacteria (No. of isolates)	Antimicrobial Agents	MIC (mg/L)		
		Range	50%	90%
<i>E. coli</i> (100)	Cefepime	0.004-1	0.062	0.125
	Ceftazidime	0.062-0.5	0.25	0.25
	Ceftriaxone	0.004-0.5	0.062	0.125
	Cefotaxime	0.031-0.5	0.062	0.125
<i>K. pneumoniae</i> (100)	Cefepime	0.031-4	0.031	0.5
	Ceftazidime	0.062-> 32	0.25	4
	Ceftriaxone	0.031-> 32	0.062	2
	Cefotaxime	0.031-> 32	0.062	2
<i>Enterobacter</i> sp. (80)	Cefepime	0.016-8	0.125	2
	Ceftazidime	0.062-> 32	0.25	> 32
	Ceftriaxone	0.031-> 32	0.25	> 32
	Cefotaxime	0.062-> 32	0.5	32
<i>P. mirabilis</i>	Cefepime	0.031-0.062	0.062	0.062
	Ceftazidime	0.062-0.25	0.125	0.125
	Ceftriaxone	0.002-0.031	0.008	0.016
	Cefotaxime	0.016-0.125	0.031	0.031
<i>Salmonella</i> sp. (40)	Cefepime	0.031-0.25	0.062	0.125
	Ceftazidime	0.125-1	0.25	0.5
	Ceftriaxone	0.062-0.25	0.062	0.125
	Cefotaxime	0.062-0.5	0.125	0.25
<i>P. aeruginosa</i> (100)	Cefepime	0.25-> 32	2	16
	Ceftazidime	0.5 -> 32	2	4
	Ceftriaxone	0.25-> 32	32	> 32
	Cefotaxime	0.5 -> 32	32	> 32
<i>A. anitratus</i>	Cefepime	1-32	4	32
	Ceftazidime	1-> 32	4	> 32
	Ceftriaxone	2-> 32	32	> 32
	Cefotaxime	2-> 32	16	> 32

**Table 2. Susceptibility of gram-positive cocci to cefepime in comparison with other cephalosporins.**

Bacteria (No. of isolates)	Antimicrobial Agents	MIC (mg/L)		
		Range	50%	90%
<i>S. aureus</i> (80) (methicillin susceptible)	Cefepime	0.25-8	4	4
	Ceftazidime	4-16	16	16
	Ceftriaxone	0.25-16	8	8
	Cefotaxime	0.5-4	4	4
<i>S. pyogenes</i> (40)	Cefepime	0.016-0.062	0.016	0.031
	Ceftazidime	0.031-0.25	0.125	0.25
	Ceftriaxone	0.004-0.062	0.031	0.062
	Cefotaxime	0.016-0.031	0.016	0.031
<i>Enterococcus</i> sp. (100)	Cefepime	16- > 32	32	> 32
	Ceftazidime	32- > 32	> 32	> 32
	Ceftriaxone	16- > 32	> 32	> 32
	Cefotaxime	4- > 32	> 32	> 32

its low affinity for chromosomally encoded betalactamases (9). Hiraoka et al, moreover, found that the calculated hydrolysis rate of cefepime at a very low concentration (0.1  $\mu$ M) of cephalosporinases was smaller than those of cefotaxime and ceftazidime (10). Apart from being a zwitterionic compound which enhances entry into the bacterial periplasmic space (3), these findings may also be the explanations of the susceptibility to cefepime in the presence of cephalosporinase in periplasmic space of some bacterial species such as *Enterobacter* sp. and *Citrobacter* sp. while resistance occurred with other compounds which have high affinity to betalactamase enzymes and undergo faster rate of hydrolysis at a very low concentration (9,10). The local susceptibility pattern to cefepime that does not differ from other parts of the world may be an indirect evidence that the epidemiology of betalactamase production by several bacterial species is not much different.

#### References

1. Tomatzu K, Ando S, Masuyoshi S, et al. Antibacterial activity of BMY-28142, a novel broad spectrum cephalosporin. *J Antibiot* 1986;39:1584-91.
2. Fuchs PC, Jones RN, Barry AL, Thornsberry C. Evaluation of the *in vitro* activity of BMY-28142, a new broad spectrum cephalosporin. *Antimicrob Agents Chemother* 1985;27:679-82.
3. Naito T, Aburaki S, Kamachi H, et al. Synthesis and structure-activity relationship of a new series of cephalosporins, BMY-28142 and related compounds. *J Antibiot* 1986;39:1092-107.
4. Hancock REW, Bellido F. Factors involved in the enhanced efficacy against gram-negative bacteria of fourth generation cephalosporins. *J Antimicrob Chemother* 1992;29(Suppl A):1-6.
5. National Committee for clinical Laboratory Standards. Standard methods for dilution antimicrobial susceptibility tests for bacteria which grow aerobically. Tentative standard, M7-T. National Committee for Clinical Laboratory Standards, Villanova, Pa, 1983.
6. Kessler RE, Bies M, Buck RE, et al. Comparison of a new cephalosporin, BMY 28142, with other broad spectrum  $\beta$ -lactam antibiotics. *Antimicrob Agents Chemother* 1985;27:207-16.
7. Tsuji A, Maniatis A, Bertram MA, Young LS. *In vitro* activity of BMY-28142 in comparison with those of other  $\beta$ -lactam antimicrobial agents. *Antimicrob Agents Chemother* 1985;27:515-9.
8. Vuye A, Pijck J. *In vitro* antibacterial activity of BMY-28142, a new extended-spectrum cephalosporin. *Antimicrob Agents Chemother* 1985;27:574-7.
9. Phelps DJ, Carlton DD, Farrell CA, Kessler RE. Affinity of cephalosporins for betalactamases as a factor in antibacterial efficacy. *Antimicrob Agents Chemother* 1986;845-8.
10. Hiraoka M, Masuyoshi S, Mitsunashi S, Tomatsu K, Inoue M. Cephalosporinase interactions and antimicrobial activity of BMY-28142, ceftazidime and cefotaxime, *J Antibiot* 1988;41:86-93.