

In Vitro Activity of Cefetamet, A New Beta-lactamase-stable Oral Cephalosporin

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Abstract

Cefetamet, a biologically active form of cefetamet pivoxyl, an orally-administered, beta-lactamase stable cephalosporin was tested against 882 recent clinical bacterial isolates obtained from patients hospitalized at Siriraj Hospital, Mahidol University, and from the National Institute of Health, Nontaburi, Thailand. Cefetamet was very active against most Enterobacteriaceae, with the majority of strains inhibited at the MIC of ≤ 2 mg/L. The drug exerted moderate activity to *Enterobacter*. Among Gram-positive bacteria, only non-enterococcal *Streptococcus* responded well to the very low MICs (≤ 0.05 mg/L). Other bacteria including *Staphylococcus*, *Enterococcus*, *M. morgani*, *A. anitratus* and *P. aeruginosa* were resistant to cefetamet. Cefetamet was affected by high inoculum of certain Gram-negative bacilli and there was no MIC/MBC discrepancy of the agent. Cefetamet might prove efficacious in treating infections caused by susceptible organisms, based on this *in vitro* study, either as an initial or follow-up regimens. The availability as an oral form might improve patients' compliance, provide a variety of choice of orally-administered anti-Gram-negative agent and reserving the use of the more potent agents, fluoroquinolone compound for the otherwise more serious infections. The inoculum effect of the agents pointed towards the need for reduction of the organisms by draining the infected tissue in clinical setting. The presumed bactericidal activity of the agent suggested that the agent might be used safely in immunosuppressed host.

เรื่องย่อ

ฤทธิ์ครอบคลุมเชื้อในหลอดทดลองของ cefetamet, เซฟาโลสปอรินส์รูปกินที่ทนทานต่อเอนไซม์เบต้าแลคตาเมส

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วารสารโรคติดเชื้อและยาต้านจุลชีพ 2533; 7:1-3.

ยา cefetamet เป็นตัวยาพื้นฐานทางชีววิทยาที่ออกฤทธิ์ของยา cefetamet pivoxyl ซึ่งทำเป็นยา รูปกิน. ยา cefetamet มีฤทธิ์ต้านเอนไซม์เบต้าแลคตาเมส, จึงเป็นยา รูปกินที่ใช้กับเชื้อแกรมลบได้หลายชนิด. ได้ทดสอบความไวของเชื้อแบคทีเรียที่แยกได้จากผู้ป่วยที่มารับการรักษาในโรงพยาบาลศิริราช และจากสถาบันวิจัยวิทยาศาสตร์สาธารณสุขแห่งชาติ จำนวน 882 สายพันธุ์, พบว่า cefetamet มีฤทธิ์ดีมากที่สุดต่อเชื้อ *Streptococcus* ที่ไม่ใช่ *Enterococcus* (ระดับ MIC₉₀ ต่ำกว่า 0.05 มก/ลิตร), Enterobacteriaceae (ระดับ MIC₉₀ ไม่เกิน 2 มก/ลิตร). ยานี้มีฤทธิ์ปานกลางสำหรับเชื้อ *Enterobacter*. เชื้อ *Staphylococcus aureus*, *M. morgani*, *A. anitratus* และ *P. aeruginosa* ตี้อย่างนี้. จำนวนเชื้อที่มากมีผลต่อฤทธิ์ของยา และยามีฤทธิ์ฆ่าเชื้อได้ (ผล MIC/MBC ไม่ต่างกัน). จากการทดสอบนี้เข้าใจว่ายา cefetamet น่าจะนำมาใช้ประโยชน์ทางคลินิกได้ในการรักษาผู้ป่วยที่ติดเชื้อที่ไวต่อยา, โดยมีการเพิ่มการยอมรับการรักษามากขึ้นเนื่องจากยาเป็นยา รูปกิน, และอาจใช้ได้ทั้งเป็นยาเริ่มต้นในการรักษาหรือใช้ตามหลังยาฉีด. แต่การนำยามาใช้ในรายที่อวัยวะติดเชื้อมีเชื้อมาก, ควรมีการระบายเชื้อในหนองออกพร้อมด้วย เนื่องจากจำนวนเชื้อที่มากมีผลทำให้ฤทธิ์ของยาลดลง. ยานี้ น่าจะใช้ได้อย่างปลอดภัยในผู้ป่วยภูมิคุ้มกันต่ำ เนื่องจากยาอาจมีฤทธิ์เป็น bactericidal.

Cefetamet is a biologically active form of cefetamet pivoxyl, a new orally administered, beta-lactamase stable cephalosporin. This compound, with a 7-aminothiazolyl-methoxyimino-acetamido-3-desacetyl structure (Figure 1), is resistant to destruction by TEM and SHV-1 plasmid beta-lactamases and also was stable to attack by the Richmond-Sykes type 1a beta-lactamase¹. The agent, however, had great affinity for the *E. cloacae* and *P. aeruginosa* beta-lactamases, but was not an effective inhibitor of the TEM-1, SHV-1, K-1 and type V beta-lactamases. It was, therefore, active for Enterobacteriaceae, but not for *P. aeruginosa*. It also was not active for Gram-positive coccal strains except for non-enterococcal *Streptococcus* species. This compound, however, with its structure similar to cefotaxime in terms of the β -acyl side chain, and with its prokinetic form, could be clinically applicable in many common infectious disease, either as a primary or a follow-up treatment regimens. We performed the *in vitro* activity of cefetamet with our clinically important bacterial isolates, to determine the local susceptibility pattern.

MATERIALS AND METHODS

Antimicrobial agent Standard powder of cefetamet (Ro 15-8074) was provided by F. Hoffman-La Roche Ltd., Basle. The compound had a potency of 909 mcg of free acid and was processed as directed by the manufacturer.

Microorganisms A total of 882 Gram-positive and Gram-negative bacteria was obtained from patients hospitalized at Siriraj Hospital, Mahidol University, Bangkok, Thailand. Salmonella strains were obtained from the National Institute of Health, Nontaburi, Thailand. These were single isolates of either community or nosocomial origins.

Susceptibility studies Susceptibility testing was performed by standard agar dilution technic² using Mueller-Hinton agar (Difco). For *Streptococcus* species, 5% blood was added in agar. Final inocula of 10^5 CFU, were applied to plates using a spot replicator. These were incubated at 35°C for 18 hours and were examined for minimal inhibitory concentrations (MICs).

Six isolates were tested using standard macrodilution broth technic³. Minimal bactericidal concentrations (MBCs) were determined by sampling of 0.01 ml of the antibiotic- 10^5 CFU inocula mixtures and plating on to antibiotic-free agar.

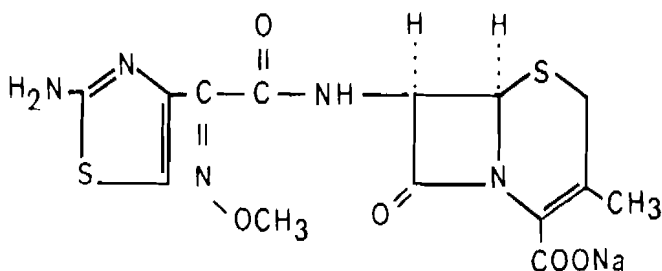


Fig. 1 Structure of cefetamet

The MBCs were defined as the 99.9% reduction of the initial inoculum. Inoculum effects were determined using the sizes of 10^3 , 10^5 and 10^7 CFU/ml.

RESULTS

Table 1 summarises the percentage of susceptibility of 882 bacterial isolates to cefetamet. *Staphylococcus aureus* and *Enterococcus* spp. were resistant to cefetamet with the MIC₉₀ of 64 and > 128 mg/L. *Streptococcus pyogenes* was highly susceptible, with the MIC₉₀ of 0.05 mg/L. Enterobacteriaceae including *E. coli*, *K. pneumoniae*, *Salmonella* group D and other groups, *P. mirabilis* were inhibited at the MIC₉₀ of 2 mg/L or less. *Enterobacter* spp. was moderately sensitive, with the MIC₅₀ of 2 mg/L, but with the MIC₉₀ of \geq 128 mg/L. *M. morgani*, *A. anitratus* and *P. aeruginosa* were all resistant.

Cefetamet was affected by the high inoculum, with the

Table 1 Susceptibility of bacterial isolates to cefetamet

Bacteria (No. of isolates)	MIC (mg/L)		
	Range	50%	90%
<i>S. aureus</i> (76) (methicillin susceptible)	32 - 128	64	128
<i>S. pyogenes</i> (44)	\leq 0.01 - 0.05	0.02	0.05
<i>Enterococcus</i> (92)	4 - \geq 128	\geq 128	\geq 128
<i>E. coli</i> (104)	0.05 - 8	0.5	1
<i>K. pneumoniae</i> (100)	0.1 - 8	0.25	1
<i>Salmonella</i> group D (50)	0.25 - 1	0.5	0.5
<i>Salmonella</i> other than group D(132)	0.25 - 4	1	2
<i>P. mirabilis</i> (50)	0.05 - 32	0.1	1
<i>M. morgani</i> (15)	1 - \geq 128	16	\geq 128
<i>Enterobacter</i> spp. (79)	0.5 - \geq 128	2	\geq 128
<i>A. anitratus</i> (35)	1 - \geq 128	16	\geq 128
<i>P. aeruginosa</i> (105)	\geq 128	\geq 128	\geq 128

Table 2 Inoculum effect to cefetamet

Organisms	MIC (mg/L)		
	10^3	10^5	10^7
<i>E. coli</i> (E 77)	0.1	0.1	0.5
<i>E. coli</i> (E 84)	0.5	0.5	1.0
<i>K. pneumoniae</i> (K 58)	0.2	0.2	8
<i>K. pneumoniae</i> (K 66)	0.1	0.1	16
<i>Enterobacter</i> spp. (En 16)	1	2	\geq 128
<i>Enterobacter</i> spp. (En 19)	2	4	\geq 128

Table 3 MIC and MBC difference of cefetamet

Organisms	MIC (mg/L)	MBC (mg/L)
<i>E. coli</i> (E 77)	0.1	0.2
<i>E. coli</i> (E 84)	0.5	0.5
<i>K. pneumoniae</i> (K 58)	0.2	0.2
<i>K. pneumoniae</i> (K 66)	0.1	0.1
<i>Enterobacter</i> spp. (En 16)	2	2
<i>Enterobacter</i> spp. (En 19)	4	8

increase of the MICs of at least five-fold in *E. coli*, to the maximum of 32-fold in *Enterobacter* spp. (Table 2). The agent appeared to be the bactericidal, with no discrepancy of MICs and MBCs for *E. coli*, *K. pneumoniae* and *Enterobacter* species (Table 3).

DISCUSSION

The susceptibility pattern of our local bacterial isolates to cefetamet was not different from those reported in the United States,^{1,4,5} United Kingdom,⁶ Switzerland,⁷ New Zealand⁸ and Hong Kong⁹. This indicated that the bacterial strains in the areas like those in developing countries where the resistance to antimicrobial agents is claimed to be high is not always true. In this study, the bacterial strains were obtained from patients hospitalized in a tertiary care teaching hospital where antimicrobials were overutilized¹⁰ and the high proportion of resistance was anticipated. It is, therefore, promising that beta-lactamase stable cephalosporin will still be useful in this setting. Moreover, the availability of oral agents active against Enterobacteriaceae other than the fluoroquinolones is preferable in lessening the overutilization of the latter agents. Cefetamet pivoxyl in a single and a multiple oral doses gave a satisfactorily serum levels, either on fasting or with food. The levels of up to 6 mg/L was reported for the single and multiple doses administered in the young and the elderly.^{11,12} This level was well above the MICs of most Enterobacteriaceae and non-enterococcal streptococci. The application of this compound either as a primary drug or a follow-up regimen in treating ambulatory patients infecting with susceptible bacterial isolates is anticipated.

Cefetamet, like other beta-lactam compound was affected by the large inoculum. We randomly selected the strains of *E. coli*, *K. pneumoniae* and *Enterobacter* spp. from pus specimens to test the inoculum effect. This indicated that in the presence of high inoculum in any clinical setting, cefetamet, inspite of its stability to destruction by several plasmid-mediated beta-lactamases, will be inactivated to a certain extent, and the draining of pus is essential in improving the

efficacy of the treatment. The drug appeared to be bactericidal to clinically important Gram-negative bacilli, and should be a useful agent in treating granulocytopenic patients infected by the susceptible strains.

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