An Open Non-Comparative Study of Antibacterial Activity and Efficacy of Cefotiam in Serious Community-Acquired Infections

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Abstract
Antibacterial activity and clinical efficacy of cefotiam were studied in an open, non-comparative study. The MIC₉₀ values of cefotiam for S. aureus, S. pneumoniae and gr. A streptococci were 0.5 mg to 1.0 mg/litre, and for E. coli, Klebsiella, Proteus and Salmonella 0.5 mg to 2 mg/litre. Virtually all isolates of Enterococci, Enterobacter, P. aeruginosa, Acinetobacter and P. pseudomallei were resistant to cefotiam (MIC₉₀ > 256 mg/litre). The overall clinical efficacy of cefotiam was 85% in this study. P. aeruginosa and Acinetobacter were two clinical isolates which were resistant to cefotiam. One patient deteriorated and needed cholecystectomy and T-tube drainage. No serious side-effect was observed. Cefotiam is an effective and safe antimicrobial for empiric therapy of various community-acquired infections.

Despite the substantial improvement in supportive care, severe community-acquired infections remain the major cause of morbidity and mortality in general population as well as patients who need hospitalization. Under this condition early institution of empiric antibiotic therapy has become standard practice for the initial management in such patients. In the past, since the availability of first-generation cephalosporins for clinical use, cephalothin or cefazolin frequently in combination with gentamicin have been used, and death due to penicillin or ampicillin-resistant bacteria has been largely overcome. However due to their relative instability among the
“older” cephalosporins to beta-lactamase produced by various Gram-negative bacilli and their lower affinity for essential PBPs in these bacteria, the causative bacteria in certain septic patients may be relatively insensitive to cefazolin than “newer” cephalosporins. The third generation cephalosporins which are currently available in Thailand are very active against the first generation cepham-resistant Gram-negative bacteria but are usually reserved for therapy of nosocomial infection.

Cefotiam is a cepham antibiotic which is active against a variety of Gram-positive and Gram-negative bacterial pathogens known to cause community-acquired infections. Its higher efficacy against certain bacteria such as Hemophilus, E. coli, Klebsiella and Proteus than the so called “first generation” cephems is an advantage for cefotiam to be used in serious infections due to such micro-organisms. The broad anti-bacterial spectrum is related to the substitution at 3 position of [1-(2-dimethyl-aminoethyl)-1 H-tetrazol-5-yl] thio-methyl group which is so far considered to be the best chemical group substituted at this position for cepham antibiotics. However, owing to the lack of methoxyimino group substituted at the acetamido side-chain, cefotiam is relatively less resistant to beta-lactamase than various “third” generation cephalosporins and is not active against Pseudomonas aeruginosa,

Material and Methods

Common pathogens, recently isolated from hospitalized patients at Siriraj Hospital were tested for their susceptibilities to cefotiam. These included S. aureus, S. pneumoniae, gr. A Streptococci, Enterococci, E. coli, K. pneumoniae, Proteus sp., Salmonella, Enterobacter, P. pseudomallei, P. aeruginosa and Acinetobacter anitratus. An inoculum size of approximately 5x10^5 colony-forming units per milliliter was prepared by diluting an overnight broth culture in Mueller-Hinton broth. Agar dilution method was used to determine the MIC of cefotiam against these bacteria. Cefotiam powder was a kind gift from Takeda Chemical Industries, Ltd. Thailand and was serially diluted in Mueller-Hinton agar ranging between 0.0625-256 mg per litre. The agar plates were incubated at 35°C overnight. The lowest antibiotic concentration resulting in the absence of visible colony was noted as the MIC.

Adult patients suspected of having severe bacterial infections who were admitted to the Medical wards at Siriraj Hospital, Bangkok between December 1986-January 1988 were enrolled in the study. They were eligible for inclusion if sepsis was clinically evident and community-acquired. Foci of infection had to be identified before treatment. Septicemia characterized by fever with chill of sudden onset and less than 10 days duration with evidence of multi-organ involvement was also included in the study. A patient known to be allergic to beta-lactam antibiotics was excluded. Blood and appropriate specimen culture were taken before initiation of antibiotics. Cefotiam (Cerdolan®) was provided by Takeda Chemical Industries, Ltd., Japan in vials containing 1 gm. sterile powder. One gram of cefotiam dissolved in 100 ml. of intravenous fluids was infused over 15 minutes every six or eight hours according to severity of infection and patients' body weight.

Table 1 summarizes the activity of cefotiam against various clinical isolates. Unlike some of the
third-generation cephalosporins, cefotiam showed strong activity against *Staphylococci*, *S. pneumoniae* and gr. *A Streptococci*. These pathogens commonly cause skin and soft tissue infection, community-acquired pneumonia and septicemia. As can be expected for any cephalosporins, *Enterococci* are completely resistant to cefotiam. With regard to the activity against Gram-negative bacteria; *E. coli*, *Klebsiella*, *Salmonella* and *Proteus* were highly sensitive to cefotiam with the MIC$_{90}$ value of 2 mg/l or less. *Enterobacter* exhibited variable susceptibility to cefotiam. *P. aeruginosa*, *P. pseudomallei* and *Acinetobacter anitratus* are consistently resistant to cefotiam.

Table 2 summarizes the type of infections and therapeutic outcome with cefotiam. The treated infections included: 8 cases of pneumonitis, 5 soft tissue infections 3 pyelonephritis, 1 salmonellosis, 1 ascending cholangitis, 1 shigellosis presented with high fever and hypotension and 1 infected bronchiectasis.

The following organisms were isolated from the infectious sites: *S. aureus* (2 cases), *S. pneumoniae* (3 cases), *S. pyogenes* (2 cases), *E. coli* (3 cases), *Klebsiella* (2 cases), *E. coli* and *Klebsiella* (1 case), *Salmonella typhi* (1 case), *Shigella flexneri* (1 case), *P. mirabilis* (1 case), *P. aeruginosa* (1 case), *A. iwoffii* (1 case). Organism could not be isolated in two cases (infected bronchiectasis and ascending cholangitis) In case of ascending cholangitis, it was unfortunate that pus specimen was not sent for anaerobic culture.

Cefotiam was markedly effective in eleven cases. Definite improvement was seen within three days of therapy. Other six cases responded favourably to cefotiam. One case of ascending cholangitis deteriorated in spite of combined treatment with gentamicin. Cefotiam was discontinued in two cases who were unexpectedly infected with *P. aeruginosa* and *A. iwoffii*. The overall clinical efficacy of cefotiam in this study was 85%.

No serious side-effect was observed during cefotiam therapy. Urticaria developed once in one case but probably not due to cefotiam and therapy with cefotiam was continued in this case with uneventful course.

### DISCUSSION

Cefotiam, a semisynthetic cephalosporin, has a broad spectrum of activity against common gram-positive organisms as well as gram-negative aerobic bacilli such as *H. influenzae*, *E. coli*, *Klebsiella*. These bacteria are recognized as common causative agents for community-acquired infections for which first-generation cephalosporin is recommended as a suitable empiric antimicrobial. The in vitro susceptibility study showed that cefotiam also possesses adequate activity against those micro-organisms. Activity of cefotiam

### Table 2 Diagnosis and clinical effectiveness of cefotiam in various severe infections.

<table>
<thead>
<tr>
<th>Type of infection</th>
<th>Number of cases</th>
<th>Cured or improved</th>
<th>Resistant pathogen isolated in</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial pneumonitis</td>
<td>8</td>
<td>6</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Soft tissue infection</td>
<td>5</td>
<td>5</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Acute pyelonephritis</td>
<td>3</td>
<td>3</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Salmonellosis</td>
<td>1</td>
<td>1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Ascending cholangitis</td>
<td>1</td>
<td>–</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Infected bronchiectasis</td>
<td>1</td>
<td>1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Shigellosis*</td>
<td>1</td>
<td>1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>17</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

*Presented with high fever, acute diarrhea and hypotension*
against gram-positive bacteria i.e., Staphylococci, S. pneumoniae and gr. A Streptococci is markedly impressive with the MIC90 for these pathogens at 1 mg/l or less. Therapy with cefotiam in seven patients with various infections due to these pathogens is also effective with rapid recovery. The favorable outcome was attributable in part to cefotiam’s good pharmacokinetic property. For gram-negative aerobic bacilli capable of causing community-acquired infection such as E. coli, Klebsiella, Proteus and Salmonella, cefotiam is also very active with the MIC90 of 2 mg/l or less. Eight patients infected with these pathogens showed good clinical response with cefotiam therapy. Another patient with systemic lupus erythematosus who clinically presented with severe diarrhea and hypotension was started on cefotiam. She definitely improved on second day of therapy. Stool culture was later positive for Shigella flexneri. Micro-organism was unable to isolate in two cases; one with infected bronchiectasis who responded to cefotiam and postural drainage and another with cholangitis who failed to respond to medical treatment alone. The infecting organisms in other two patients are unexpectedly due to P. aeruginosa and Acinetobacter that are known to resist cefotiam and the antimicrobial was changed according to the result of culture and susceptibility test.

Although the causative agents of infected bronchiectasis are commonly anaerobes. The bacteriological etiology can not be identified in this case. The initial presentation was acute pneumonia and it was at the recovery phase that the final accurate diagnosis was reached by typical chest-roentgenogram and history taking about previous clinical course. Gram-stain of the sputum revealed a mixture of bacteria, predominated by gram-negative bacilli. It is possible that the major pathogen in this case may be an enterobacteria which is sensitive to cefotiam. Postural drainage is an additional factor contributed to successful therapy. Since susceptibility of anaerobes to cefotiam was not determined in our study and cefotiam is relatively unstable against attack by beta-lactamases of both plasmid and chromosome found in various gram-negative anaerobic bacteria such as Bacteroides sp., cefotiam is usually not recommended for treatment of anaerobic infection. The failure of cefotiam to treat the case with ascending cholangitis may be explained by type of causative micro-organism which could be anaerobes. Thus cefotiam can not be used for therapy of anaerobic infection unless it is combined with potent anti-anaerobe drugs.

Types of infection successfully treated with cefotiam in this study included acute pneumonitis, soft tissue infection, acute pyelonephritis, Salmonellosis, infected bronchiectasis and shigellosis. The therapeutic failure of ascending cholangitis is due to localized abscess which warranted surgical intervention.

Clinical toxicity was very mild and limited to slight discomfort at the injection site if cefotiam was infused rapidly. In one case, urticaria was reported to develop immediately after the end of intravenous infusion. However, under close observation, it did not occur again in the next occasion when cefotiam was infused slowly in 30 minutes. Laboratory abnormalities were not observed during therapy. Prothrombin time was evaluated before and after cefotiam therapy in two cases and no coagulation defect was detected. No bleeding was observed clinically. Superinfection did not occur in the study even in a patient in whom cefotiam was given as long as three weeks. The overall untoward drug effect due to cefotiam was nearly absent in the study. This is in part due to small sample size and short duration of therapy in majority of cases.

In this study, cefotiam appears to be a relatively safe and highly effective antibiotic for the therapy of infections such as those described herein, and may be appropriate as empiric mono-therapy or in combination with gentamicin in the severely ill patient with an unknown source of community-acquired infection. For the latter, dengue-hemorrhagic fever, scrub typhus, melioidosis, malaria and perhaps salmonellosis should be ruled out before initiation of cefotiam.

Finally, the results of this study should not be extended to patients with absolute neutrophil count of less than 1000 cells/cu. mm. for whom therapy with anti-Pseudomonas aeruginosa antimicrobial may be more appropriate. Patient with presumed bacterial infections which originate during hospitalization should not be treated with cefotiam. Up to present, data are inadequate to support the effectiveness of cefotiam for therapy of non-bacteroides anaerobic infection and bacterial meningitis. Our results do indicate that cefotiam alone or combined with aaminoglycoside such as gentamicin should be suitable for empiric therapy of serious community-acquired infections due to gram-positive and gram-negative bacteria described herein. The drug is safe, effective and should be considered when there is indication to use a first or second-generation cephalosporin.

REFERENCES


