In Vitro Activity and Pharmacokinetics in Patients of Cefamandole, a New Cephalosporin Antibiotic

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Cefamandole nafate, a new cephalosporin for parenteral use, was evaluated in vitro against 231 recent clinical isolates and in 12 patients. Cefamandole had activity equivalent to cefazolin against Staphylococcus aureus, Escherichia coli, and Klebsiella pneumoniae. Cefamandole was more active than cephalothin or cefazolin against Proteus mirabilis. Both cefamandole and cefazolin were as active as cephalothin against S. aureus, were slightly more active against K. pneumoniae, and were considerably more active against E. coli. All strains of indole-positive Proteus sp. were inhibited by 6.3 μg of cefamandole per ml but only 20% were inhibited by 25 μg of cefazolin or cephalothin per ml. Eighty-eight percent of Enterobacter sp. was inhibited by 25 μg of cefamandole per ml, but only 20 and 5% were inhibited by the same concentration of cefazolin and cephalothin, respectively. Peak levels of cefamandole ranged from 6.0 to 110 μg/ml in serum and levels ranged from 440 to 16,800 μg/ml in a 4- to 6-h collection of urine after a 500-mg or 1-g intramuscular dose (6.1 to 17.3 mg/kg) in patients with endogenous creatinine clearances of ≥31 ml/min. These levels were done after the first dose, at mid-therapy, and at the end of therapy. There was no evidence of accumulation with the 500-mg or 1-g dose given every 4 to 6 h. The percentage of the dose excreted in the urine within the first 4 to 6 h after administration of cefamandole was ≥43%. The half-life of cefamandole in serum was 49 to 126 min.

Cefamandole nafate, the sodium salt of the O-formyl ester of cefamandole, 7-O-mandelamido-3-[(1-methyl-1H-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid, is a new cephalosporin antibiotic for parenteral use. The ester undergoes rapid hydrolysis to cefamandole in vivo (J. S. Wold, R. R. Joost, H. R. Black, and K. E. Briscoe, Abstr. 9th Int. Congr. Chemother. M225, 1975). Cefamandole is bactericidal against strains of gram-positive and gram-negative bacteria including Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, and Proteus mirabilis, as are other cephalosporin antibiotics (3, 7, 10). Unlike cephalothin, cefamandole has been reported to be also active against Enterobacter sp. and indole-positive Proteus sp. (3, 7, 10).

The present investigation was undertaken to determine the in vitro antibacterial activity of cefamandole in comparison with cefazolin and cephalothin, and to determine the levels of cefamandole in serum and urine in patients after intramuscular administration.

MATERIALS AND METHODS

In vitro susceptibility tests. The following strains of bacteria were isolated from patients: 49 strains of S. aureus, 50 strains of E. coli, 28 strains of P. mirabilis, 49 strains of K. pneumoniae, 15 strains of indole-positive Proteus species, and 40 strains of Enterobacter species.

The susceptibility of the organisms to cefamandole, cefazolin sodium, and cephalothin sodium was determined by an agar-dilution method in heart infusion agar at pH 7.4. The lithium salt of cefamandole was used in preference to the sodium salt because of its greater stability; both salts are reported to have equal antimicrobial activity (R. B. Kammer, D. A. Preston, and J. R. Turner, 9th Int. Congr. Chemother. M226, 1975). The antibiotics were diluted in twofold steps in heart infusion broth. One milliliter of each dilution of antibiotic was added to 9 ml of molten agar to obtain final antibiotic concentrations of 0.098 to 50 μg/ml. Bacteria were inoculated onto the surface of these plates using the replicating device of Steers et al. (9). The replicator delivered approximately 0.001 ml of a 10^-1 dilution of an overnight culture (10^9 bacteria) of each strain in heart infusion broth. The minimal inhibitory concentration was considered to be the lowest concentration of antibiotic that prevented more than one colony from growing after 24 h of incubation at 37 C. Susceptibility to a 10-μg ampicillin disk was done by the Bauer-Kirby technique (1).

Determination of antibiotic concentrations in serum and urine. Serum and urine concentrations...
of cefamandole were determined during 1 to 40 days of therapy in 12 patients treated for a variety of acute infections with cefamandole nafate. Cefamandole nafate was administered intramuscularly in a dosage of 0.5 or 1.0 g (dissolved in 2 and 4 ml of sterile water, respectively) every 4 to 6 h. Blood was obtained 0.5, 1, 2, 3, 4, 5, and 6 h after administration of a dose of cefamandole nafate. Urine specimens were obtained by having the patient void before receiving a dose of cefamandole and collecting urine voided during and at the end of the following 4- or 6-h interval. Serum was separated and stored at −20 °C until the time of assay. Urine was stored at −20 °C. The concentrations assayed as cefamandole lithium in serum and urine were determined by a modification of the agar diffusion method with the use of paper disks (9).

Levels of cefamandole in serum decreased linearly after the peak when the logarithms of the concentrations were plotted against time. The half-life (t½) in serum was calculated by the method of least squares (6).

RESULTS AND DISCUSSION

In vitro antibacterial activity of cefamandole lithium and comparison with cefazolin sodium and cephalothin sodium. All strains of S. aureus were inhibited by 1.6 μg of cefamandole, cefazolin, and cephalothin per ml (Fig. 1). Cefazolin and cefamandole had equivalent in vitro activity against E. coli. Both antibiotics inhibited over 90% of strains of E. coli at 12.5 μg/ml and all strains, at 50 μg/ml (Fig. 2). However, 44% of strains of E. coli were resistant to 12.5 μg of cephalothin per ml and 24% were resistant to 50 μg/ml. Of the 12 strains of E. coli resistant to 59 μg of cephalothin per ml, 10 were susceptible to 6.3 μg of cefamandole per ml and 11 were susceptible to the same concentration of cefazolin. Ten of the 50 E. coli strains were resistant by disk-sensitivity testing to ampicillin. Five of the 10 ampicillin-resistant strains were resistant to 12.5 μg of cefamandole per ml, 2 strains to 12.5 μg of cefazolin per ml, and 6 to 12.5 μg of cephalothin per ml. All strains of P. mirabilis were inhibited by 6.3 μg of cefamandole per ml, 12.5 μg of cephalothin per ml, and 25 μg of cefazolin per ml (Fig. 3). All strains of K. pneumoniae were inhibited by 6.3 μg of cefazolin per ml, 12.5 μg of cefamandole per ml, and 25 μg of cephalothin per ml (Fig. 4).

Of particular interest was the inhibition of certain indole-positive Proteus sp. and Enterobacter sp. by cefamandole, in contrast to the relative resistance of these strains to cefazolin and cephalothin. All strains of indole-positive Proteus sp. (two strains of P. rettgeri, five strains of P. morganii, and eight strains of P. vulgaris) were inhibited by 6.3 μg of cefamandole per ml, whereas only 20% were inhibited by 25 μg of cefazolin or cephalothin per ml (Fig. 5). Eight-eight percent of Enterobacter sp. was inhibited by 25 μg of cefamandole per ml, but only 20 and 5% by the same concentration of cefazolin or cephalothin (Fig. 6). Inhibition of certain Enterobacter sp. and indole-positive Proteus sp. confirms previous studies (3, 6, 9), which attributed this greater activity to increased stability of cefamandole to cephalosporinase activity (6, 9). Twenty of 25 Enterobacter cloacae strains were inhibited by 1.6 to 25 μg and all 15 strains of Enterobacter aerogenes by 0.8 to 6.3 μg of cefamandole per ml. This is in contrast to a previous report in which E. cloacae were almost all

![Fig. 1. Comparison of susceptibility of 49 strains of Staphylococcus aureus to cefamandole, cephalothin, and cefazolin.](image1.png)

![Fig. 2. Comparison of susceptibility of 50 strains of Escherichia coli to cefamandole, cephalothin, and cefazolin.](image2.png)
tions between 0.8 and 1.7 mg% (endogenous 
creatinine clearances, 31 to 123 ml/min) were 
treated with a dose of either 500 mg or 1 g of 
cefamandole nafate (6.1 to 17.3 mg/kg) intra-
muscularly every 4 to 6 h. After 6 to 10 mg of 
cefamandole nafate per ml in four patients, the 
peak serum concentration was ranged from 6.0 
to 20.5 μg/ml at 0.5 to 2 h after administration. 
The mean serum concentration ±1 standard 
de deviation (obtained from the mean concentra-
tion for each patient) was 13.7 ± 3.0 μg/ml at 
0.5 h, 13.5 ± 2.6 μg/ml at 1 h, 7.6 ± 2.6 μg/ml at 
2 h, 4.7 ± 1.6 μg/ml at 3 h, 2.8 ± 0.7 μg/ml at 4 
h, and 1.8 ± 0.5 μg/ml at 5 h after 6 to 10 mg of 
cefamandole per kg intramuscularly (Fig. 7). 
At 6 h the serum levels were usually ≤1.0 μg/ml

resistant to cefamandole, as determined by a 
brroth-dilution technique (7).

The difference in results may be related to 
the difference in the techniques used in deter-
mning cefamandole susceptibility. In compari-
sion to cefamandole, cefoxitin, another cepha-
losporin with an increased spectrum of activ-
ity against gram-negative bacilli, has been re-
ported to be active against indole-positive 
Proteus sp., but much less active against 
facultative aerobic gram-positive cocci, such as 
pneumococci, group A streptococci, and S. 
aureus, and not as active against Enterobacter 
sp. (2).

Serum and urine levels. As shown in Table 1, 
12 patients with serum creatinine concentra-

![Cumulative percent of strains inhibited vs. concentration](image1)

**Fig. 3.** Comparison of susceptibility of 28 strains of Proteus mirabilis to cefamandole, cephalothin, and cefazolin.

![Cumulative percent of strains inhibited vs. concentration](image2)

**Fig. 4.** Comparison of susceptibility of 49 strains of Klebsiella pneumoniae to cefamandole, cephalothin, and cefazolin.

![Cumulative percent of strains inhibited vs. concentration](image3)

**Fig. 5.** Comparison of susceptibility of 15 strains of indole-positive Proteus sp. to cefamandole, cephalothin, and cefazolin.

![Cumulative percent of strains inhibited vs. concentration](image4)

**Fig. 6.** Comparison of susceptibility of 16 strains of Enterobacter sp. to cefamandole, cephalothin, and cefazolin.
Table 1. Pharmacodynamics of cefamandole nafate in patients

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<th>Creatinine clearance (ml/min)</th>
<th>IM dose (g)*</th>
<th>Serum cefamandole concn (μg/ml) at hours after dose</th>
<th>Serum t½ (min)</th>
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*IM, Intramuscular. Results in parentheses in milligrams per kilogram of body weight.

*0 to 6 h after dose.

*0 to 4 h after a dose.

...and not measurable (i.e., <0.6 μg/ml) in three of the four patients.

After an 11- to 17-mg/kg dose in nine patients, the peak serum concentrations ranged from 13.8 to 110 μg/ml and occurred at 0.5 to 2 h after administration. The mean serum cefamandole concentration ± 1 standard deviation was 31.0 ± 17.8 μg/ml at 0.5 h, 27.5 ± 14.4 μg/ml at 1 h, 16.1 ± 4.8 μg/ml at 2 h, 9.7 ± 4.0 μg/ml at 3 h, 5.5 ± 3.3 μg/ml at 4 h, 3.5 ± 2.3 μg/ml at 5 h, and 1.7 ± 0.7 μg/ml at 6 h after 11 to 17 mg/kg intramuscularly (Fig. 7). With repeated dosing, there was no evidence of drug accumulation. Urine concentrations of cefamandole ranged from 440 to 16,800 μg/ml, and at least 43% was excreted in a 4- to 6-h period after drug administration.

Fig. 7. Mean concentration of cefamandole in serum after intramuscular (i.m.) administration.
Serum $t_{1/2}$ was 49 to 126 min, which is longer than that reported for cefoxitin (2) and cephalothin (5), similar to cephaloridine (4, 5), but shorter than cefamandole (6). When cefamandole serum $t_{1/2}$ as a geometric function, was plotted against creatinine clearance, as a linear function, the slope of this line was 0.0, calculated by the method of least squares (6): there was no relation between endogenous creatinine clearances $\geq$31 ml/min and serum $t_{1/2}$. Six of the patients had bacterial infections confirmed by culture (S. pneumoniae pneumonia, three patients; S. aureus pneumonia, one patient; Hae-
mophillus influenzae pneumonia, one patient; and Staphylococcus epidermidis endarteritis after aortotomy, one patient) were cured. Intramuscular administration of cefamandole nafate was well tolerated; only one patient complained of pain at the site of intramuscular injection. Diarrhea, which ceased at the end of cefamandole therapy, occurred in one patient. One patient with pneumonia and glucose-6-phosphate dehydrogenase deficiency had a fall in hematocrit from 37 to 18.6% after 2 weeks of therapy. Subsequently, incubation of her erythrocytes in vitro in the presence of up to 100 $\mu$g of cefamandole per ml failed to induce Heinz body formation. Two patients developed mild eosinophilia. Two patients developed a rise in creatine phosphokinase and serum glutamic oxalacetic transaminase, perhaps associated with intramuscular cefamandole administration. Another patient developed a transient mild rise in alkaline phosphatase, serum glutamic oxalacetic transaminase and serum glutamic pyruvic transaminase.

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LITERATURE CITED