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# Cefamandole: In Vitro and Clinical Pharmacokinetics

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Cefamandole has a broader spectrum and greater potency than the other cephalosporins. It includes *Haemophilus influenzae*, most strains of *Enterobacter*, and many strains of indole-positive *Proteus* and *Bacteroides*, with a lower minimal inhibitory concentration for *Escherichia coli*, *Klebsiella*, etc. Concentrations of drug in the serum after the parenteral injection of cefamandole exceed manyfold the minimal inhibitory concentrations of over 82% of the bacteria studied. Approximately 65 to 85% is excreted in a biologically active form in the urine. This antibiotic offers advantages of antibacterial effectiveness and at the same time retains the safety of penicillin G and cephalothin in animals.

The clinical efficacy of the cephalosporin antibiotics has been well established (10, 11). Cephalothin, because of pain with intramuscular injection of greater than 0.5- to 1-g doses, is usually administered intravenously. Cephaloridine, virtually painless with intramuscular injection, has been associated with nephrotoxicity. Cefazolin produces high and prolonged serum concentrations, but has relatively high protein binding with slow dissociation, resulting in a low volume of distribution. As a result of molecular manipulation (Fig. 1), cefamandole offers advantages of antibacterial effectiveness and at the same time retains the safety of penicillin G and cephalothin in animals.

## MATERIALS AND METHODS

**Antibiotic.** The lithium salt of cefamandole for in vitro studies was supplied in 20-mg ampoules by Eli Lilly & Co. The cefamandole for clinical use, CT-2883-4F, was cefamandole nafate furnished as 1 g of cefamandole activity per ampoule.

**Bacterial strains.** A total of 1,152 strains of bacteria were isolated from clinical material at Wishard Memorial and University Hospitals, Indianapolis, Ind.

**Susceptibility testing.** A serial twofold broth dilution procedure with a Canalco Autotiter IV (Canalco, Inc., Rockville, Md.) was used to establish the minimal inhibitory concentration (MIC) for all strains of bacteria except the *Bacteroides*. These were tested in an anerobic atmosphere with a manually operated Canalco Autotiter.

Mueller-Hinton broth was the medium employed for all of the aerobes and facultative anaerobes. When strains of streptococci and pneumococci were tested, 5% sheep blood was added to the broth. *Haemophilus influenzae* was tested by adding Filtes supplement. The inoculum for these procedures was $10^5$ bacteria/ml of media. The MIC was recorded after 18 h of incubation at 37°C. Susceptibility of the *Neisseria* species was evaluated by using solid chocolate agar and a Steers replicator. The inoculum for the Steers replicator was prepared as for the International Collaborative Study agar dilution method.

**Protein binding.** The percentage of inactivation by human serum (protein binding) was estimated by comparing serum and urine standard curves obtained during the blood and urine assays.

**Subjects.** Volunteers were ambulatory adult males and females between the ages of 25 and 55 years with no overt physical or laboratory abnormalities. Diet was not restricted.

**Injection of antibiotic.** For intramuscular injection 3 ml of distilled water was added to each 1-g ampoule of cefamandole. Proportionate amounts of the resulting solution were used to achieve the 250-mg, 500-mg, or 1-g intramuscular dose. The injection was given in the gluteal muscle through a 1.5 inch (ca. 3.8-cm) 20-gauge needle.

For intravenous administration, the 1-g ampoules were placed in solution using 3 ml of distilled water. The dose to be given was then added to 50 ml of 5% glucose and infused rapidly into the antecubital vein over a 10-min period.

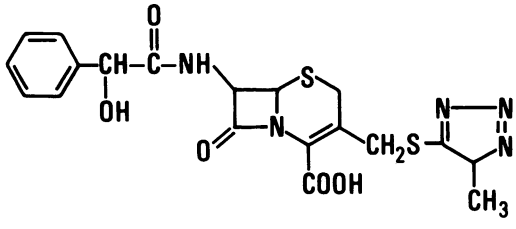
**Serum assays.** Blood samples were drawn before and at intervals after the administration of single doses of cefamandole (see Tables 3 and 5). The blood samples were centrifuged and the sera were frozen until assayed. Serum concentrations were measured using the *Bacillus subtilis* cup plate method (4).

**Urine assays.** Urine was collected at the intervals shown in Tables 4 and 6. These were assayed using an Elanco Autoturb (Elanco Products Co., Indianapolis, Ind.) with a *Klebsiella* strain as the indicator organism.

## RESULTS

**Susceptibility studies.** Table 1 lists the number of bacterial strains in each species studied and their susceptibility to a given concentration of cefamandole. For ease of interpretation, the cumulative percentage of the susceptible strains is shown in Table 2.

A total of 90 to 100% of the methicillin-susceptible *Staphylococcus aureus*, group A and B streptococci, pneumococci, and gonococci required 2 μg or less of cefamandole per ml for inhibition. A concentration of 64 μg/ml (readily achieved in the urine after a 250-mg dose of cefamandole intramuscularly) inhibited the 19 strains of enterococci studied. Seventy percent of the *Escherichia coli* and indole-negative *Proteus* were inhibited by 4 μg of cefamandole per ml. Eighty percent of the *Bacteroides fragilis* subsp. *fragilis* were inhibited by 32 μg/ml, a concentration achieved by the administration of 1 g or greater doses intravenously.




CEFAMANDOLE

FIG. 1. *Structure of cefamandole.*

All 42 strains of *H. influenzae* and the two strains of *Salmonella typhosa* were inhibited by 2 μg of cefamandole per ml.

Sixty-five percent of the 20 strains of *Serratia* were inhibited by 64 μg of cefamandole per ml. A concentration of 8 μg/ml inhibited 82% of the 55 strains of *Proteus mirabilis*, whereas this same concentration inhibited 59% of the 65 indole-positive *Proteus* strains studied. Seventy-one percent of the 24 *Citrobacter* strains were susceptible to 8 μg of cefamandole per ml. Of the 98 strains of *Enterobacter*, 28% were susceptible to 8 μg, 37% to 16 μg, and 46% to 32 μg or less of cefamandole per ml. Therapy of systemic infections due to these organisms and the enterococci obviously would require relatively high intravenous doses daily.

**Protein binding.** Using a cup plate method, 5 μg of cefamandole per ml in urine produced a

TABLE 1. *Number of isolates susceptible to cefamandole*

| Organism | No. of isolates | No. susceptible at an MIC (μg/ml) of: | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 0.12 | 0.25 | 0.5 | 1 | 2 | 4 | 8 | 16 | 32 | 64 | >64 |
| Gram-positive cocci | | | | | | | | | | | | |
| *S. aureus* | 63 | 23 | 9 | 30 | 50 | 60 | 62 | 62 | 62 | 62 | 63 | |
| *S. aureus*[a] | 38 | | | | | | 22 | 36 | 38 | 38 | 38 | |
| β-hemolytic streptococci | | | | | | | | | | | | |
| Lancefield group A | 27 | 25 | 26 | 26 | 27 | 27 | 27 | 27 | 27 | 27 | 27 | |
| Lancefield group B | 13 | 7 | 7 | 9 | 11 | 13 | 13 | 13 | 13 | 13 | 13 | |
| Lancefield other[b] | 7 | 6 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | |
| Group D enterococcus | 19 | | | | | | | | | 8 | 19 | |
| Group D non-enterococcus | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| *Streptococcus pneumoniae* | 15 | 12 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | |
| Gram-negative cocci | | | | | | | | | | | | |
| *Neisseria gonorrhoeae* | 90 | 42 | 63 | 71 | 77 | 80 | 85 | 88 | 90 | 90 | 90 | |
| Gram-negative rods | | | | | | | | | | | | |
| *E. coli* | 358 | | 6 | 19 | 69 | 168 | 262 | 312 | 312 | 346 | 348 | 10 |
| *Klebsiella* sp. | 114 | 2 | | 10 | 53 | 88 | 104 | 106 | 108 | 108 | 113 | 1 |
| *H. influenzae* | 42 | | | 13 | 40 | 42 | 42 | 42 | 42 | 42 | 42 | |
| *P. mirabilis* | 55 | | 2 | 6 | 31 | 39 | 42 | 45 | 49 | 51 | 54 | 1 |
| *Proteus* sp. (indole positive) | 64 | | | 2 | 16 | 25 | 30 | 38 | 40 | 42 | 43 | 21 |
| *Enterobacter* sp. | 98 | | | | 7 | 11 | 20 | 27 | 36 | 45 | 54 | 44 |
| *Serratia* | 20 | | | | | | 1 | 1 | 3 | 5 | 13 | 7 |
| *Salmonella* sp. | 20 | | | 2 | 11 | 15 | 19 | 20 | 20 | 20 | 20 | |
| *S. typhosa* | 2 | | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | |
| *Shigella* sp. | 3 | | | | 1 | 1 | 1 | 2 | 3 | | | |
| *Citrobacter* sp. | 24 | | | | 5 | 11 | 16 | 17 | 19 | 20 | 20 | 4 |
| *Acinetobacter* | 4 | | | | | | | | | 1 | 2 | 2 |
| *B. fragilis* subsp. *fragilis* | 72 | | | | | | 4 | 19 | 44 | 58 | 62 | 10 |
| Cumulative total | 1,152 | 121 | 140 | 215 | 426 | 608 | 778 | 883 | 934 | 1,007 | 1,052 | 100 |

[a] Methicillin resistant.
[b] Not class A, B, C, or G.

TABLE 2. *Percentage of isolates susceptible to cefamandole*

| Organism | No. of isolates | Isolates (%) susceptible at an MIC (μg/ml) of: | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 0.125 | 0.25 | 0.5 | 1 | 2 | 4 | 8 | 16 | 32 | 64 | >64 |
| Gram-positive cocci | | | | | | | | | | | | |
| *S. aureus* | 63 | 5 | 14 | 46 | 94 | 95 | 98 | 98 | 98 | 98 | 100 | |
| *S. aureus*[a] | 38 | | | | | | 58 | 95 | 100 | | | |
| β-hemolytic streptococci | | | | | | | | | | | | |
| Lancefield group A | 27 | 93 | 96 | 96 | 100 | | | | | | | |
| Lancefield group B | 13 | 54 | 54 | 69 | 85 | 100 | | | | | | |
| Lancefield other[b] | 7 | 86 | 100 | | | | | | | | | |
| Group D enterococcus | 19 | | | | | | | | | 42 | 100 | |
| Group D non-enterococcus | 4 | 100 | | | | | | | | | | |
| *S. pneumoniae* | 15 | 80 | 100 | | | | | | | | | |
| Gram-negative cocci | | | | | | | | | | | | |
| *N. gonorrhoeae* | 90 | 47 | 70 | 79 | 86 | 89 | 94 | 98 | 100 | | | |
| Gram-negative rods | | | | | | | | | | | | |
| *E. coli* | 358 | 1 | 2 | 5 | 19 | 47 | 73 | 87 | 87 | 97 | 97 | 3 |
| *Klebsiella* sp. | 114 | | | 9 | 46 | 77 | 91 | 93 | 95 | 95 | 99 | 1 |
| *H. influenzae* | 42 | | | 31 | 95 | 100 | | | | | | |
| *P. mirabilis* | 55 | | 4 | 11 | 56 | 71 | 76 | 82 | 89 | 93 | 98 | 2 |
| *Proteus* sp. (indole positive) | 65 | | | 3 | 25 | 29 | 47 | 59 | 63 | 66 | 67 | 33 |
| *Enterobacter* sp. | 98 | | | | 7 | 11 | 20 | 28 | 37 | 46 | 55 | 45 |
| *Serratia* | 20 | | | | | | 5 | 5 | 15 | 25 | 65 | 35 |
| *Salmonella* sp. | 20 | | | 10 | 55 | 75 | 95 | 100 | | | | |
| *S. typhosa* | 2 | | | | 100 | | | | | | | |
| *Shigella* sp. | 3 | | | | | | | | 100 | | | |
| *Citrobacter* sp. | 24 | | | | 21 | 46 | 67 | 71 | 79 | 83 | 83 | 17 |
| *Acinetobacter* | 4 | | | | | | | | | | 50 | 50 |
| *B. fragilis* subsp. *fragilis* | 72 | | | | | | 6 | 26 | 61 | 80 | 86 | 14 |
| Total | 1,152 | | | | | | | | | | | |
| Cumulative Susceptible (%) | | 11 | 12 | 19 | 37 | 53 | 68 | 77 | 81 | 87 | 91 | 9 |

[a] Methicillin resistant.
[b] Not class A, B, C, or G.

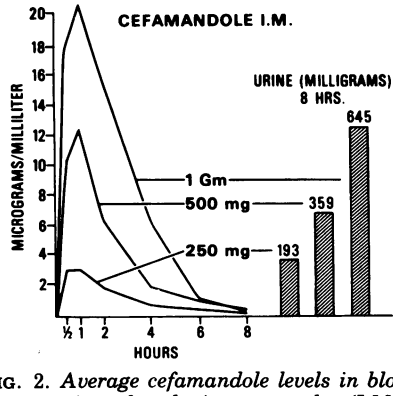



FIG. 2. *Average cefamandole levels in blood and urine excretion after the intramuscular (I.M.) injection of 250, 500, and 1,000 mg.*

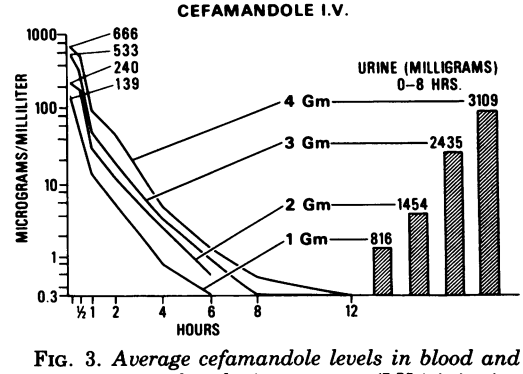



FIG. 3. *Average cefamandole levels in blood and urine excretion after the intravenous (I.V.) injection of 1, 2, 3, and 4 g.*

zone size of 37.4 mm. This was reduced to 30.7 mm when the same concentration in serum was studied. Thus, serum reduced the zone size by 18%. From the standard curve, it was apparent that an 18% reduction of zone size was the same as lowering the concentration of cefamandole from 5 to 1.0 μg/ml, or 80% binding by serum proteins.

When an ultracentrifuge was used to deter-

mine protein binding, 70% of the cefamandole went with the protein fraction. These values are similar to those reported for cephalothin by Kirby and Regamey, using the ultrafiltration method (5).

**Pharmacology.** Figure 2 shows the average levels of cefamandole in the blood and urine excretion after the intramuscular injection of 250, 500, and 1,000 mg. Levels with each dose at 1 h were 2.7, 12.2, and 20.6 μg/ml, respectively. Assayable amounts were still present at 4 h after the 250-mg dose and at 6 to 8 h after the 500-mg and 1-g doses.

The total amount of cefamandole excreted over the 8-h collection period was approximately 65 to 85% after the intramuscular injection. The average concentration in the urine for the 8-h period was 210 μg/ml after the 250-mg dose, 254 μg/ml after the 500-mg dose, and 1,357 μg/ml after the 1-g dose.

Figure 3 compares the average levels of cefamandole in blood and urine excretion after the

TABLE 3. *Concentration of cefamandole in serum after intramuscular administration*

| Patient | Concn in serum at h: | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0 | 0.5 | 1 | 2 | 4 | 6 | 8 |
| 250-mg dose | | | | | | | |
| AB | 0 | 2.8 | 2.6 | 1.9 | 0.8 | 0.3 | |
| RD | 0 | 3.4 | 2.8 | 1.0 | <0.3 | <0.3 | |
| ME | 0 | 4.8 | 3.1 | 1.0 | 0.3 | <0.3 | |
| AF | 0 | 4.5 | 3.5 | 1.9 | 0.6 | <0.3 | |
| HG | 0 | 2.2 | 2.4 | 1.3 | 0.5 | <0.3 | |
| JH | 0 | 2.6 | 2.7 | 1.8 | 0.6 | <0.3 | |
| TH | 0 | 1.7 | 2.5 | 1.8 | 0.7 | <0.3 | |
| RM | 0 | 1.5 | 1.9 | 1.8 | 0.8 | 0.3 | |
| AP | 0 | 3.8 | 3.0 | 1.6 | 0.4 | <0.3 | |
| DW | 0 | 2.7 | 2.2 | 0.9 | <0.3 | <0.3 | |
| Mean | 0 | 3.0 | 2.7 | 1.5 | 0.5 | | |
| SD[a] | 0 | 1.1 | 0.5 | 0.4 | | | |
| 500-mg dose | | | | | | | |
| AB | 0 | 12.2 | 20.3 | 4.4 | 1.1 | 0.8 | <0.3 |
| RD | 0 | 15.8 | 15.8 | 4.4 | 0.7 | <0.3 | <0.3 |
| ME | 0 | 16.2 | 15.7 | 5.6 | 1.6 | <0.3 | <0.3 |
| AF | 0 | 12.2 | 15.8 | 9 | 2 | 0.4 | <0.3 |
| HG | 0 | 12.2 | 5.7 | 5.4 | 1.6 | 0.3 | <0.3 |
| JH | 0 | 3.4 | 7.5 | 5.7 | 2 | 0.4 | <0.3 |
| TH | 0 | 3.4 | 7.7 | 7.3 | 2.3 | 0.3 | <0.3 |
| RM | 0 | 1 | 3.9 | 5 | 3 | 0.8 | <0.3 |
| AP | 0 | 8.3 | 15.7 | 8.3 | 1.8 | 0.3 | <0.3 |
| DW | 0 | 12 | 13.9 | 7.3 | 0.4 | <0.3 | <0.3 |
| Mean | 0 | 9.7 | 12.2 | 6.2 | 1.6 | 0.5 | |
| SD | 0 | 5.4 | 5.5 | 1.6 | 0.8 | 0.2 | |
| 1-g dose | | | | | | | |
| AB | 0 | 25 | 16 | 10.8 | 3.5 | 1.2 | 0.4 |
| RD | 0 | 47.6 | 26.6 | 14.3 | 2.5 | 0.5 | <0.25 |
| ME | 0 | 29.3 | 43.5 | 21.4 | 2.5 | 0.4 | <0.25 |
| HG | 0 | 17.1 | 16.7 | 17.6 | 4.9 | 0.8 | <0.25 |
| JH | 0 | 9 | 9 | 9.7 | 6.3 | 2.2 | 0.6 |
| TH | 0 | 4.4 | 12.3 | 14.4 | 2.9 | 0.8 | <0.25 |
| RM | 0 | 5.8 | 14 | 15.1 | 6.2 | 2.2 | 1.1 |
| AP | 0 | 22.4 | 40.2 | 20.4 | 6.2 | 1.6 | 1.2 |
| DW | 0 | 19.5 | 20.1 | 13.1 | 4.0 | 0.7 | <0.25 |
| RB | 0 | 4.1 | 7.1 | 20.1 | 6.0 | 0.9 | 0.3 |
| Mean | 0 | 18.4 | 20.6 | 15.7 | 4.5 | 1.1 | 0.4 |
| SD | 0 | 13.7 | 12.5 | 4.1 | 1.6 | 0.7 | |

[a] SD, Standard deviation.

TABLE 4. *Concentrations of cefamandole in urine after intramuscular administration*

| Patient | 0–2 h | | | 6–8 h | | |
|---|---|---|---|---|---|---|
| | μg/ml | Total volume (ml) | Total mg | μg/ml | Total volume (ml) | Total mg |
| 250-mg dose | | | | | | |
| AB | 165 | 480 | 79 | 880 | 130 | 114 |
| RD | 250 | 474 | 118 | 235 | 405 | 95 |
| ME | 120 | 1,000 | 120 | 185 | 350 | 64 |
| AF | 400 | 450 | 182 | 625 | 50 | 31 |
| HG | 205 | 600 | 123 | 340 | 350 | 119 |
| JH | 95 | 550 | 52 | 240 | 450 | 108 |
| TH | 80 | 460 | 37 | 340 | 180 | 61 |
| RM | 90 | 800 | 72 | 290 | 450 | 130 |
| AP | 190 | 500 | 95 | 150 | 850 | 127 |
| DW | 270 | 450 | 121 | 445 | 180 | 80 |
| Mean | 186 | 576 | 100 | 373 | 339 | 93 |
| SD[a] | 100 | 183 | 42 | 225 | 22 | 34 |
| 500-mg dose | | | | | | |
| AB | 300 | 1,030 | 309 | 820 | 100 | 82 |
| RD | 100 | 1,120 | 112 | 320 | 850 | 272 |
| ME | 380 | 890 | 338 | 265 | 450 | 119 |
| AF | 130 | 1,160 | 150 | 350 | 540 | 189 |
| HG | 210 | 700 | 147 | 500 | 550 | 275 |
| JH | 120 | 960 | 115 | 300 | 600 | 180 |
| TH | 160 | 900 | 144 | 350 | 550 | 192 |
| RM | 150 | 700 | 105 | 230 | 550 | 126 |
| AP | 320 | 560 | 179 | 390 | 450 | 175 |
| DW | 220 | 890 | 195 | 350 | 550 | 192 |
| Mean | 209 | 891 | 179 | 388 | 519 | 180 |
| SD | 95 | 192 | 81 | 160 | 184 | 62 |
| 1-g dose | | | | | | |
| AB | 1,365 | 230 | 324 | 4,875 | 640 | 312 |
| RD | 2,973 | 160 | 476 | 1,043 | 255 | 266 |
| ME | 4,800 | 80 | 384 | 1,352 | 170 | 230 |
| HG | 1,037 | 100 | 104 | 1,997 | 310 | 619 |
| JH | 750 | 190 | 143 | 1,495 | 380 | 568 |
| TH | 3,857 | 95 | 366 | 1,295 | 220 | 285 |
| RM | 1,780 | 115 | 205 | 1,059 | 340 | 360 |
| AP | 797 | 240 | 191 | 833 | 420 | 350 |
| DW | 1,520 | 210 | 319 | 1,320 | 200 | 264 |
| RB | 1,185 | 100 | 119 | 2,178 | 270 | 588 |
| Mean | 2,006 | 156 | 262 | 1,745 | 320 | 384 |
| SD | 1,395 | 62 | 127 | 1,176 | 137 | 149 |

[a] SD, Standard deviation.

intravenous injection of 1, 2, 3, and 4 g. Average peak levels at 10 min after the completion of the 10-min intravenous infusion of cefamandole were 139 μg/ml for the 1-g dose and 240, 524, and 666 μg/ml for the 2-, 3-, and 4-g doses, respectively. After equilibration, the corresponding 30-min levels were 54, 196, 279, and 428 μg/ml. Each increase in the amount given prolonged the duration of measurable levels. The antibiotic level was less than 0.3 μg/ml at 8 h after the 2-g dose and was not assayable at 12 h after the 3- and 4-g doses.

A total of 75 to 85% of the intravenous dose was recovered in the urine during the 8-h postinjection period. The average concentration for the 8-h period was 750 μg/ml after the 1-g dose, 1,380 μg/ml after the 2-g dose, 2,110 after the 3-g dose, and 2,550 after the 4-g dose. For closer scrutiny, the actual blood levels and urine excretion for each individual receiving cefaman-

dole are shown in Tables 3 through 6. The average values for the blood levels and urine excretion used for preparing Fig. 2 and 3 are shown in Table 7.

## DISCUSSION

The bacteria most frequently isolated from nonhospitalized patients with infection are streptococci, pneumococci, staphylococci, and *E. coli*. Infections caused by these organisms are usually treated with relatively low doses of antibiotics administered orally. Patients with serious infections are usually admitted to a hospital. At the Wishard Memorial Hospital in Indianapolis, 12% of the admissions are related to bacterial infections. An additional 7% are from nosocomial sources (Committee on Infection Control, Wishard Memorial Hospital). This incidence is similar to that reported by others (1). The distribution of the bacteria tested for antibiotic susceptibility (other than group A streptococci and pneumococci) are

TABLE 5. *Concentrations of cefamandole in serum after intravenous administration*

| Patient | Concn in serum at h: | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 0 | 0.17 | 0.5 | 1 | 2 | 4 | 6 | 8 | 12 |
| 1-g dose | | | | | | | | | |
| RB | 0 | 214.2 | 106.1 | 13.5 | 5.9 | 0.8 | <0.3 | | |
| AF | 0 | 128.5 | 68.7 | 24 | 8.6 | 1.3 | <0.3 | | |
| GL | 0 | 92.3 | 22.2 | 13.3 | 5.2 | 0.7 | <0.3 | | |
| HL | 0 | 198.5 | 31.4 | 13.3 | 1.6 | 0.3 | <0.3 | | |
| BO | 0 | 145.1 | 78.9 | 14 | 3.3 | 0.3 | <0.3 | | |
| CK | 0 | 85.1 | 40.1 | 14 | 5.5 | 1.1 | <0.3 | | |
| GM | 0 | 100 | 33.2 | 14.2 | 4.0 | 1.4 | 0.4 | | |
| Mean | 0 | 139.1 | 54.4 | 15.2 | 4.9 | 0.8 | | | |
| SD[a] | 0 | 54.1 | 30.8 | 3.9 | 2.2 | 0.4 | | | |
| 2-g dose | | | | | | | | | |
| RB | 0 | 313.8 | 278 | 24.5 | 2.4 | 1.7 | 0.5 | <0.3 | |
| AF | 0 | 228.1 | 198.5 | 38.4 | 10 | 4.5 | 0.8 | <0.3 | |
| GL | 0 | 137.7 | 88.6 | 22.8 | 4.5 | 1.8 | 0.3 | <0.3 | |
| HL | 0 | 109.8 | 64.1 | 15 | 4.4 | 0.6 | 0.3 | <0.3 | |
| BO | 0 | 301.3 | 195 | 23.3 | 6.4 | 1 | 0.3 | <0.3 | |
| CK | 0 | 308.5 | 274.7 | 49.1 | 22.5 | 2.4 | 0.5 | <0.3 | |
| GM | 0 | 284 | 274.7 | 40.2 | 27 | 3.6 | 1.1 | 0 | |
| Mean | 0 | 240.5 | 196.2 | 30.5 | 11 | 2.2 | 0.5 | | |
| SD | 0 | 85 | 89.5 | 12.2 | 9.7 | 1.4 | 0.3 | | |
| 3-g dose | | | | | | | | | |
| CK | 0 | 644.6 | 318 | 66.2 | 26 | 3.5 | 1.1 | 0.3 | <0.3 |
| GM | 0 | 526 | 249.6 | 54.8 | 30.9 | 4.3 | 1.5 | 0.6 | <0.3 |
| BO | 0 | 370 | 151.8 | 63.6 | 34.6 | 1.9 | 0.4 | 0.3 | <0.3 |
| RM | 0 | 588 | 288.7 | 68.2 | 16.2 | 1.9 | 0.5 | <0.3 | <0.3 |
| CS | 0 | 540 | 389.2 | 86 | 27.9 | 2.7 | 1 | 0.3 | <0.3 |
| Mean | 0 | 533.7 | 279.5 | 67.8 | 27.1 | 2.9 | 0.9 | 0.3 | |
| SD | 0 | 102.6 | 87.8 | 11.4 | 6.9 | 1 | 0.5 | | |
| 4-g dose | | | | | | | | | |
| CK | 0 | 747 | 675.2 | 65.2 | 55.4 | 4.8 | 1.6 | 0.5 | <0.3 |
| GM | 0 | 684.4 | 486 | 92.7 | 38.7 | $6_{e6}$ | 2.6 | 1 | <0.3 |
| BO | 0 | 413.6 | 326.7 | 68.9 | 31.6 | 2.5 | 0.6 | 0.3 | <0.3 |
| RM | 0 | 654.4 | 376.8 | 67.7 | 41.1 | 1.8 | 1 | 0.3 | <0.3 |
| CS | 0 | 833.1 | 777.6 | 100.7 | 39 | 4 | 0.8 | 0.3 | <0.3 |
| Mean | 0 | 666.3 | 528.5 | 79 | 41.2 | 3.9 | 1.3 | 0.5 | |
| SD | 0 | 156.9 | 193.1 | 16.4 | 8.7 | 1.9 | 0.8 | 0.3 | |

[a] SD, Standard deviation.

shown in Table 8 (Committee on Infection Control, Wishard Memorial Hospital).

All of the group A streptococci and pneumococci and 95% of the methicillin-susceptible *S. aureus* in this study were shown to be susceptible to concentrations of 2 μg or less per ml, easily achieved by doses of 250 mg of cefamandole intramuscularly. Eighty-two percent of the bacterial isolates were inhibited by serum concentrations of 8 μg or less per ml, an amount exceeded after the 500-mg and 1-g doses intramuscularly. Intravenous doses of greater than 1 g gave serum concentrations manyfold higher than the susceptibility of most of the bacterial strains studied. Relatively low therapeutic doses of cefamandole, 0.5 to 1 g intramuscularly or 1 to 2 g intravenously every 6 h, should be clinically effective in infections that would include virtually all of the commonly encountered bacterial organisms, i.e., beta-hemolytic strep-

TABLE 6. *Urine concentration and excretion of cefamandole after intravenous administration*

| Patient | 0–2 h | | | 2–4 h | | | 4–6 h | | | 6–8 h | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | μg/ml | Volume (ml) | Total mg | μg/ml | Volume (ml) | Total mg | μg/ml | Volume (ml) | Total mg | μg/ml | Volume (ml) | Total mg |
| 1-g dose | | | | | | | | | | | | |
| RB | 1,780 | 390 | 694 | 510 | 380 | 194 | 29 | 390 | 11 | 16 | 630 | 10 |
| AF | 1,550 | 420 | 651 | 400 | 310 | 124 | 29 | 80 | 2 | 12 | 305 | 4 |
| GL | 3,100 | 150 | 465 | 600 | 140 | 84 | 16 | 190 | 3 | 14 | 210 | 3 |
| HL | 1,800 | 320 | 576 | 490 | 330 | 162 | 30 | 130 | 4 | 11 | 200 | 2 |
| BO | 1,000 | 700 | 700 | 500 | 320 | 160 | 45 | 140 | 6 | 30 | 230 | 7 |
| CK | 2,700 | 220 | 594 | 450 | 350 | 158 | 220 | 120 | 26 | 33 | 130 | 4 |
| GM | 1,600 | 590 | 944 | 1,225 | 70 | 86 | 329 | 95 | 31 | 36 | 64 | 2 |
| Mean | 1,933 | 399 | 661 | 596 | 271 | 138 | 100 | 164 | 12 | 22 | 252 | 5 |
| SD[a] | 721 | 195 | 149 | 284 | 118 | 42 | 124 | 106 | 12 | 11 | 183 | 3 |
| 2-g dose | | | | | | | | | | | | |
| RB | 3,460 | 520 | 1,799 | 1,110 | 85 | 94 | 45 | 400 | 18 | 18 | 290 | 5 |
| AF | 1,900 | 530 | 1,007 | 1,675 | 190 | 318 | 50 | 230 | 12 | 38 | 380 | 14 |
| GL | 3,740 | 360 | 1,346 | 455 | 485 | 221 | 33 | 450 | 15 | 30 | 150 | 5 |
| HL | 2,800 | 460 | 1,288 | 770 | 280 | 216 | 36 | 220 | 8 | 20 | 170 | 3 |
| BO | 2,300 | 615 | 1,415 | 1,550 | 120 | 186 | 40 | 100 | 4 | 31 | 130 | 4 |
| CK | 4,170 | 120 | 500 | 1,375 | 275 | 378 | 40 | 250 | 10 | 35 | 110 | 4 |
| GM | 6,000 | 170 | 1,020 | 2,420 | 120 | 290 | 34 | 50 | 2 | 32 | 100 | 3 |
| Mean | 3,481 | 396 | 1,196 | 1,336 | 222 | 243 | 40 | 243 | 10 | 29 | 190 | 5 |
| SD | 1,369 | 189 | 407 | 643 | 139 | 94 | 6 | 145 | 6 | 8 | 105 | 4 |
| 3-g dose | | | | | | | | | | | | |
| CK | 6,950 | 275 | 1,911 | 780 | 290 | 226 | 110 | 150 | 17 | 37 | 125 | 5 |
| GM | 5,600 | 410 | 2,296 | 800 | 200 | 160 | 380 | 50 | 19 | 104 | 20 | 2 |
| BO | 2,200 | 1,040 | 2,288 | 840 | 420 | 353 | 112 | 150 | 17 | 38 | 105 | 4 |
| RM | 3,950 | 515 | 2,034 | 960 | 250 | 240 | 410 | 150 | 62 | 38 | 170 | 7 |
| CS | 3,750 | 520 | 1,950 | 1,235 | 400 | 494 | 400 | 190 | 76 | 47 | 330 | 16 |
| Mean | 4,490 | 552 | 2,095 | 923 | 312 | 295 | 282 | 138 | 38 | 53 | 150 | 7 |
| SD | 1,828 | 290 | 185 | 188 | 95 | 131 | 157 | 52 | 29 | 29 | 114 | 5 |
| 4-g dose | | | | | | | | | | | | |
| CK | 7,500 | 310 | 2,325 | 1,710 | 250 | 428 | 640 | 120 | 77 | 38 | 155 | 6 |
| GM | 5,000 | 420 | 2,100 | 7,600 | 50 | 380 | 780 | 30 | 23 | 108 | 75 | 8 |
| BO | 4,500 | 800 | 3,600 | 1,000 | 450 | 450 | 500 | 120 | 60 | 92 | 420 | 39 |
| RM | 9,500 | 250 | 2,375 | 1,740 | 235 | 409 | 175 | 450 | 79 | 120 | 395 | 47 |
| CS | 6,750 | 380 | 2,565 | 1,200 | 415 | 498 | 275 | 255 | 70 | 26 | 265 | 7 |
| Mean | 6,650 | 432 | 2,593 | 2,650 | 280 | 433 | 474 | 195 | 62 | 77 | 262 | 21 |
| SD | 2,013 | 216 | 537 | 2,786 | 160 | 45 | 250 | 164 | 23 | 42 | 149 | 20 |

[a] SD, Standard deviation.

TABLE 7. *Serum concentrations and urine excretion of cefamandole after intramuscular and intravenous administration*

| Dose | No. of subjects | Concn in serum at h: 0.17 | 0.5 | 1 | 2 | 4 | 6 | 8 | 12 | Urine excretion at 0–8 h: Avg (μg/ml) | Total (mg) | % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Intramuscular | | | | | | | | | | | | |
| 250 mg | 10 | | 3 | 2.7 | 1.5 | 0.5 | <0.3 | | | 210 | 193 | 77 |
| 500 mg | 10 | | 9.7 | 12.2 | 6.2 | 1.6 | 0.5 | <0.3 | | 254 | 359 | 72 |
| 1 g | 10 | | 18.4 | 20.6 | 15.7 | 4.5 | 1.1 | 0.4 | | 1,357 | 646 | 65 |
| Intravenous | | | | | | | | | | | | |
| 1 g | 7 | 139 | 54 | 15 | 5 | 0.8 | <0.3 | | | 750 | 816 | 82 |
| 2 g | 7 | 240 | 196 | 30 | 11 | 2.2 | 0.5 | <0.3 | | 1,383 | 1,454 | 73 |
| 3 g | 5 | 533 | 279 | 68 | 27 | 2.9 | 0.9 | 0.3 | <0.3 | 2,114 | 2,435 | 81 |
| 4 g | 5 | 666 | 528 | 79 | 41 | 3.9 | 1.3 | 0.5 | <0.3 | 2,660 | 3,109 | 78 |

TABLE 8. *Incidence of bacteria isolated for susceptibility testing at Wishard Memorial Hospital, Indianapolis, Ind.*

| Determination | Isolates (%)/mo in: 1968 (707)[a] | 1969 (1,419) | 1970 (1,646) | 1973 (1,712) | 1974 (1,026) |
|---|---|---|---|---|---|
| *S. aureus* | 20 | 16 | 17 | 17 | 17 |
| *S. epidermis* | 5 | 15 | 21 | 24 | 5 |
| *E. coli* | 25 | 22 | 21 | 19 | 26 |
| *Citrobacter* | 8 | 9 | 8 | 1 | 1 |
| *Proteus* sp. | 11 | 10 | 10 | 8 | 9 |
| *Klebsiella-Enterobacter* | 22 | 14 | 11 | 13 | 19 |
| *Pseudomonas* | 7 | 7 | 7 | 10 | 9 |
| *Serratia* | | 4 | 1 | 1 | 2 |

[a] Numbers in parentheses indicate the total number of isolates.

TABLE 9. *Mean MIC of isolates susceptible to 64 μg or less of cefamandole per ml*

| Organism | Mean MIC | % |
|---|---|---|
| Gram-positive cocci | | |
| *S. aureus* | 1.83 | 100 |
| *S. aureus* (methicillin resistant) | 6.11 | 100 |
| β-hemolytic streptococci | | |
| Group A | 0.16 | 100 |
| Group B | 1.6 | 100 |
| Other | 0.14 | 100 |
| Group D enterococcus | 50.5 | 100 |
| Group D non-enterococcus | 0.1 | 100 |
| *S. pneumoniae* | 0.14 | 100 |
| Gram-negative cocci | | |
| *N. gonorrhoeae* | 1.14 | 100 |
| Gram-negative rods | | |
| *E. coli* | 4.7 | 97 |
| *Klebsiella* | 4.6 | 99 |
| *P. mirabilis* | 1 | 98 |
| Indole-positive *Proteus* sp. | 6.5 | 67 |
| *Enterobacter* sp. | 20.4 | 55 |
| *Salmonella* sp. | 2.1 | 100 |
| *H. influenzae* | 0.9 | 100 |
| *Citrobacter* sp. | 5.5 | 83 |
| *B. fragilis* subsp. *fragilis* | 21.9 | 86 |

tococci, pneumococci, staphylococci, *E. coli*, *Klebsiella*, etc. (Table 9).

Young and Hewitt have used an inhibitory index to illustrate the relative potency of an antibiotic (12). This method has been used to compare the effect of increasing doses of cefamandole (Table 10). Presumably, protein binding would not appreciably affect the antibacterial activity of cefamandole and, therefore, has not been included in the calculations in Table 10. Like penicillin G and cephalothin, cefamandole is rapidly dissociated from the serum proteins, as evidenced by the relatively short half-life and rapid appearance in the urine.

It is obvious that as the dose is increased the number of bacterial species that can be included in the spectrum of cefamandole is also increased. If one utilizes somewhat less stringent criteria (corresponding to an MIC of 32 μg or less per ml, levels that can readily be achieved with parenteral therapy), 80% of the *Bacteroides* strains tested would be susceptible to cefamandole therapy. These results are similar to the median of 32 μg/ml reported by Ernst et al. (2). A similar observation has been made by Moellering et al. for cefoxitin (6).

Although most of the *P. mirabilis* indole-negative strains are susceptible to the cephalosporins, including cefamandole, Eykyn and coworkers called attention to the promising results observed with cefamandole against other enterobacteriaceae (3). However, they found *P. vulgaris* strains were consistently resistant to cefamandole. These findings are in accord with our data. *P. mirabilis* strains required only 8

TABLE 10. *Inhibitory index[a] for cefamandole*

| Organism | Mean MIC | Inhibitory index after dose (g) of: | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Intramuscular | | | Intravenous | | | |
| | | 0.25 (3.0)[b] | 0.5 (12.2) | 1 (20.6) | 1 (54) | 2 (196) | 3 (270) | 4 (528) |
| Gram-positive cocci | | | | | | | | |
| *S. aureus* | 1.83 | 2 | 7 | 11 | 30 | 107 | 152 | 288 |
| *S. aureus* (methicillin resistant) | 6.11 | | 2 | 3 | 9 | 32 | 46 | 86 |
| β-hemolytic streptococci | | | | | | | | |
| Group A | 0.16 | 19 | 76 | 128 | 338 | 1,225 | 1,744 | 3,300 |
| Group B | 1.6 | 2 | 8 | 13 | 34 | 122 | 174 | 330 |
| Other | 0.14 | 21 | 87 | 147 | 385 | 1,400 | 1,993 | 3,771 |
| Group D enterococcus | 50.4 | | | | 1 | 4 | 6 | 10 |
| Group D non-enterococcus | 0.1 | 30 | 122 | 206 | 540 | 1,960 | 2,790 | 5,280 |
| *S. pneumoniae* | 0.14 | 21 | 87 | 147 | 385 | 1,400 | 1,993 | 3,771 |
| Gram-negative cocci | | | | | | | | |
| *N. gonorrhoeae* | 1.14 | 3 | 11 | 18 | 47 | 172 | 245 | 463 |
| Gram-negative rods | | | | | | | | |
| *E. coli* | 4.7 | | 3 | 4 | 11 | 42 | 59 | 112 |
| *Klebsiella* | 4.6 | | 3 | 4 | 12 | 43 | 61 | 115 |
| *P. mirabilis* | 1 | 3 | 12 | 20 | 54 | 196 | 279 | 528 |
| Indole-positive *Proteus* sp. | 6.5 | | 2 | 3 | 8 | 30 | 43 | 81 |
| *Enterobacter* sp. | 20.4 | | | 1 | 3 | 10 | 14 | 26 |
| *Salmonella* sp. | 2.1 | 1 | 6 | 10 | 26 | 93 | 133 | 251 |
| *H. influenzae* | 0.9 | 3 | 14 | 23 | 60 | 217 | 310 | 587 |
| *Citrobacter* sp. | 5.5 | | 2 | 4 | 10 | 36 | 51 | 96 |
| *B. fragilis* subsp. *fragilis* | 21.9 | | | 1 | 2 | 9 | 13 | 24 |

[a] Ratio between the mean peak serum levels and the mean MIC of the isolates susceptible to 64 μg or less per ml.

[b] Numbers in parentheses indicate mean peak blood level in micrograms per milliliter.

μg/ml to inhibit 82%, whereas 59% of the indole-producing strains of *Proteus* were inhibited by this concentration.

We found that 46% of the 98 strains of *Enterobacter* were susceptible to 32 μg of cefamandole per ml, whereas Washington reported 73% of 30 strains of *E. aerogenes* and 67% of 51 strains of *E. cloacae* were inhibited by 8 μg/ml (9). Eykyn emphasized that there is often a striking inoculum effect among organisms with moderate to high MIC values, with only partial inhibition of large inocula by concentrations of cefamandole (3). Inoculum effect has been observed with other cephalosporins and penicillins (8).

In addition to the inoculum effect, the discrepancies in the cefamandole MICs of *Enterobacter* reported by other workers are apparently associated with whether the susceptibility tests were performed in broth or agar (3, 7, 9).

The higher cefamandole MICs in broth (as used in our study) may reflect an emergence of resistant variants from the heterogenous composition of the culture, not detected by lower inocula or by the end-point criteria usually used in agar dilution methods (C. M. Findell and J. C. Sherris, Abstr. Annu. Meet. Am. Soc. Microbiol. 1976, A14, p. 3).

Since the strains of *Enterobacter*, indole-positive *Proteus*, and enterococci vary in susceptibility, laboratory tests should be used as a guide to selection of antibiotic therapy. *Pseudomonas* strains are universally resistant to cefamandole.

In conclusion the majority (82%) of the bacterial strains isolated from hospitalized patients with infection were susceptible to the peak serum concentrations (8 to 16 μg/ml) obtained after 500-mg to 1-g doses of cefamandole administered intramuscularly.

A total of 65 to 85% of the parenterally injected cefamandole appeared as the biologically active form in urine over an 8-h collection period.

Very high serum concentrations of 270 and 528 μg/ml were obtained 0.5 h after a 10-min infusion of 3 and 4 g of cefamandole intravenously. As has been shown with other antibiotics, higher doses would be needed only for the

treatment of infections due to less susceptible organisms or in those patients with severe or overwhelming infections.

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