Comparative Pharmacokinetics of Cefoperazone and Cefamandole

SUBRAMANIAM SRINIVASAN, ELLIOT L. FRANCKE, AND HAROLD C. NEU†*

Departments of Medicine and Pharmacology, Division of Infectious Diseases, College of Physicians and Surgeons, Columbia University, New York, New York 10032

The pharmacokinetics of cefoperazone, a new β-lactam antibiotic, were studied in normal volunteers and compared with the pharmacokinetics of cefamandole. After a 30-min infusion of 2 g of cefoperazone, the mean serum level was 256 μg/ml; at 4 h, the serum level was 20 μg/ml, and at 12 h, the level was 1.25 μg/ml, compared with levels of cefamandole of 188 μg/ml at the end of infusion, 1.8 μg/ml at 4 h, and none detected thereafter. The mean half-life of cefoperazone was 1.6 h, compared with 0.7 h for cefamandole. The apparent volume of distribution for cefoperazone was 9.9 liters/1.73 m² compared with 12.5 liters/1.73 m² for cefamandole. Serum clearance of cefoperazone was 85 ml/min, and renal clearance was 25 ml/min, compared with a serum clearance of 224 ml/min and a renal clearance of 213 ml/min for cefamandole. Urine levels exceeded 25 μg/ml in the first 8 h after injection. Renal recovery of cefoperazone was only 29%.

There has been a constant search for newer β-lactam antibiotics which are resistant to inactivation by the β-lactamases of Enterobacteriaceae and Pseudomonas species. Cefoperazone is a piperazino cephalosporin which combines many of the properties of cefamandole and piperacillin in its in vitro spectrum with greater activity than either agent (7). The purpose of this study was to compare the pharmacokinetics of cefoperazone and cefamandole after a single intravenous dose (2 g) to determine whether the serum levels achieved would allow a two- or three-times-per-day dosing program.

MATERIALS AND METHODS

Cefoperazone and cefamandole were supplied by Pfizer Pharmaceuticals and Lilly Research Laboratories, respectively. The antibiotics were reconstituted in sterile water for administration. Seven normal male subjects between the ages of 24 and 35 were used in this study. All subjects were judged healthy on the basis of normal physical examinations, complete blood counts, urinalysis, and blood chemical studies. Informed, written consent in accordance with the institutional guidelines was obtained from each subject. The mean age of the subjects was 28 years (range, 24 to 35); the mean weight was 72.5 kg (range, 68 to 86); and the mean body surface area was 1.88 m² (range, 1.29 to 2.1).

Each of the seven subjects received either 2 g of cefoperazone or 2 g of cefamandole infused intravenously through a small-bore needle over a 30-min period. The drugs were given by random allotment, with 1-week interval between infusions. Blood samples were drawn through a scalp vein needle fitted with a heparin lock inserted in a vein of the opposite arm. Before sampling, 1.5 ml of blood was discarded to avoid heparin contamination of samples.

Samples of blood were drawn before infusion and at 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 12, and 24 h after the start of the infusion. Urine samples were collected after 2, 4, 8, and 24 h after intravenous infusion. When the blood samples had clotted, they were immediately centrifuged, and the serum was decanted. Duplicate samples for each time point were stored at −20°C. Standards of lithium cefamandole and sodium cefoperazone were prepared in pooled human serum obtained from the same subjects before beginning the study and which had been shown to lack antibacterial activity. Urine samples were also immediately frozen and subsequently diluted in 0.05 M potassium phosphate buffer, pH 7.0, and assayed against antibiotic standards prepared in the same buffer. Both cefamandole and cefoperazone are stable under these conditions (7, 8). Furthermore, samples of cefoperazone and cefamandole at concentrations of 100 and 1 μg/ml were prepared in the serum on the day of infusion, frozen, and assayed when all the samples were assayed.

Cefoperazone and cefamandole were assayed by the agar well diffusion technique, using antibiotic medium no. 2 (Difco Laboratories) as previously described (6, 7). Cefoperazone was assayed with an Escherichia coli strain from our collection, and cefamandole was measured in a similar fashion with Staphylococcus aureus ATCC 3472. All samples were tested in quadruplicate. Five standards in quadruplicate were included on each assay plate. The assay for cefoperazone could detect 0.4 μg/ml and gave linear results over concentrations ranging from 0.4 to 100 μg/ml. The assay of cefamandole could detect 0.4 μg/ml and was linear from 0.4 to
FIG. 1. Mean serum concentrations of cefoperazone and cefamandole ± standard errors after 30-min intravenous infusion (2 g).

FIG. 2. Mean urinary recoveries of cefoperazone and cefamandole ± standard errors.

80 μg/ml. Samples which gave results outside the linear part of the curve were diluted in pooled serum which lacked antibacterial activity and re assayed with samples which had not been thawed.

Calculations. Pharmacokinetic parameters were determined with standard methodology (3). Regression lines were determined statistically by the method of least squares. A two-compartment analysis was used (3), and the effect of infusion was considered (5). The basic equation was $C = Ae^{-kt} + Be^{-2kt}$, with volume of distribution ($V_d$) expressed as $V_d = (Dose/[β(A/α + B/β)])$ and the rate constants expressed at $k_{10} = αβ/ K_{21}, K_{21} = (αβ + Ba)/(A + B)$, and $K_{21} = α + β - k_{21} - k_{10}$. The area under the curve (AUC) after the infusion was determined by Simpson’s rule (2). The serum clearance (in milliliters per minute per 1.73 m²) was determined by $C = (Dose)/(AUC × 60) × 1.73/BSA$, where the dose is in micrograms and BSA is the body surface area.

RESULTS

The mean serum concentration of cefoperazone after a 30-min intravenous infusion of 2 g is shown in Fig. 1. The mean serum level at the end of infusion was 256 μg/ml, with a range of 200 to 326 μg/ml. At 1 h, the mean serum level was 108 μg/ml; at 4 h, the mean level was 20 μg/ml; at 6 h, the mean level was 11 μg/ml; at 8 h, the mean level was 4.2 μg/ml; and at 12 h, the mean level was 0.25 μg/ml. We did not detect any drug at 24 h. The mean half-life for cefoperazone was 1.6 h. The apparent volume of distribution was 9.9 liters/1.73 m². Both the serum and renal clearances of cefoperazone were low, with a serum clearance of 85 ml/min and a renal clearance of 25 ml/min. Urine levels of cefoper-
azone ranged from 250 to 3,000 µg/ml in the first 8 h, and most of the excretion took place in the first 4 h after infusion. The urinary recovery of cefoperazone was 29.3% (Fig. 2).

The comparative data for cefamandole are shown in Fig. 1 and 2 and in Table 1. The mean peak serum concentration of cefamandole at the end of the infusion was 188 µg/ml, with levels of 27 µg/ml at 1 h, 11.5 µg/ml at 2 h, 1.8 µg/ml at 4 h, and none detected thereafter. The half-life was 0.72 h, and the apparent volume of distribution was 1.25 liters/m². The serum clearance and renal clearance of cefamandole were much greater than those of cefoperazone, with a serum clearance of 224 ml/min and a renal clearance of 214 ml/min. The area under the serum curve was 356 µg/ml per h for cefoperazone, which was three times that of cefamandole.

Both cefoperazone and cefamandole were well tolerated, but one subject on cefoperazone not included in the calculations developed a urticarial eruption which resolved with administration of diphenhydramine hydrochloride. Three of eight subjects noted loose stools after administration of cefoperazone, but this was resolved within 24 h.

**DISCUSSION**

Cefoperazone has many of the in vitro antibacterial properties of both the antipseudo- 
monad penicillins and cephalosporins since it is 
stable to most of the common β-lactamases of 
both gram-positive and gram-negative bacteria (7). Cefoperazone is active against most Enter-
bacteriaceae at lower concentrations than are 
cefazolin, cefamandole, or cefoxitin. It also in-
hibits the majority of Pseudomonas aeruginosa 
isolates at concentrations of 25 µg/ml, including isolates resistant to carbenicillin (7).

The pharmacokinetic parameters of cefoper-
azone found in this study demonstrate that 
intravenous infusion of a 2-g dose provides serum 
levels for at least 8 h, far in excess of the inhibi-
tory concentrations of most susceptible bacte-
ria, with Pseudomonas excepted. Thus, it could 
be used in a three-times-daily dosage schedule.

The half-life of cefoperazone in this study is 
twice that of cefamandole and only 15% less than 
that of cefazolin (1, 6). Although the serum and 
renal clearances of cefoperazone are similar to 
those of cefazolin, urinary recovery is only 25%, 
compared with a reported recovery of 70 to 90% 
for cefazolin and other cephalosporins (6). The 
results of this study are in close agreement 
with those of three studies published after the man-
uscript was submitted for publication (1, 4, 8).

In patients with tubes in the common bile 
duct, we can account for another 35% of the
drug. Shimizu (8) showed that cefoperazone was not metabolized and that high concentrations could be found in the bile. In ill patients with biliary obstruction, we have recovered the majority of the drug in the urine (95%; manuscript in preparation).

LITERATURE CITED