Pharmacokinetics of Ceforanide in Patients with End Stage Renal Disease on Hemodialysis

JOHN R. HESS, STEVEN J. BERMAN, WILLIAM H. BOUGHTON, JARED G. SUGIHARA, JAMES E. MUSGRAVE, EUGENE G. C. WONG, and ARNOLD M. SIEMSEN

Department of Medicine, John A. Burns School of Medicine, University of Hawaii, Honolulu, Hawaii 96844, and The Renal Institute, St. Francis Hospital, Honolulu, Hawaii 96817

The pharmacokinetics of ceforanide were evaluated in 11 patients with end stage renal disease (creatinine clearance < 5 ml/min). A single intravenous dose of 750 mg/m² produced peak plasma concentrations of 123 ± 29 µg/ml. The plasma half-life (T1/2) of the drug was 19.1 ± 2.5 h. A 5.5 h hemodialysis session removed 53% of the drug and reduced the T1/2 to 5 ± 0.7 h. Plasma concentrations greater than 10 µg/m² were maintained without adverse effects with a 1.5-g/m² dose administered three times a week for 2 weeks.

Ceforanide is a new semisynthetic cephalosporin with a broad antibacterial spectrum (4, 7). It is at least as active as other available cephalosporins against strains of Escherichia coli, Klebsiella, Proteus mirabilis, and Salmonella (1, 4, 7). Comparative testing with cefamandole, cephalaxin, cefoxitin, cephalothin, and cephapirin in vitro discloses that ceforanide is less potent against gram-positive cocci (1, 7), but these observable differences may not be a practical problem in the clinical setting where in vitro mean inhibitory concentrations are exceeded severalfold (4). Like other cephalosporins, ceforanide is predominantly eliminated by the kidney and may accumulate with decreasing renal function (7). The purpose of this study is to describe the pharmacokinetics of ceforanide in patients with end stage renal disease while on hemodialysis (HD) and in the interdialytic period.

MATERIALS AND METHODS

Patient population. Seven male and four female volunteers, ages 26 to 71 years, participated in this study. All patients had a creatinine clearance of <5 ml/min and were considered clinically stable and free of active intercurrent disease. Five were hospitalized for revision of vascular access sites; the others were outpatients. The patients had been undergoing HD treatments for periods ranging from 1 month to 5.5 years, but these observable differences may be a clinical problem in the clinical setting where in vitro mean inhibitory concentrations are exceeded severalfold (4). Like other cephalosporins, ceforanide is predominantly eliminated by the kidney and may accumulate with decreasing renal function (7).

### Table 1. Patient and dialysis system characteristics

| Patient no. | Body surface area (m²) | Blood flow (ml/min) | Dialyser | Dialysate flow (ml/min) |
|-------------|------------------------|---------------------|----------|------------------------|
| 1           | 1.77                   | 250                 | Extracorporeal Ex 23 | 280         |
| 2           | 1.73                   | 250                 | Travenol 1400       | 600         |
| 3           | 1.49                   | 250                 | Extracorporeal Ex 25 | 300         |
| 4           | 1.93                   | 250                 | Extracorporeal Ex 29 | 325         |
| 5           | 1.95                   | 250                 | Extracorporeal Ex 25 | 500         |
| 6           | 1.90                   | 250                 | Extracorporeal Ex 25 | 550         |

### Table 2. Venous plasma ceforanide concentrations and half-life, interdialysis

| Patient no. | Base line | 1h | 4h | 12h | 24h | 36h | Half-life (h) |
|-------------|-----------|----|----|-----|-----|-----|---------------|
| 7           | 0         | 70 | 66 | 47  | 37  | 15 | 16.6          |
| 8           | 0         | 150| 120| 97  | 75  | 38 | 19.4          |
| 9           | 0         | 110| 120| 69  | 50  | 37 | 17.0          |
| 10          | 0         | 175| 140| 95  | 85  | 54 | 22.7          |
| 11          | 0         | 125| 110| 85  | 45  | 40 | 19.9          |
| Mean        | 0         | 126| 109| 78  | 58  | 37 | 19.1          |
| SD*         | 40        | 31 | 21 | 21  | 14  | 14 | 2.5           |

* After 750 mg/m² given intravenously over 10 min starting 30 min before end of HD.

* SD, Standard deviation.
years. All received vitamins and antacids, and none received antibiotics for 3 weeks before or during the study. Complete blood count, serum glutamic oxaloacetic transaminase, alkaline phosphatase, bilirubin, and Coomb’s tests were performed before ceforanide was administered, after 1 week, and after completion of ceforanide treatment. Recirculating single-pass dialysis machines with varying surface areas and dialysate flow rates were used (Table 1). All HD sessions lasted 5.5 h.

**Interdialysis pharmacokinetics.** Five inpatient volunteers were administered ceforanide, 750 mg/m² of body surface area, in 150 ml of normal saline intravenously through the blood access site over 10 min starting 30 min before HD was completed. Forearm blood samples were obtained from the vascular access site at 1, 4, 12, 24, and 36 h after the end of HD, and just before the next HD session.

**Pharmacokinetics during HD.** Six outpatient volunteers received intravenous ceforanide, 750 mg/m² of body surface area, diluted in 100 ml of 5% dextrose and water and administered through the vascular access site over a 10-min period. HD was started 30 min later. Blood samples from the arterial and venous sides of the dialyzer and dialysate samples were obtained after 0, 1, 2, 3, 4, and 5.5 h of HD. All dialysate was collected from one of the patients and assayed.

**Multiple-dose pharmacokinetics.** Six outpatient volunteers each received 1.5 g of ceforanide per m² in 50 ml of normal saline given over 10 min, starting 30 min before the completion of HD, for five consecutive HD sessions spaced at 48 or 72 h apart. Blood samples were obtained from the arterial vascular access just before (trough) and 20 min after (peak) each successive dose.

**Assay for ceforanide.** Blood samples (4 ml) were collected in heparinized vacuum tubes and immediately placed on ice. Plasma was separated within 1 h and frozen until assayed. Dialysate was collected directly into sterile tubes and frozen immediately. Specimens were assayed by the agar plate cup bioassay method using *Bacillus subtilis* spore suspension (Difco Laboratories, Detroit, Mich.) in a nutrient agar overlay. Antibiotic-free human plasma was the diluent for all specimens except for the dialysate assay, in which antibiotic-free dialysate was used. These methods have been previously described (2, 3, 6).

**Kinetic calculations.** The half-life ($T_{1/2}$) of ceforanide was determined by the formula $T_{1/2} = \ln 2/K_e$ where $\ln$ is the natural logarithm and $K_e$ is the exponential elimination rate determined by the least-squares method.

**RESULTS**

The $T_{1/2}$ of ceforanide in patients with end-stage renal disease was 19.1 ± 2.5 h in the interdialysis period (Table 2). HD reduced the $T_{1/2}$ to 5 ± 0.7 h in six other patients (Tables 1 and 3). Of the administered dose, 46% of ceforanide was recovered in the full volume of dialysate collected from one patient (no. 1).

Ceforanide, 1.5 g/m² of body surface area, administered to six patients at the conclusion of

---

**Table 3. Plasma and dialysate ceforanide concentrations and arterial half-life during HD.**

| Patient no. | Ceforanide (mg/l) at 0 h | Ceforanide (mg/l) at 3 h | Arterial half-life (h) |
|-------------|--------------------------|--------------------------|-----------------------|
| 1           | 10                      | 98                      | 3.5                   |
| 2           | 70                      | 55                      | 2.5                   |
| 3           | 50                      | 45                      | 1.5                   |
| 4           | 30                      | 25                      | 1.0                   |
| 5           | 20                      | 15                      | 0.5                   |
| 6           | 10                      | 5                       | 0.1                   |

---

**Table 4. Distribution and elimination of ceforanide.**

| Mean        | 100 % | 50 % | 25 % | 10 % | 5 % | 1 % |
|-------------|-------|------|------|------|-----|-----|
| 200 mg/m²   | 64    | 32   | 16   | 8    | 4   | 2   |
| 100 mg/m²   | 60    | 30   | 15   | 7    | 3.5 | 1.5 |
| 50 mg/m²    | 55    | 27.5 | 13.75| 6.875| 3.4375|1.71875|

---

*After 750 mg/m² of body surface area given intravenously over 10 min with 30 min of equilibration before HD.

---

*Standard deviation.
**Table 4. Plasma ceforanide concentrations with thrice-weekly dosing**

| Patient no. | Baseline | Day 1 peak | Day 3 Peak | Day 5 Peak | Day 8 Peak | Day 10 Peak | Day 12 Peak |
|-------------|----------|------------|------------|------------|------------|-------------|-------------|
|             |          | Trough     | Trough     | Trough     | Trough     | Trough      | Trough      |
| 1           | 0        | 500        | 25         | 280        | 11         | 370         | 25          | 500         | 27          |
| 2           | 0        | 350        | 52         | 310        | 50         | 340         | 57          | 400         | 78          | 54          |
| 3           | 0        | 400        | 44         | 350        | 62         | 330         | 43          | 380         | 71          | 400         | 70          |
| 4           | 0        | 650        | 41         | 400        | 45         | 400         | 38          | 370         | 89          | 400         | 65          |
| 5           | 0        | 380        | 37         | 380        | 50         | 510         | 60          | 300         | 60          | 440         | 43          |
| 6           | 0        | 430        | 40         | 380        | 60         | 350         | 40          | 340         | 36          | 49          |
| Mean        |          | 470        | 40         | 350        | 48         | 383         | 41          | 365         | 60          | 440         | 51          |
| SD          |          | 104        | 9          | 46         | 16         | 67          | 17          | 26          | 25          | 37          | 16          |

*Dose of 1.5 g/m² intravenously given through the dialyzer over 10 min, 30 min before end of HD.

*Peak, At end of HD; Trough, at 5 h of HD.

*SD, Standard deviation.

We gratefully acknowledge the help of the patients and staff of The Renal Institute of St. Francis Hospital, Honolulu, Hawaii.

**LITERATURE CITED**

1. Asawapokee, N., P. Asawapokee, K. P. Fu, and H. Neu. 1978. In vitro activity and beta-lactamase stability of BL-768 compared with those of other cephalosporins. Antimicrob. Agents Chemother. 14:1-5.

2. Berman, S. J., W. H. Boughton, J. G. Sugihara, E. G. C. Wong, M. M. Sato, and A. W. Siemsen. 1978. Pharmacokinetics of cephaloridine in patients with end stage renal disease and during hemodialysis. Antimicrob. Agents Chemother. 14:281-283.

3. Berman, S. J., W. H. Boughton, J. G. Sugihara, E. G. C. Wong, and A. W. Siemsen. 1977. Hemodialysis-associated infectious treatment with cephradin. Antimicrob. Agents Chemother. 13:4-6.

4. Burch, K. H., D. Plohlod, L. D. Savalatas, T. Hadhavan, D. Kiani, E. L. Quinn, R. Del Busto, J. Cardenas, and E. J. Fisher. 1979. Ceforanide: in vitro and clinical evaluation. Antimicrob. Agents Chemother. 18:396-391.

5. Craig, W. A., P. G. Welling, T. C. Jackson, and C. M. Kunin. 1973. Pharmacology of cefapirin and other cephalosporins in patients with renal insufficiency. J. Infect. Dis. 128:537-535.

6. Groves, D. C., and W. A. Randall. 1965. Assay methods of antibiotics: a laboratory manual. New York Medical Encyclopedia, Inc., New York.

7. Leitner, F., M. Misiek, T. A. Pursiano, R. E. Buck, D. R. Chiaholm, R. G. Derigis, Y. H. Tsai, and K. E. Price. 1976. Laboratory evaluation of BL-S786, a cephalosporin with broad-spectrum antibacterial activity. Antimicrob. Agents Chemother. 10:426-435.

8. Nightingale, C. H., D. S. Greene, and R. Quintilliani. 1975. Pharmacokinetics and clinical use of cephalosporin antibiotics. J. Pharm. Sci. 64:1899-1929.

9. Shadomy, S., G. Wagner, and M. Carver. 1978. In vitro and in vivo studies with BL-S786, cefoxitin, and cephamandole. Antimicrob. Agents Chemother. 13:412-415.

10. Weaver, S. S., B. M. LeBlanc, and G. P. Bodey. 1978. BL-S786 (ceforanide), a new parenteral cephalosporin: in vitro studies. Antimicrob. Agents Chemother. 18:315-322.

**DISCUSSION**

The pharmacokinetics of ceforanide were studied in patients with end stage renal disease. The plasma $T_{1/2}$ of ceforanide (19.1 ± 2.5 h) suggests that it is a more stable compound than cephapirin ($T_{1/2} = 12$ h) (5), cephalexin ($T_{1/2} = 11$ h) (5), and cefamandole ($T_{1/2} = 12$ h) (S. J. Berman, unpublished data), but not cefazolin ($T_{1/2} = 35$ h) (5). Unfortunately, published data obtained during HD are not easily compared due to variances in coil sizes, blood and dialysate flow rates, and duration of HD. Most studies do agree that the cephalosporins are readily removed by currently available HD systems. Ceforanide follows this pattern.

A purpose of this study was to develop guidelines for clinical trials using ceforanide in infected patients. Based on these data, a loading dose of 750 mg/m² of body surface area, followed by a similar dose after each HD session, would seem to be a suitable schedule to provide an effective antibacterial plasma concentration against susceptible organisms.

**ACKNOWLEDGMENTS**

This work was supported in part by a grant from Bristol Research Laboratories, Syracuse, N.Y.

We gratefully acknowledge the help of the patients and staff of The Renal Institute of St. Francis Hospital, Honolulu, Hawaii.