

## Pharmacokinetic Evaluation of Cefoperazone in Infants

MATHEW VARGHESE, ABDUL J. KHAN,\* KUSUM KUMAR, WARREN ROSENFELD, HENRY A. SCHAEFFER, AND HUGH E. EVANS

Department of Pediatrics, Interfaith Medical Center, State University of New York Downstate Medical Center, Brooklyn, New York 11213

Received 31 December 1984/Accepted 29 April 1985

**The pharmacokinetics of cefoperazone were evaluated in 25 infants (mean age, 26 days) after intramuscular and intravenous routes of administration. The levels in blood that were achieved were severalfold higher than those required to inhibit common pathogens. The mean half-life of 240 min was one-half of that observed in 1- to 2-day-old infants but about twice that seen in adults. Further evaluation is needed to study the efficacy of the drug in infants and children.**

Cefoperazone (CPZ) is a new semisynthetic third-generation cephalosporin antibiotic with a broad antimicrobial spectrum which includes *Pseudomonas aeruginosa*, *Serratia marcescens*, *Staphylococcus aureus*, ampicillin-resistant *Haemophilus influenzae*, and *Streptococcus agalactiae* or group B streptococcus in addition to other common gram-negative and gram-positive pathogens (3, 7, 9). It has a longer half-life than other third-generation cephalosporins (8) and crosses the blood brain barrier in therapeutic concentrations (4, 5). Studies in adults have revealed CPZ to be useful in various bacterial infections (6, 10), including meningitis (5). In the pediatric age group, including neonates, the drug has not been well studied. Single doses administered during the first week of life were safe and revealed a prolonged half-life (11). We now report the pharmacokinetics of this drug in infants older than 2 weeks.

(This paper was presented at the 83rd Annual Meeting of the American Society for Microbiology, March 1983, New Orleans, La.)

A total of 25 full-term infants, 9 to 21 days of age (mean age, 19 days), were treated with CPZ for pustular skin infection due to *Staphylococcus aureus* susceptible to the drug. CPZ was administered in doses of 12.5 mg/kg every 12 h by the intravenous (i.v.) or intramuscular (i.m.) route, or

tered 15 to 16 h after the previous therapeutic dose was modified to subdivide the infants into four dosage subgroups, including (i) 25 mg/kg i.v. (ii) 25 mg/kg i.m., (iii) 12.5 mg/kg i.v., and (iv) 12.5 mg/kg i.m. The i.v. dose diluted to a concentration of 25 mg/ml was infused in a peripheral vein over a 5-min period. Blood was then collected by heel pricks at six different time intervals in each (see Table 1). An additional specimen was collected just before the dose in the i.m. groups and at the end of infusion in the i.v. groups. Serum was separated immediately and kept frozen at  $-20^{\circ}\text{C}$ . The specimens were shipped in dry ice within 2 to 6 weeks of collection to the University of Tennessee, where they were received in a frozen state. The concentration of CPZ was determined by high-performance liquid chromatography by using a Waters Associates HPLC system with a model 440, 254-fixed-wave-length detector and a Bondapak C-18 column (10  $\mu\text{m}$  by 13.9 mm by 30 cm). Samples were run isocratically with hydrochlorothiazide as an internal standard. The serum half-life ( $t_{1/2}$ ) and volume of distribution were determined by plotting the serum concentration against time by using a semilogarithmic graph as previously described (11). The  $t_{1/2}$  was calculated when the level in blood was declining exponentially during the elimination phase by utilizing the formula  $t_{1/2} = \ln 2/k$  where  $k$  is the elimination rate constant,

TABLE 1. Levels of CPZ in blood

Dose (mg/kg) and route	n	Levels in blood ( $\mu\text{g/ml}$ ) <sup>a</sup> at h:								
		Predose	0 <sup>b</sup>	0.25	0.5	1	2	4	8	24
25 i.m.	7	0.0		70.7 (30.6)	66.3 (18.9)	68.4 (14.3)	65.5 (17.5)	43.1 (11.3)	21.6 (8.3)	3.7 (4.3)
25 i.v.	5		169.0 (95.0)	123.7 (52.6)	93.1 (34.6)	85.4 (31.8)	64.5 (19.0)	44.4 (14.8)	21.5 (9.3)	5.2 (4.2)
12.5 i.m.	7	0.0		35.6 (13.2)	41.2 (14.0)	37.3 (11.5)	32.1 (12.5)	20.3 (8.8)	12.1 (4.8)	1.5 (2.7)
12.5 i.v.	6		66.8 (19.0)	54.7 (12.8)	45.0 (8.7)	43.3 (7.5)	36.4 (6.4)	23.3 (3.8)	13.2 (4.1)	3.0 (1.7)

<sup>a</sup> Values represent the mean ( $\pm$  standard deviation) and were similar for the i.v. and i.m. groups beyond 0.25 h (i.m. versus i.m. and i.v. versus i.v. levels,  $P < 0.05$ ).

<sup>b</sup> End of i.v. infusion. Compare the levels at 0.25 h for the i.m. and i.v. 25-mg/kg doses and for the i.m. and i.v. 12.5-mg/kg doses ( $P < 0.05$ ).

both, for an average of 7 days. Written informed consent was obtained from the parents of each infant.

Pharmacokinetic studies were performed after the last dose, when the mean age was 26 days. The dose adminis-

represented by the slope of the regression line determined by the method of least squares. The volume of distribution was determined by dividing the dose in micrograms by the area under the curve. For statistical analysis Student's  $t$  test and regression analysis were utilized.

The drug levels in blood (Table 1) after the i.m. dose

\* Corresponding author.

TABLE 2.  $t_{1/2}$ , volume of distribution, and area under the curve of CPZ<sup>a</sup>

Dose (mg/kg) and route	<i>n</i>	Area under the curve ( $\mu\text{g} \cdot \text{h/ml}$ )	Volume of distribution <sup>c</sup> (ml/kg)	$t_{1/2}$ (min)
25 i.m.	7	364.7 (83.0)	243.3 (53.3)	234 (66)
25 i.v.	5	423.9 (131.4)	196.5 (43.0)	240 (78)
12.5 i.m.	7	185.7 (67.3)	271.5 (121.1)	264 (30)
12.5 i.v.	6	222.2 (39.8)	201.0 (68.4)	257 (60)

<sup>a</sup> Values represent the mean ( $\pm$  standard deviation).<sup>b</sup> Compare the i.m. and i.v. values ( $P < 0.05$ ).<sup>c</sup> Compare the i.m. and i.v. values ( $P > 0.05$ ).

peaked between 30 and 60 min. The mean peak drug levels, ranging from 41 to 169  $\mu\text{g/ml}$  (with different doses and routes), declined slowly to a mean of 1.5 to 5.2  $\mu\text{g/ml}$  at 24 h. The mean level at 0.25 h with the i.v. route was significantly higher ( $P < 0.05$  in each instance) than that with the i.m. route, but subsequent levels were similar (Table 1). The mean level in serum with the 25-mg/kg dose was significantly higher than the levels obtained with the 12.5-mg/kg dose ( $P < 0.05$  at each time interval). The mean area under the curve with the i.v. route was apparently larger (Table 2) and the volume of distribution was apparently smaller compared with the values with the i.m. route, but these differences did not achieve statistical significance. The mean  $t_{1/2}$  of ca. 240 min or 4 h was approximately the same in each dose group.

These studies indicate the CPZ was quickly absorbed after the i.m. dose and achieved levels in blood comparable to those obtained with i.v. infusions. Levels in blood during 15 to 30 min after the dose were 12 to 100 times the MIC for 90% of the strains of common pathogens, including *Escherichia coli* and *Proteus mirabilis* (9) and 17 to 30 times more than necessary to inhibit 90% of the strains of *Staphylococcus aureus* (9). Levels in blood observed in this study were lower than those reported in 1- to 2-day-old infants, including premature infants (11). This difference may be due to a larger dose (50 mg/kg) and also immature renal and liver functions at that age, as CPZ is excreted both by the renal

and biliary tracts. This is also reflected in a very prolonged  $t_{1/2}$  of almost 7 to 8 h in 1- to 2-day-old infants (11) compared with ca. 3 to 4 h (Table 2) in the present study. The  $t_{1/2}$  in the present study is about twice as long as that reported in adults (1) and is consistent with administration every 12 h in this age group of infants. The result of this and other studies suggest that CPZ may be further evaluated in newborn infants with various bacterial infections.

## LITERATURE CITED

1. Bolton, W. K., W. M. Scheld, D. A. Spyker, and M. A. Sande. 1981. Pharmacokinetics of cefoperazone in normal volunteers and subjects with renal insufficiency. *Antimicrob. Agents Chemother.* 19:821-825.
2. Bosso, J. A., G. M. Chan, and J. M. Matsen. 1983. Cefoperazone pharmacokinetics in preterm infants. *Antimicrob. Agents Chemother.* 23:413-415.
3. Brogdon, R. N., A. Carmine, R. C. Heel, P. A. Morley, T. M. Speight, and G. S. Avery. 1981. Cefoperazone: a review of its *in vitro* antimicrobial activity, pharmacological properties and therapeutic efficacy. *Drugs* 22:423-460.
4. Durack, D. T., and J. R. Perfect. 1981. Cefoperazone in bacterial meningitis: experimental studies. *Drugs* 22(Suppl. 1):60-64.
5. Ellis-Pegler, R. B., and S. D. R. Lang. 1981. Cefoperazone in *Klebsiella* meningitis. *Drugs* 22(Suppl. 1):108-118.
6. Gerber, A. U., and W. A. Craig. 1981. World wide clinical experience with cefoperazone. *Drugs* 22(Suppl. 1):69-71.
7. Jones, R. N., P. C. Fuchs, A. L. Barry, T. L. Gavan, H. M. Somers, and E. H. Gerlach. 1980. Cefoperazone (T-1551), a new semisynthetic cephalosporin: comparison with cephalothin and gentamicin. *Antimicrob. Agents Chemother.* 17:743-749.
8. Kemmerich, B., H. Lode, G. Belmega, T. Jendroschek, K. Borner, and P. Koeppe. 1983. Comparative pharmacokinetics of cefoperazone, cefotaxime, and moxalactam. *Antimicrob. Agents Chemother.* 23:429-434.
9. Muijtens, H. L., and J. van der Ros-van de Repe. Comparative activities of 13  $\beta$ -lactam antibiotics. *Antimicrob. Agents Chemother.* 21:925-934.
10. Park, S. C., J. H. Lee, S. Y. Kim, and Y. H. Kim et al. 1981. A clinical trial with cefoperazone in pneumonia and pyelonephritis. *Drugs* 22(Suppl. 1):72-75.
11. Rosenfeld, W., H. E. Evans, R. Batheja, R. C. Jhaveri, K. Vohra, and A. J. Khan. 1982. Pharmacokinetics of cefoperazone in full-term and premature neonates. *Antimicrob. Agents Chemother.* 23:866-869.