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Pharmacokinetics of Cefoperazone in Full-Term and Premature Neonates

WARREN N. ROSENFELD,* HUGH E. EVANS, ROMA BATHEJA, RAMESH C. JHAVERI, KIRAN VOHRA, AND ABDUL J. KHAN

Division of Newborn Medicine, Department of Pediatrics, Interfaith Medical Center, Brooklyn, New York 11238

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The pharmacokinetics of cefoperazone were evaluated in 28 newborn infants who were being treated for sepsis. A dose of 50 mg/kg was administered intravenously on days 0 to 2 in all, with a second dose administered on days 5 to 7 in 14 infants. Cerebrospinal fluid penetration was also studied in seven neonates. The mean peak concentration of cefoperazone in the serum of premature infants <33 weeks of gestational age, 159 (standard deviation, ±22) μg/ml, was higher than concentrations in premature infants 33 to 36 weeks of age and full-term infants (110 ± 41 and 109 ± 29 μg/ml, respectively). The mean concentrations 24 h after dosage were similar in all three groups, 13 to 17 μg/ml. The mean serum half-lives were similar in the three subgroups and ranged from 7 to 9 h. After the dose at 5 to 7 days, mean blood levels in the subgroups at 0.5 h were 149, 112, and 112 μg/ml; 24-h levels ranged from 9 to 12 μg/ml. The mean serum half-lives ranged from 5 to 7 h. Cerebrospinal fluid levels in patients with meningitis ranged from 2.8 to 9.5 μg/ml and in patients without meningitis from 1 to 7 μg/ml. Peak blood levels were 15 to 1,000 times higher than the 90% minimal inhibitory concentration of common pathogens found in newborns. These observations support the potential efficacy of cefoperazone in treatment of infections, including meningitis, in newborn infants.

Cefoperazone (CPZ), a recently introduced broad-spectrum cephalosporin, is active in vitro against most gram-positive organisms, including group B streptococci, and gram-negative organisms, including *Pseudomonas* spp. (2–4). In adults, it has been effective in the treatment of various bacterial infections, including meningitis (2, 4). We have studied the pharmacokinetics, safety, and cerebrospinal fluid (CSF) penetration of CPZ in term and preterm neonates as a first step toward evaluating its protection against systemic infections in that age group.

MATERIALS AND METHODS

Twenty-eight neonates admitted for evaluation and treatment of documented or suspected sepsis were enrolled after written, informed consent from their parents was obtained. All were receiving aqueous penicillin and gentamicin. Sepsis evaluation, including blood, urine, stool, and CSF cultures, was completed before conventional therapy.

CPZ was administered in a single dose of 50 mg/kg of body weight as an intravenous infusion over a 3-min period. Of the 25 patients included in the pharmacokinetics study, 13 received the dose on day 1 and 12 received the dose on day 2 of life. Of these 25, 11 were full-term infants (gestational age, ≥37 weeks) with a mean birth weight of 3,068 g. Of the 25, 14 were preterm infants, including 9 infants 33 to 36 weeks old (mean weight, 1,896 g) and 5 infants 27 to 32 weeks old (mean weight, 1,220 g). A second dose of CPZ (50 mg/kg) was administered intravenously between days 5 and 7 to 14 of 25 infants, including 5 full-term and 9 preterm infants. The remaining three infants (two premature and one full-term) with documented meningitis were given CPZ between 2 and 3 weeks of life.

Blood samples (0.5 ml), drawn before CPZ administration and at 0.5, 1, 2, 4, 8, 12, and 24 h thereafter, were centrifuged immediately after collection. The separated serum was stored at −20°C. Urine was collected for 24 h after dosage; the volume was measured, and a sample was stored at −20°C. CSF and blood samples were obtained simultaneously from seven infants and stored at −20°C; four of those infants had documented meningitis.

Serum, urine, and CSF were analyzed for CPZ content by high-pressure liquid chromatography by the Division of Biopharmaceutics and Pharmacokinetics, College of Pharmacy, University of Tennessee, Knoxville. A high-pressure liquid chromatography system (Water's Associates) with a 254-nm fixed wavelength detector (model 440) and a Bondapak C-18 column (10 μm by 13.9 mm by 30 cm) were used in these analyses. Samples were run isocratically with hydrochlorothiazide as an internal standard. The serum half life ($t_{1/2}$) was determined by the formula $t_{1/2}$ =

ln 2/k, where k is the elimination rate constant represented by the slope of the regression line, determined by plotting the log of drug concentration against time. The volume of distribution (V_d) was determined by the formula: V_d = dose (milligrams × 1,000)/Ec (milligrams per milliliter) × weight (kilograms). Complete blood count, blood urea nitrogen, serum electrolytes, creatinine, bilirubin, serum glutamic oxalacetic transaminase, serum glutamic pyruvic transaminase, and urinalysis were performed before and 24 to 48 h after the dose of CPZ.

The Student t test and regression analysis were used for statistical evaluation.

RESULTS

Concentrations of CPZ in serum and pharmacokinetic parameters of 25 infants who received this drug on days 1 and 2 of life are presented in Table 1. In full-term neonates, the mean peak levels of 109 μg/ml observed at 0.5 h slowly declined over 24 h to 13 μg/ml. Serum levels observed at 0.5 h (110 μg/ml) and 24 h (14 μg/ml) in nine premature neonates, 33 to 36 weeks old, were similar to those of full-term neonates. The mean $t_{1/2}$ of 7.19 and 7.63 h, mean V_d of 450 and 477 ml/kg, and the area under the curve (AUC) of 1,113 and 1,150 μg · h/ml, for full-term and premature neonates of 33 to 36 weeks gestation, respectively, were also comparable. In the five premature infants of less than 33 weeks gestation, the mean blood levels attained at 0.5 h (159 μg/ml) and 12 h (48 μg/ml) were significantly higher than those observed in the two more mature groups ($P < 0.01$ and 0.05, Table 1). The mean $t_{1/2}$ (8.94 h) of these five infants was significantly longer ($P > 0.05$) than that of the other two groups (Table 1).

A comparison of results obtained for 14 infants on days 1 and 2 and 5 to 7 is presented in Table 2. The serum levels, $t_{1/2}$, AUC, and V_d observed on the first 2 days were similar to those observed on days 5 to 7, except in the most premature group (<33 weeks of gestation). The mean blood level of 112 μg/ml at 0.5 h on days 5 to 7 was lower than the 162 μg/ml observed on days 1 and 2 ($P < 0.01$); the mean $t_{1/2}$ of 9.42 h on days 1 and 2 observed in this group decreased to 7.08 h on days 5 to 7 ($P < 0.05$).

The percentage of the total dose of CPZ excreted in urine on days 1 and 2 was highest in the most premature patients (mean, 55%; range, 28 to 93%), but was not statistically different from that of the full-term (mean, 37%; range, 27 to 55%) and 33- to 36-week group (mean, 34%; range, 24 to 41%). After dosage on days 5 to 7, excretion of CPZ decreased in the full-term (mean, 27%; range, 15 to 32%) and 33- to 36-week infants (mean, 18%; range, 7 to 35%). Excretion of CPZ in the most premature infants remained high (mean, 55%; range, 33 to 68%)

TABLE 1. Serum CPZ levels and pharmacokinetics on days 1 and 2

Gestational age of patients (no. of patients)	Mean μg of CPZ per ml of serum ± SD at the following times (h)						Mean $t_{1/2}$ ± SD (h)	Mean V_d ± SD (μg/ml)	Mean AUC ± SD (μg · h/ml)
	0.5	1	2	4	8	12	24			
Full-term (11)	109 ± 29	109 ± 30	97 ± 24	77 ± 22	56 ± 18	34 ± 16	13 ± 9	7.19 ± 1.97	450 ± 96	1,113 ± 385
33 to 36 wk (9)	110 ± 41	105 ± 40	93 ± 33	82 ± 29	52 ± 25	38 ± 25	14 ± 17	7.63 ± 3.12	477 ± 144	1,150 ± 620
<33 wk (5)	159[a] ± 22	120 ± 25	97 ± 20	83 ± 17	61 ± 15	48[b] ± 13	17 ± 11	8.94 ± 2.13	441 ± 43	1,298 ± 97

[a] $P < 0.01$.
[b] $P < 0.05$ when compared to full-term and 33- to 36-week groups.

TABLE 2. Comparison of serum CPZ levels and pharmacokinetics during the first week of life

Gestational age of patients (no. of patients)	Day of study	Mean μg of CPZ per ml of serum ± SD at the following times (h)						Mean $t_{1/2}$ ± SD (h)	Mean V_d ± SD (μg/ml)	Mean AUC ± SD (μg · h/ml)
		0.5	1	2	4	8	12	24			
Full-term (5)	1–2	124[a] ± 33	125 ± 32	111 ± 25	84 ± 30	68 ± 18	41 ± 20	14 ± 13	7.21 ± 2.06	399 ± 101	1,271 ± 475
	5–7	149 ± 13	142 ± 15	123 ± 27	90 ± 17	60 ± 12	35 ± 7	12 ± 5	6.37[b] ± 1.04	346 ± 59	1,265 ± 235
33–36 wk (5)	1–2	85[b] ± 25	84 ± 30	75 ± 18	71 ± 8	42 ± 7	27 ± 3	7 ± 1	6.51[b] ± 1.02	547 ± 138	939 ± 232
	5–7	112 ± 39	102 ± 31	86 ± 31	69 ± 24	39 ± 18	30 ± 15	9 ± 5	5.86[b] ± 2.07	465 ± 140	964 ± 402
<33 wk (4)	1–2	162[a,b,c] ± 25	117 ± 25	95 ± 23	81 ± 19	63 ± 17	47 ± 15	18 ± 12	9.42[b,d] ± 2.08	459 ± 101	1,321 ± 379
	5–7	112[c] ± 14	102 ± 25	81 ± 15	71 ± 11	45 ± 10	33 ± 7	9 ± 7	7.08[d] ± 0.32	509 ± 80	978 ± 226

[a] Infants <33 weeks old (days 1 and 2) versus full-term infants and infants 33 to 36 weeks old: $P < 0.05$.
[b] Infants <33 weeks old (days 1 and 2) versus full-term infants and infants 33 to 36 weeks old: $P < 0.02$.
[c] Infants <33 weeks old (days 1 and 2) versus infants <33 weeks old (days 5 to 7): $P < 0.01$.
[d] Infants <33 weeks old (days 1 and 2) versus infants <33 weeks old (days 5 to 7): $P < 0.05$.

and was significantly greater ($P < 0.05$ and $P < 0.03$) than in the other two groups.

The $t_{1/2}$, V_d, and AUC did not correlate with pre- and postdose bilirubin or creatinine concentrations on days 1 and 2. However, at days 5 to 7, the $t_{1/2}$ ($m = 80$; $b = 581$; $r = 0.6500$; $P < 0.02$) and AUC ($m = 76$; $b = 612$; $r = 0.6364$; $P < 0.02$) were related, and V_d was inversely related ($m = 0.014$; $b = 12.53$; $r = 0.6338$; $P < 0.02$) to bilirubin levels.

The concentrations of CPZ in the CSF of seven infants are presented in Table 3. Four patients with meningitis had CPZ concentrations that ranged from 2.8 to 9.5 μg/ml and CSF to serum ratios that ranged from 4.2 to 31.7%. In two of three infants without meningitis, CSF levels were 1.14 and 7 μg/ml, with CSF to serum ratios of 0.4 and 9.2%, respectively. The remaining patient had a CSF concentration of <1 μg/ml.

All infants tolerated the single dose of CPZ well. None developed adverse side effects. Laboratory tests repeated after CPZ administration did not vary from pre-CPZ values. Two patients with meningitis who were severely ill before CPZ administration died of meningitis.

DISCUSSION

Our study shows that a single dose of CPZ administered during the first week of life produced high serum levels for 24 h after the dose. Although the peak levels achieved were similar to those in adults, there was a three-fold prolongation of the $t_{1/2}$ and a two-fold increase in the AUC in the newborns (1, 6). During the first days of life, renal excretion of CPZ was greater in the newborns than in adults (1, 6), and its effect persisted for 7 days in the premature infants of ≤32 weeks gestation.

The higher serum levels and prolonged $t_{1/2}$ in newborns may result from their relatively poor renal function and immaturity of hepatic func-

TABLE 3. Distribution of CPZ in CSF

Status of patient		CSF culture	Time of sample (h after dose)	μg of CPZ per ml		
Birth wt (g)	Length of gestation (wk)			CSF	Serum	Ratio of CSF to serum (%)
3,600	40	GBS[a]	2	2.8	59	4.7
1,580	38	*E. coli*	18	9.5	30	31.7
2,240	36	GBS	1	9.0	214	4.2
3,600	40	GBS	4	6.8	76	9.0
1,540	32		4	7	76	9.2
2,220	33		2	1	88	
2,830	40		2	1.14	83	1.4

[a] Group B streptococcus.

tion. In adults, more than 69% of the administered dose is excreted by the hepatic route (1; W. A. Craig, R. Greenfield, M. Goetz, and B. Vogelman, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 21st, Chicago, Ill., abstr. no. 756, 1981). Renal impairment in adults does not affect the $t_{1/2}$, but liver disease causes a two- to three-fold prolongation (21st ICAAC, abstr. no. 756). Neonates may compensate for diminished hepatic excretion of CPZ by increasing renal excretion, suggested by the recovery of a large proportion of the administered dose in all three groups of neonates, especially those of <33 weeks gestation. In this latter group, hepatic function presumably remained immature at 5 to 7 days, and their renal excretion may have remained high (51%) as a compensatory mechanism. Conversely, a decline in renal excretion in the full-term and 33- to 36-week group was observed, suggesting that hepatic function had matured and the primary route of CPZ excretion via the biliary tree was now available. The correlation of $t_{1/2}$ and serum bilirubin at 5 to 7 days also suggests that the state of hepatic maturity is important in the pharmacokinetics of this drug.

In the neonates studied, the mean peak level of CPZ at 0.5 h was 15 to 100 times the concentration required to inhibit 90% of common pathogens, including *Escherichia coli, Proteus mirabilis*, and *Staphylococcus aureus* (3). Levels at 24 h were two times the concentration required to inhibit 90% of these organisms. Against group B streptococcus, a leading cause of neonatal sepsis and meningitis, levels at 0.5 and 24 h were 1,000 and 100 times greater than that needed to inhibit 100% of strains (3). Likewise, CSF levels in the three patients with meningitis caused by group B streptococcus were between 224 and 720 times higher than the concentration, ≤0.125 μg/ml, required to inhibit 100% of strains. The CSF concentration in two of three patients without meningitis was 9 to 500 times the concentration required to inhibit 100% of group B streptococcus organisms.

These findings suggest that CPZ has potential for the treatment of meningitis in this age group. This potential assumes greater significance in view of the relative inability of other newly developed cephalosporins to cross the blood-brain barrier (5–7). These observations support the use of cefoperazone against infections in premature and full-term neonates.

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