

Cefoperazone Pharmacokinetics in Preterm Infants

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The elimination pharmacokinetics of cefoperazone, a new cephalosporin, were studied in 15 preterm infants ranging in gestational age from 32 to 36 weeks and in postnatal age from 1 to 6 days. The infants received a single dose of either 50 or 250 mg of cefoperazone per kg by intravenous infusion. Blood samples were collected at specified times after completion of the drug infusion and then assayed for cefoperazone. Pharmacokinetic parameters were determined by noncompartmental analysis. Mean values for plasma half-life, elimination rate constant, apparent steady-state volume of distribution, and total body clearance were 5.53 h, 0.15 h^{-1} , 124 ml/kg, and 36 ml/h per kg, respectively, for the group receiving a 50-mg/kg dose and 5.76 h, 0.14 h^{-1} , 111 ml/kg, and 35 ml/h per kg, respectively, for the group receiving a 250-mg/kg dose. Positive correlations between gestational age and clearance and elimination rate were detected. A 50-mg/kg dose every 12 h ensured adequate serum levels for most of the common neonatal pathogens. Other than a transient rise in eosinophils in four subjects, no adverse effects were noted.

Cefoperazone is a new cephalosporin which has a broad antibacterial spectrum (6-8, 15) and differs from other β -lactams in the extent to which it is excreted in the bile (13) and the stability of its elimination pharmacokinetics in the presence of renal impairment (3). Experience to date has revealed a low incidence of side effects (10-12). The activity of cefoperazone against organisms commonly found in neonatal infections suggests that it would be useful in this age group. The purpose of this study was to determine cefoperazone pharmacokinetics in preterm infants so that appropriate dosage regimens could be devised for this age group.

MATERIALS AND METHODS

Patients. The cefoperazone concentrations in serum were determined in 15 premature neonates after a 15-min intravenous infusion of either 50 or 250 mg/kg. The study population was composed of 4 males and 11 females ranging in gestational age from 32 to 36 weeks and in postnatal age from 1 to 6 days. Body weight ranged from 1.42 to 2.81 kg. A physical examination and laboratory test battery including hematology (hemoglobin, hematocrit, leukocyte count with differential, erythrocyte count, reticulocyte count, and platelet count) and chemistry (complete urinalysis, blood urea nitrogen, total bilirubin, serum glutamic oxalacetic transaminase, and serum glutamic pyruvic transaminase) were performed to assess the suitability for entry of the patients into the study. The study protocol was approved by the Institutional Review Board, and informed consent was obtained from the parents of each subject. All subjects were being treated with antibiotics (ampicillin and gentamicin) for suspected or

confirmed bacterial infections and had no evidence of renal or hepatic impairment or evidence or history of allergy to penicillin or cephalosporins. Other medications administered concomitantly to one or more of these subjects included morphine, pentobarbital, and digoxin.

Procedure. All patients were confined to the University of Utah Medical Center Newborn Intensive Care Unit during this study. The subjects received either 50-mg/kg ($n = 12$) or 250-mg/kg ($n = 3$) doses of cefoperazone over 15 min by intravenous infusion. Whenever possible and within the constraints of clinical care, blood samples (0.3 ml) were obtained from an umbilical artery catheter at 5, 10, 15, and 30 min and 1, 2, 4, 8, and 12 h after the completion of the infusion. Samples were not collected from every patient at all times because of technical difficulties. The laboratory test battery referred to above was repeated at 12 and 24 h after cefoperazone administration. In addition, patients were closely monitored for any clinical signs of adverse effects (vital signs, temperature, injection site, lethargy, irritability, feeding, ankle clonus, Moro sign, and general tone). Specimens were immediately centrifuged to harvest serum, which was then frozen at -20°C until it was assayed.

Antibiotic assay. The cefoperazone concentrations in serum were measured in the laboratory of James Wu at the University of Utah, Salt Lake City, Utah, by gradient elution high-pressure liquid chromatography by the procedure developed by J. Dokladolva, Pfizer Quality Control, Pfizer, Inc., Groton, Conn. The assay was performed on a Varian 5000 system (Varian, Palo Alto, Calif.) with a μ -Bondapak C_{18} column (Waters Associates, Milford, Mass.). UV light absorbance detection was utilized at a wavelength of 254 nm. Mobile phase A consisted of 1.2 ml of 1 M triethylamine-acetic acid and 2.8 ml of 1 M acetic acid in sufficient distilled

water to a volume of 1,000 ml. Mobile phase B consisted of 1.2 ml of 1 M triethylamine-acetic acid, 2.8 ml of 1 M acetic acid, and 300 ml of acetonitrile in sufficient distilled water to a volume of 1,000 ml. The gradient consisted of a change in mobile phase B from 25 to 40% over a 15-min period after injection. Separation of cefoperazone from its metabolites and other antibiotics was accomplished with this procedure. The standard deviation for the assay ranged from 3.3 to 5.5% over the concentration range encountered.

Pharmacokinetic analysis. Data from each subject were treated independently to determine the pharmacokinetic parameters for each subject. The data were later grouped to generate mean values. The terminal half-lives were determined by least-squares analysis of the natural log of the serum concentration versus time. The slope of this line is the elimination rate constant (K_{el}). The half-life was determined by dividing 0.693 by the K_{el} . The apparent steady-state volume of distribution (V_{dss}) and total body clearance (Cl_{tot}) were calculated by noncompartmental analysis as described by Benet and Galeazzi (2) corrected for infusion time (9). This method utilized the following relationships:

$$V_{dss} = \text{dose (AUMC)} / (\text{AUC})^2 - b \text{ dose} / 2 (\text{AUC})$$

and

$$Cl_{tot} = V_{dss} K_{ss}$$

where AUMC and AUC are the area under the first moment of the serum concentration-time curve and the area under the serum concentration-time curve, respectively, calculated by the trapezoidal rule (5), b is the infusion time, and K_{ss} is the residence rate constant at steady state determined from the relationship: $K_{ss} = 1/t$, where t = mean transit time = AUMC/AUC. Correlations between pharmacokinetic parameters and gestational age, postnatal age, total bilirubin, blood urea nitrogen, and barbiturate administration were examined.

RESULTS

Preliminary pharmacokinetic treatment of the data revealed that, although cefoperazone elimination followed a classic two-compartment open model (Fig. 1), the distribution phase contributed in a very minor way (mean, 5%) to the total AUC. Thus, determination of the pharmacokinetic values, assuming a one-compartment open model, would introduce little error. However, because collection of all samples during the distribution phase was not possible on all patients, owing to clinical constraints, a noncompartmental analysis was used.

Although mean peak concentrations of cefoperazone in serum for those subjects receiving 250 mg/kg varied considerably from those receiving 50 mg/kg ($720 \pm 264 \mu\text{g/ml}$ versus $136 \pm 28 \mu\text{g/ml}$), the pharmacokinetic parameters did not, suggesting first-order kinetics. Moreover, the mean AUC for the subjects receiving 250 mg/kg, ($9,669 \mu\text{g} \cdot \text{h/ml}$) is approximately five times that of the subjects receiving 50 mg/kg ($1,924 \mu\text{g} \cdot \text{h/ml}$). Mean values (\pm standard deviation) for K_{el} , plasma half-life, Cl_{tot} , and V_{dss} for

the two dosing groups are shown in Table 1. The mean plasma half-life was 5.53 ± 1.70 h for the 50-mg/kg dose and was slightly higher, 5.76 ± 1.69 h, for the 250-mg/kg dose. Both K_{el} and Cl_{tot} were essentially identical, whereas V_{dss} was 124 ± 11 ml/kg with the 50-mg/kg dose and 111 ± 11 with the 250-mg/kg dose.

Other than a transient rise in eosinophils in four subjects, no adverse effects were noted. Although correlations between gestational age and clearance ($\alpha = 0.01$; $r = 0.67$) and elimination rate ($\alpha = 0.05$; $r = 0.57$) were found, no other correlations between pharmacokinetic parameters and gestational or postnatal age, total bilirubin, blood urea nitrogen, or barbiturate administration were detected.

DISCUSSION

In this study, we report the pharmacokinetics of cefoperazone in preterm infants. The elimination of cefoperazone in this age group was determined by noncompartmental analysis but could be adequately described by a one-compartment open model because of a very short (15- to 30-min) distribution phase. As expected, the pharmacokinetic values determined in this age group vary considerably from those reported in adults. The average terminal K_{el} and plasma half-life, Cl_{tot} and V_{dss} reported for adults are 0.37 h^{-1} , 1.8 h, 70 ml/h per kg, and 0.19 liter/kg, respectively (1, 3, 4, 14). The smaller Cl_{tot} reported for our subjects than for adults probably can be explained by immature renal and hepatic functions.

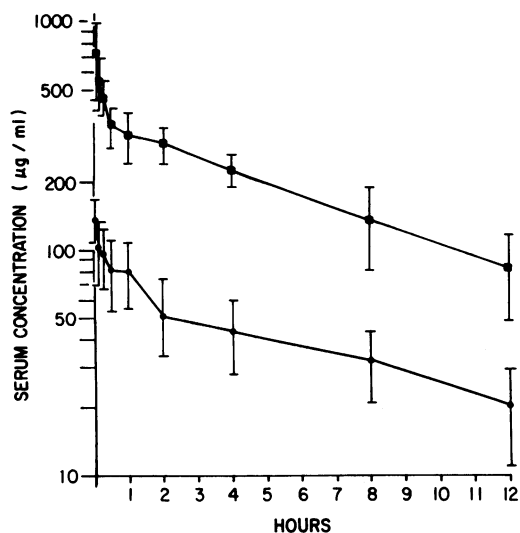


FIG. 1. Mean \pm standard deviation cefoperazone concentrations in serum after a 15-min intravenous infusion of 50 (●) and 250 (■) mg/kg versus time.

TABLE 1. Comparison of mean pharmacokinetic parameters for two dose groups

Dose (mg/kg)	Pharmacokinetic parameters: ^a			
	$t_{1/2}$ (h)	K_{el} (h^{-1})	V_{dss} (ml/kg)	Cl_{tot} (ml/h per kg)
50 ($n = 12$)	5.53 \pm 1.70 (2.66–7.70)	0.14 \pm 0.06 (0.09–0.26)	124 \pm 11 (38–489)	36 \pm 6 (10–91)
250 ($n = 3$)	5.76 \pm 1.69 (4.62–7.70)	0.13 \pm 1.03 (0.09–0.15)	111 \pm 11 (32–152)	35 \pm 6 (13–47)

^a Mean \pm standard deviation (range). $t_{1/2}$, Plasma half-life.

The finding of correlations between gestational age and clearance and gestational age and elimination rate are of interest; however, the study population was too small and the age ranges too narrow to offer any conclusions about its implications. The possibility of correlations between pharmacokinetic parameters and total bilirubin and renal function (blood urea nitrogen) was also explored. Because cefoperazone depends on both renal and hepatic routes for elimination, it was theorized that derangement of one or both functions might affect elimination of the drug. Furthermore, the concomitant administration of a barbiturate could stimulate hepatic metabolism. Although no such correlations were detected, this may be owing to an insufficiently large population size.

Our data indicate that the elimination kinetics are linear (not dose dependent) over a large dosage range. Additionally, secondary to a relatively long half-life, cefoperazone could probably be administered in a 50- to 75-mg/kg dose every 12 h which would maintain adequate serum concentrations for most common pathogens in this age group (7). It should be noted, however, that the postnatal and gestational age ranges of our study population were relatively small. It would be unwise, therefore, to extrapolate this dosage recommendation to infants in other age ranges until pharmacokinetic studies have been performed. Although the drug appears to be safe, studies of efficacy and cerebrospinal fluid penetration must be conducted in this age group before it can be recommended for routine use in infants.

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