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Pharmacokinetics of Ceftazidime in Newborn Infants

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Doses of 50 mg of ceftazidime per kg were administered intravenously to 29 newborn infants every 8 or 12 h for 3 to 5 days. Mean peak concentrations in plasma ranged from 102 to 124 μg/ml. Mean elimination half-life values ranged from 2.9 to 6.7 h and varied inversely with gestational age and plasma clearances. Peak and trough plasma bactericidal titers against an *Escherichia coli* and a group B streptococcus strain were at least 1:16 and 1:32, respectively.

Ceftazidime has a broad spectrum of antimicrobial activity, including the principal pathogens that cause neonatal sepsis and meningitis. This led us to study the plasma concentrations and pharmacokinetics of ceftazidime in 31 newborn infants. These patients ranged from 28 to 41 weeks in gestational age, 1 to 22 days in postnatal age (25 infants were 7 days of age or less), and 805 to 4,170 g in birthweight. The infants were from the nurseries and neonatal intensive care unit of Parkland Memorial Hospital, Dallas, Tex. The study was approved by the Institutional Review Board for Human Research, and written informed consent was obtained from the parents before enrollment of the infants in the study. Antimicrobial therapy was prescribed for possible neonatal sepsis; no study infants had documented bacterial disease.

Ceftazidime was administered as 15- to 20-min intravenous infusions to 29 infants for 3 to 5 days; 3 of these infants and 2 additional infants were given a single dose intramuscularly. These five infants were from 2 to 9 days of age (mean, 4 days) at the time of the intramuscular dose. The dosage used was 50 mg of ceftazidime per kg given every 12 h in week 1 of life and every 8 h thereafter. Plasma samples were taken from an indwelling venous line or by finger stick just before and at various intervals after the dose was administered. All patients also received ampicillin intravenously; the two drugs were always given at separate times to avoid pharmacological interaction.

The concentrations of ceftazidime in plasma were determined by an agar-disk diffusion micromethod with *Morganella morganii* (NTCC 235) as the test organism. The lowest concentration measured by this technique was 1.0 μg/ml. The samples and laboratory standards were prepared identically in 100% pooled human plasma. The intraassay coefficient of variation with 25 measurements of the reference standard was 5.4%. The interassay coefficient of variation determined in a 4-week period in which the reference standard was measured 38 times was 10.8%. Ampicillin activity in plasma was inactivated by the addition of penicillinase (Difco Laboratories); this had no effect on the concentration of ceftazidime. The plasma bactericidal activity of ceftazidime against a strain of *Escherichia coli* K1 (MBC, 0.06 μg/ml) and a group B streptococcus (MBC, 0.03 μg/ml), both isolated from the cerebrospinal fluid of neonates with meningitis, was determined by a standard microtiter technique (3). Dilutions were made in Todd-Hewitt broth for group B streptococcus and in Mueller-Hinton broth for *E. coli*. Penicillinase was added to the media before dilutions were made. A model independent pharmacokinetic analysis was performed by a computer program for each patient. The AUC value was calculated by successive trapezoid approximation, extrapolated to infinity, and corrected for the previous dose when multiple doses were administered. The elimination or beta half-life was determined from $0.693/K$, where K represents the slope that was calculated from the regression analysis of the log concentrations in plasma versus time, from the peak time to 8 h. The plasma clearance (CL_P) was calculated from the formula CL_P = total dose (milligrams)/AUC for the dosing interval, and the volume of distribution (V) was calculated from the formula V = dose (milligrams per kilogram)/AUC × K.

There was considerable variation in the plasma concentrations of ceftazidime (Table 1). The peak values occurred at 0 to 1 after the dose, depending on the gestational age of the infant. The largest concentrations (C_{max}) were observed after multiple doses; these plasma values correlated with smaller volumes of drug distribution than those observed after the first or second dose of ceftazidime (Table 2). The predose plasma concentrations after multiple doses were smaller in the term infants (≥38 weeks of gestation) than in premature infants (<38 weeks of gestation).

The mean ± standard deviation (SD) elimination half-life values after one or two doses were from 6.7 ± 2.6 h in the most premature infants (≤32 weeks) to 4.2 ± 1.2 h in term infants; after multiple doses, the values were from 2.9 ± 1.3 to 3.7 ± 1.3 h in the three study groups. The clearances of ceftazidime from plasma were larger in the more mature infants and after multiple doses; the mean ± SD values ranged from 59 ± 14 to 108 ± 15 ml/kg per h.

The mean ± SD C_{max} of ceftazidime after intramuscular administration in five infants was 108 ± 18.6 μg/ml, and the mean ± SD AUC value was 528 ± 161 μg · h/ml. The mean ± SD plasma half-life was 2.9 ± 1.4 h, and the mean ± SD CL_P was 101 ± 26 ml/kg per h. These pharmacokinetic values were similar to those observed in the group of 33 to 37-week gestational age infants who received multiple doses (Table 2). The gestational ages of the five infants who received ceftazidime intramuscularly were from 34 to 42 weeks (mean, 38 weeks).

These plasma concentrations and pharmacokinetic values are similar to those reported by Boccazzi and associates (1), who also administered doses of 50 mg of ceftazidime per kg to newborn infants. For example, the mean ± SD elimination half-life in their 5 infants with gestational ages of 33 to 36 weeks was 4.5 ± 1.7 h compared with 4.9 ± 1.6 h in 14 of our infants with similar gestational ages. The mean C_{max} in their five infants was 112 ± 23 μg/ml, whereas in our comparably aged subjects, it was 118 ± 28 μg/ml.

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TABLE 1. Plasma concentrations after dosages of 50 mg of ceftazidime per kg in newborn infants

Gestational age (wk)	No. of previous doses[a]	No. of infants	Plasma concn (mean [μg/ml] ± SD) at designated times (h)						
			Pre[b]	0[b]	0.5	1	2	4	8
≤32	0–1	7	ND[c]	98 ± 37	109 ± 15	94 ± 25	76 ± 16	59 ± 13	41 ± 8
	≥5	5	19 ± 5	ND	121 ± 19	118 ± 23	ND	64 ± 15	ND
33–37	0–1	14	ND	135 ± 39	109 ± 18	98 ± 21	75 ± 18	54 ± 12	31 ± 9
	≥5	13	16 ± 5	ND	101 ± 19	117 ± 41	ND	53 ± 14	ND
≥38	0–1	8	ND	98 ± 27	95 ± 18	98 ± 17	66 ± 9	50 ± 10	29 ± 8
	≥5	5	14 ± 1	ND	95 ± 34	85 ± 15	ND	46 ± 6	ND

[a] Plasma concentrations were determined after zero or one (0–1) or multiple (≥5) previous doses of ceftazidime.
[b] Plasma samples were obtained immediately before the dose (Pre) and at the completion of the 15- to 20 -min infusion (0).
[c] ND, Not done.

TABLE 2. Pharmacokinetics of ceftazidime in newborn infants[a]

Gestational age (wk)	No. of previous doses[b]	No. of infants	Mean ± SD				
			C_{max} (μg/ml)	$AUC_{0-\infty}$ (μg · h/ml)	$t_{1/2\beta}$ (h)	CL_p (ml/kg per h)	V (ml/kg)
≤32	0–1	7	111 ± 15†	912 ± 203	6.7 ± 2.6	59 ± 14	529 ± 123
	≥5	7	123 ± 21	641 ± 180	3.7 ± 1.3	94 ± 43	423 ± 86
33–37	0–1	14	118 ± 28	691 ± 156	4.9 ± 1.6	75 ± 15	512 ± 120
	≥5	13	124 ± 38	510 ± 155	2.9 ± 1.3	106 ± 29	425 ± 162
≥38	0–1	8	102 ± 18	619 ± 151	4.2 ± 1.2	85 ± 19	482 ± 87
	≥5	5	108 ± 42	468 ± 62	3.5 ± 0.7	108 ± 15	546 ± 160

[a] Dose was 50 mg of ceftazidime per kg.
[b] See Table 1 for explanation.

Bactericidal titers were determined in 48 peak and 25 trough plasma samples. Medium (range) titers against *E. coli* and group B streptococcus were 1:256 (1:64 to ≥1:1024) and 1:512 (1:32 to ≥1:1024), respectively, in peak specimens and 1:128 (1:16 to 1:512) and 1:256 (1:32 to ≥1:1024), respectively, in trough specimens.

Single and multiple doses of ceftazidime were well tolerated, and there were no adverse effects observed in the 31 infants. The largest plasma concentrations exceeded the 90% MIC of most gram-negative enteric bacilli and *Pseudomonas aeruginosa* by at least 25- to 50-fold, and trough (12-h or predose) concentrations were equal to or several-fold greater (2, 4). Against group B streptococci, the principal bacterial pathogen of neonates, peak and trough plasma levels exceeded the 90% MICs by ca. 200- and 20-fold, respectively. The peak and trough bactericidal titers against a single *E. coli* and group B streptococcus strain were at least 1:16 and 1:32, respectively, and frequently exceeded 1:512.

Because only six infants in our study were older than 7 days of age, it is impossible to make definitive recommendations regarding dosing intervals in these infants. Until additional studies are performed to establish the pharmacokinetics of ceftazidime in older newborn infants, the following provisional dosage schedule is suggested: 50 mg/kg given every 12 h in week 1 of life and every 8 h thereafter.

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