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Pharmacokinetics of Cefotaxime in Newborn Infants

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The pharmacokinetics of cefotaxime were determined in newborn infants who were 1 to 7 days of age. Mean peak serum concentrations of 116 and 132 μg/ml were observed at completion of a 10-min intravenous infusion of 50 mg of cefotaxime per kg in low and average birth weight infants, respectively. The mean elimination half-lives were 4.6 and 3.4 h and rates of clearance from serum were 23 and 44 ml/min per 1.73 m^2, respectively. A dosage schedule for cefotaxime in newborn infants is presented.

Cefotaxime has broad antibacterial activity against gram-positive and gram-negative microorganisms. Although approved by the Food and Drug Administration for use in adults only, cefotaxime has potential for the therapy of neonatal infections because it is effective in vitro (3) and in experimental meningitis (2) against group B streptococci and gram-negative enteric bacilli, the pathogens responsible for most neonatal sepsis and meningitis cases.

The purpose of this study was to determine the pharmacokinetics of cefotaxime in newborn infants. Thirty infants were selected from the nursery of Parkland Memorial Hospital, Dallas, Tex. All infants were receiving ampicillin and gentamicin for suspected sepsis. After informed, written parental consent was obtained, a single 50-mg/kg dose of cefotaxime was given intravenously over a 10-min period. The dose was administered in addition to the antibiotics already prescribed. There were 17 male and 13 female infants enrolled in the study. Approximately 0.2 ml of blood was obtained by heelstick technique at 0 (end of the infusion), 0.5, 1, 2, 4, and 6 h after the infusion. The serum was stored at −20°C until assayed within 4 days of collection. A single, untimed urine specimen was obtained during the 6-h study period.

Concentrations of cefotaxime in serum and urine were assayed by an agar-disk diffusion method, using *Escherichia coli* ATCC 10536 as the test strain. The minimal inhibitory concentrations of cefotaxime and desacetyl cefotaxime for this strain were 0.015 and 0.25 μg/ml, respectively. The lowest concentration of drug measured by the bioassay technique was 1.25 μg/ml. Inactivation of ampicillin was accomplished by incubating the specimen for 15 min with 8,000 U of penicillinase (Difco Laboratories) per ml in 1% phosphate buffer (pH 6.0). This procedure did not affect the activity of cefotaxime. The dilutions of the samples used for assay eliminated an inhibitory effect of the aminoglycoside on the *E. coli* (gentamicin minimal inhibitory concentration, 1.5 μg/ml). Based on analysis of 15 cefotaxime reference curves, the error of the bioassay was ±7% for concentrations of 1.25 to 20 μg/ml.

The serum concentration-time curves for each subject were analyzed by nonlinear least-squares regression analysis with the AUTOAN program (4). The curves were fitted to the bioexponential equation $C(t) = Ae^{-\alpha t} + Be^{-\beta t}$, where $C(t)$ is the serum concentration (micrograms per milliliter) at time t, A and B are preexponential terms in units of concentration, and α and β are hybrid first-order rate constants. The half-lives were obtained by dividing 0.693 by the elimination rate constant. Areas under the serum concentration-time curve (AUC) were calculated by the trapezoidal rule. The volume of distribution (V_d) and total serum clearance (Cl_s) of cefotaxime were calculated by the following formulas: $V_d = D/(AUC_{0-\infty})\beta$ and $Cl_s = D/AUC_{0-\infty}$, where D is the dose. A one-way analysis of variance was applied to evaluate the significance of differences between infant groups.

Thirty infants who were from 1 to 7 days of age were studied. One infant was eliminated from analysis because cefotaxime was mistakenly administered over 45 min. The infants were divided into two groups: group 1 consisted of 14 infants whose mean age ± 1 standard deviation was 4.0 ± 1.6 days and mean birth weight ± 1 standard deviation was 1,103 ± 216 g. Group 2 was composed of 15 infants who had a mean age ± 1 standard deviation of 3.5 ± 1.7 days and mean birth weight ± 1 standard deviation of 2,561 ± 607 g. The infusion of cefotaxime was well tolerated by all 30 infants.

The serum concentrations of cefotaxime are shown in Table 1. Peak values of 115.9 and 132.7

TABLE 1. Serum concentrations of cefotaxime in neonates 1 to 7 days of age

Time (h)	Concn. (μg/ml) after intravenous dose for:	
	Group 1[a] (n = 14)	Group 2[b] (n = 15)
0	115.9 ± 38.1[c] (46–186)	132.7 ± 37.7 (76–208)
0.5	95.6 ± 11.2 (72–112)	106.6 ± 38.8 (72–204)
1	83 ± 18.6 (48–122)	85 ± 23.7 (77–128)
2	69.8 ± 12.5 (48–100)	78.9 ± 15.1 (62–112)
4	48.4 ± 13.6 (18–65)	52.2 ± 10.2 (36–71)
6	34.4 ± 12.1 (6–50)	38.1 ± 6.9 (30–49)

[a] Group 1: mean age 4 ± 1.6 days and birth weight 1,103 ± 216 g.
[b] Group 2: mean age 3.5 ± 1.7 days and birth weight 2,561 ± 607 g.
[c] Mean ± 1 standard deviation (range of values).

μg/ml were observed at the end of the 10-min infusion in group 1 and 2 infants, respectively. The serum concentration-time curves of 18 of 29 subjects were fitted to an open two-compartment IV pharmacokinetic model (correlation coefficients, 0.994 to 1.000). Preliminary results from our laboratory and from deLouvois and associates (J. deLouvois, A. Mulhall, and R. Hurley, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 21st, Chicago, Ill., abstr. no. 135, 1981) using a high-pressure liquid chromatographic assay indicate that in neonates desacetyl cefotaxime accounts for approximately one half of the peak and three fourths of the trough concentrations of total cefotaxime determined by bioassay.

The pharmacokinetics of cefotaxime in neonates are shown in Table 2. The mean elimination half-life was 4.6 h in the low birth weight infants and 3.4 h in average birth weight infants ($P \leq 0.01$). These values are similar to those reported by Kafetzis and co-workers (D. A. Kafetzis, C. Brater, A. N. Kapiki, C. B. Papas, H. D. Dellagrammaticas, and G. J. Papadatos, J. Pediatr., in press) in preterm and term infants. The mean V_d was significantly smaller in group 2 (440 ml/kg) than in group 1 (510 ml/kg) infants, which correlates with the larger mean peak serum concentration in the former group of infants. The mean clearance of cefotaxime from serum was significantly larger in group 2 (43.9 ml/min per 1.73 m^2) compared with group 1 infants (23 ml/min per 1.73 m^2).

TABLE 2. Pharmacokinetic properties of cefotaxime in 29 newborn infants

Group[a]	Mean ± 1 SD for parameter:			
	$t_{1/2}$ (h)	$AUC_{0-6\ h}$ (μg.h/ml)	V_d (ml/g)	Cl_s (ml/min per 1.73 m^2)
1	4.63 ± 1.06	400 ± 55.6	510 ± 60	23 ± 4.9
2	3.37 ± 0.94	392 ± 76.6	440 ± 70	43.9 ± 19.8
P value	≤0.01	>0.05	≤0.01	≤0.001

[a] See Table 1, footnotes *a* and *b* for descriptions of infant groups.

The concentrations of cefotaxime in randomly collected urine samples ranged from 300 to 1,575 μg/ml. The mean concentrations in group 1 and 2 infants were 859 and 846 μg/ml, respectively.

A tentative dosage schedule of 50 mg of cefotaxime per kg given every 12 h to infants 0 to 7 days of age and every 8 h to infants 7 to 28 days of age is suggested. This regimen, which must be confirmed by additional studies in newborn infants, is consistent with pharmacokinetic data for other beta-lactam antibiotics in neonates (1) and with results of a clinical trial of cefotaxime for therapy of meningitis in infants and children (D. A. Kafetzis, K. Bruch, and J. Young, 21st ICAAC, abstr. no. 457). In the latter study of 82 patients, 25 of whom were neonates, cefotaxime was judged to be effective for therapy of bacterial meningitis.

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