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Ceftriaxone Pharmacokinetics in Newborn Infants

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Ceftriaxone pharmacokinetics were determined in 40 newborn infants who were 1 to 45 days of age. Mean peak plasma concentrations of 136 to 173 μg/ml were observed at the completion of a 15-min intravenous infusion of 50 mg of ceftriaxone per kg. Mean half-life values were 5.2 to 8.4 h, and mean plasma clearances were 0.7 to 1.8 ml/min. Rectal swab cultures from 14 of 16 infants had either reduced numbers of aerobic and anaerobic bacteria or no growth during therapy. A once-daily dosage schedule is suggested for ceftriaxone therapy in newborn infants.

Ceftriaxone is exceedingly active in vitro against group B streptococci (90% minimal inhibitory concentration [MIC_{90}], 0.12 μg/ml) (6) and gram-negative enteric bacilli (MIC_{90}, 0.06 μg/ml) (7), the two principal pathogens of neonatal sepsis and meningitis. In experimental group BIII streptococcal meningitis in rabbits, ceftriaxone produced cerebrospinal fluid bactericidal titers of 1:64 and a reduction in organisms of 4.6 $\log_{10}$ CFU/ml of cerebrospinal fluid after 9 h of continuous infusion therapy (6). Similarly, in experimental *Escherichia coli* K1 meningitis, cerebrospinal fluid bactericidal titers of 1:64 and a decline in concentrations of bacteria of 4.8 $\log_{10}$ CFU/ml of cerebrospinal fluid were observed (6). These results in the rabbit meningitis model were comparable or superior to results obtained with all other antimicrobial agents (netilmicin, ampicillin, cefotaxime, cefoperazone, moxalactam, and ceftazidime) studied in our laboratory (4-6).

Ceftriaxone pharmacokinetics were determined in newborn infants who had suspected sepsis at Parkland Memorial Hospital, Dallas, Tex. After informed parental consent was obtained, a single dose of 50 mg of ceftriaxone per kg was administered intravenously over a period of 15 min to 26 infants. Multiple doses of 50 mg/kg were given every 12 h for 4 to 10 days to 14 infants, 5 of whom received some doses intramuscularly. The infants were concomitantly treated with ampicillin. Approximately 0.2 ml of blood was obtained from each of the 26 infants by heel-stick technique just before the ceftriaxone dose and at 0 (end of infusion), 0.5, 1, 2, 4, and 6 h after infusion. In infants who received multiple doses, plasma specimens were obtained at initiation and completion of therapy, except in one infant, who had specimens obtained on separate occasions because therapy was given for 10 days. A single untimed urine specimen was obtained during the 6-h study period.

Ceftriaxone concentrations in plasma and urine were assayed by an agar disk diffusion method with *Escherichia coli* (RO1346) as the test strain (1). The smallest concentration detectable by this method was 0.75 μg/ml. Inactivation of ampicillin was accomplished by incubating the specimens for 15 min with 8,000 U of penicillinase (Difco Laboratories, Detroit, Mich.) per ml in 1% phosphate buffer (pH 6.0). Laboratory standards and plasma samples were identically processed with pooled plasma from healthy donors. Urine was diluted in 1% phosphate buffer (pH 6.0) and compared with standards prepared in buffer. The error of the bioassay was 9%.

Ceftriaxone pharmacokinetics were calculated with values obtained from 0.5 to 6 h after the dose was administered and assuming a one-compartment model. The half-life was determined by dividing the $\log_{10}2$ by the slope of the serum concentration-time curve. Area under the serum concentration-time curve was calculated by the trapezoidal rule (3). Volume of distribution and plasma clearance values were calculated by standard formulae (2, 3).

Rectal swab specimens were obtained from 16 ceftriaxone-treated infants during and after therapy. The specimens were cultured by standard aerobic and anaerobic techniques, and anaerobes were identified by gas-liquid chromatography and by the Minitek Anaerobe II kit (BBL Microbiology Systems, Cockeysville, Md.).

Plasma concentrations and ceftriaxone pharmacokinetics values in 26 newborn infants aged 1 to 45 days were categorized by birth weight and chronological age groups (Table 1). The largest plasma concentrations were observed at

TABLE 1. Plasma concentrations and ceftriaxone pharmacokinetics in 26 newborn infants[a]

Mean wt (g) at birth	Mean age (days)	No. of infants	Mean concn (μg/ml) in plasma at following time (h):					Half-life (h)	Vol of distribution (ml/kg)	Plasma clearance (ml/min)
			0	0.5	1	2	4	6			
1,164	3.2	10	145 ± 18	99 ± 3.3	91 ± 3.3	80 ± 3.9	70 ± 2.9	66 ± 3.3	7.7 ± 0.6	608 ± 24	1.0 ± 0.2
1,176	6.7	3	136 ± 8.9	120 ± 17	108 ± 8.4	91 ± 1.8	76 ± 1.5	71 ± 4.4	8.4 ± 1.6	530 ± 27	0.73 ± 0.1
2,670	2.8	9	158 ± 9.1	118 ± 8.6	112 ± 7.3	108 ± 8.4	79 ± 7.1	74 ± 5.4	7.4 ± 0.5	520 ± 39	1.8 ± 0.2
2,112	22.5	4	173 ± 23	128 ± 5	116 ± 7	112 ± 9	86 ± 9	67 ± 12	5.2 ± 0.6	497 ± 50	1.6 ± 0.1

[a] Values are expressed as mean ± standard error of the mean.

completion of the 15-min infusion (0 time), and the mean values were 136 to 173 μg/ml. The mean plasma half-life values were longest (7.7 to 8.4 h) in infants weighing ≤1,500 g at birth, as compared with values (5.2 to 7.4 h) in those weighing >1,500 g. The shortest half-life values (4.8 and 3.5 h) were noted in the two oldest infants, aged 33 and 45 days, respectively. The mean volume-of-distribution values were 497 to 608 ml/kg; the smaller values were found in the larger and older infants and were associated with larger plasma concentrations. The mean plasma clearance values were similar for the four study groups.

Of nine infants who received multiple ceftriaxone doses intravenously every 12 h for 4 to 9 days, five showed evidence of drug accumulation in plasma. The concentrations increased from 20 to 208% (mean, 82%) at 0.5 h and from 15 to 165% (mean, 53%) at 6 h after 50-mg/kg doses. In one 1,520-g infant who was given 25 mg of ceftriaxone per kg every 12 h for 10 days, peak plasma concentrations were 58, 78, 119, and 140 μg/ml after 1, 7, 13, and 19 doses, respectively. The half-life values in this infant declined from 60 h after dose 1 to 9.4 h after dose 19. The plasma concentration-time curves of five infants were compared after intravenous administration on one day and intramuscular administration on another. The interval between the two doses was 1 to 5 days. Bioequivalence was shown by the area under the serum concentration-time curve values, which were 576 and 574 μg · h/ml after intravenous and intramuscular administrations, respectively.

Ceftriaxone concentrations in randomly collected urine samples ranged from 113 to 3,350 μg/ml (median, 618 μg/ml).

Ceftriaxone was well tolerated, and there was no evidence of hematological or hepatic toxicity after multiple doses. Preliminary results of aerobic and anaerobic cultures of rectal swab specimens performed on 16 ceftriaxone-treated patients were compared with those from nontreated healthy infants of comparable weights and ages. During ceftriaxone therapy, cultures from nine infants had no growth, and those from five infants showed reduced numbers of bacteria and fewer genera. Of nine infants who had sequential cultures during and after therapy, one had abnormal results in all cultures; six had abnormal findings during therapy, in five of whom relatively normal flora was established at 3 to 12 days after therapy and two had normal bacterial flora on all cultures. Additional studies are in progress to determine the significance of these observations.

The conclusion from these pharmacokinetic data is that ceftriaxone can most likely be administered once daily to newborn infants who

have suspected or proven bacterial diseases. Plasma concentrations should exceed the MIC_{90}s for group B streptococci and gram-negative enteric bacilli by at least 500-fold at 0.5 h, 100-fold at 12 h, and 50-fold at 24 h after a single dose of 50 mg of ceftriaxone per kg (6, 7). Final determination of dosage schedules must await results of clinical efficacy and safety trials performed in newborn infants.

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