

Ceftriaxone Distribution Between Maternal Blood and Fetal Blood and Tissues at Parturition and Between Blood and Milk Postpartum

DIMITRIS A. KAFETZIS,¹ D. CRAIG BRATER,^{2*} J. E. FANOURGAKIS,¹ J. VOYATZIS,¹ AND P. GEORGAKOPOULOS¹

Second Department of Pediatrics, A. Kyriakou Children's Hospital, University of Athens, Athens, Greece,¹ and Departments of Pharmacology and Internal Medicine, University of Texas Health Science Center at Dallas, Dallas, Texas 75235²

Received 22 November 1982/Accepted 6 April 1983

The penetration of ceftriaxone into the fetus at parturition was studied in 17 subjects. Despite its high protein binding, ceftriaxone quickly reached the umbilical cord blood, amniotic fluid, and placenta, achieving substantial concentrations, which then disappeared, with elimination half-lives of approximately 6 h, identical to that of the mother. The elimination half-life of ceftriaxone of 5 to 6 h in these mothers was somewhat shorter than that reported for normal subjects. The concentrations of ceftriaxone achieved in fetal tissues were sufficient for therapeutic effects. The penetration of ceftriaxone into milk was studied 3 days postpartum in 20 other patients. This antimicrobial agent entered breast milk rapidly and disappeared with a half-life of 12 to 17 h. The concentrations achieved were only 3 to 4% of those in maternal serum and were most likely of little clinical relevance.

Broad-spectrum cephalosporins could prove to be highly useful for the prophylaxis or treatment of maternal or fetomaternal infections or both (9). Since ceftriaxone has exhibited no serious toxicity in early use and since animal studies indicate no teratogenicity, one may anticipate the use of this drug in pregnancy (9). We, therefore, investigated in 17 subjects the time course of the disappearance of ceftriaxone from the mother and its distribution into the umbilical cord blood, placenta, amniotic fluid, and urine of the neonate. In 20 additional subjects, we assessed the distribution into breast milk.

MATERIALS AND METHODS

Study protocols. (i) **Distribution of ceftriaxone to the fetus.** Seventeen healthy women aged 22 to 42 years, at 38 to 41 weeks of gestation, volunteered for this phase of the study after giving informed consent. These patients were hospitalized for the premature rupture of membranes. All were in active labor. Delivery was induced by an intravenous infusion of oxytocin in 13 patients. Caesarean section was performed in four. Each patient received 2.0 g of ceftriaxone dissolved in a total volume of 20 ml of sterile water as an intravenous bolus over 2 to 5 min. The interval from dosing to tissue sampling was determined by the time of expulsion or of removal of the fetus. The characteristics of this group are shown in Table 1.

Maternal and umbilical cord blood, placenta samples, and an aliquot of amniotic fluid were collected

immediately after delivery. Placenta samples were extensively washed in sterile normal saline, weighed, and homogenized in a Colwarth Stomacher 80 with a triple weight in up to 3 ml of Sorensen buffer, pH 7.2. In addition, in five newborn infants, the first voided urine was collected for analysis.

(ii) **Penetration of ceftriaxone into milk.** Twenty healthy mothers aged 19 to 34 years, who had been breast feeding for the 2 preceding days, participated in the study after giving informed consent. On day 3 postpartum, a 1.0-g dose of ceftriaxone in a volume of 10 ml was administered by intravenous bolus over 2 to 5 min to 10 mothers and by intramuscular injection in a volume of 4 ml to the remaining 10 subjects. Milk samples were obtained immediately before drug administration and 1, 2, 3, 4, 5, 6, 7, 8, 11, 12, 13, 21, 22, 23, and 24 h after dosing. Blood samples were obtained 2, 8, and 24 h after dosing.

(iii) **Assays.** The concentrations of ceftriaxone in milk and the placenta were measured by the agar well-plate technique, with *Sarcina lutea* NTCC 8340 as the indicator organism. The use of this indicator organism made it possible to measure samples from 0.015 to 1.0 µg of ceftriaxone per ml. A strain of *Escherichia coli* (kindly provided by Hoffmann-La Roche Inc.) was used as the indicator organism for the analyses of serum, urine, and amniotic fluid and covered concentrations from 0.62 to 200 µg of ceftriaxone per ml. Samples were stored at -20°C until assayed. Standards, as well as samples, were measured in triplicate. Standard curves were constructed from seven different concentrations. For both assays, the coefficient of variation throughout the concentration range was approximately 10%. Standards were prepared in human

TABLE 1. Ceftriaxone concentrations at parturition

Time elapsed between ceftriaxone dose and parturition (h)	Deliv-ery ^a	Gesta-tional age (wk)	Ceftriaxone concn (μg/ml) ^b in:				Newborn's urine
			Maternal serum	Umbilical cord serum	Amniotic fluid	Placenta ^c	
1	N	40	83.0 (106)	7.5 (19.5)	1.1 (3.8)	18.8 (12.9)	17.0
	C	38	83.0	20.5	3.0	26.0	
2	N	40	152	30.5	7.3	17.9	37.0
	N	40	66.0 (83.0)	13.5 (20.5)	15.8 (14.6)	14.1 (15.5)	
	N	40	105	28.0		22.1	
	N	40	78.0	20.0	13.5	10.2	
4	N	39	75.9 (53.3)	28.8 (26.8)		10.8 (13.7)	15.7
	N	40	44.0	28.5		11.7	
	C	39	40.0	23.0			
6	N	41	37.0 (42.3)	27.0 (21.7)	(17.0)	15.6 (11.4)	53.0
	C	40	58.0	28.0	25.0	14.1	
	C	39	32.0	10.0	9.0	4.4	
12	N	39	12.5 (14.4)	12.5 (13.5)	18.5 (12.6)	4.2 (5.3)	92.0
	N	40	17.4	15.6	6.7	4.1	
	N	38	13.2	12.5		7.7	
24	N	38	2.8 (3.1)	3.2 (3.7)	2.9 (2.9)	<1.0	6.0
	N	39	3.4	4.2		<1.0	

^a N, Normal; C, caesarean.

^b The mean for the group is given in parentheses.

^c Ceftriaxone concentrations in placenta are expressed in micrograms per gram.

milk, horse serum, Sorensen buffer (pH 7.2), human amniotic fluid, and human urine for the assays of ceftriaxone concentrations in milk, serum, placenta, amniotic fluid, and urine, respectively. The use of horse serum for standards in the maternal and umbilical cord serum assays could have been a source of error if the binding of ceftriaxone to proteins in horse serum differs from that in human serum (normally 83 to 96%). It would not affect derived half-lives, although it might result in either over- or underestimates of total serum concentrations. Tissue antibiotic concentrations were calculated (in micrograms per gram) as [(tissue weight + buffer weight) × assay concentration]/tissue weight.

(iv) **Data analysis.** The kinetic parameters of the penetration of ceftriaxone into milk were derived for individual subjects. The average values for these parameters were then calculated. Ceftriaxone distribution to the fetus was assessed by the analysis of semilogarithmic plots of average concentrations versus the time interval between the administration of ceftriaxone and delivery. The areas under the curve (AUC) of concentrations of ceftriaxone in serum, milk, amniotic fluid, and placenta were calculated by the trapezoidal rule without extrapolation to infinity (6, 12).

Except for the analysis of the AUC of the maternal serum concentrations of ceftriaxone after intravenous administration, the first datum was assumed to represent zero concentration at zero time, i.e., no lag time was incorporated. In quantifying the AUC in maternal serum after intravenous administration of the drug, the first datum was the extrapolated y-intercept at zero time.

The half-life of the elimination of ceftriaxone from serum was calculated by least-squares linear regression of the logarithm of the serum concentration

versus time, using the three data points. The half-lives of the disappearance from the umbilical cord serum, amniotic fluid, and placenta were determined by least-squares linear regression of the terminal log-linear segments of plots of the logarithm of tissue concentration versus time. The kinetic parameters of ceftriaxone in maternal milk were quantified in each subject by nonlinear least-squares iterative fitting (NONLIN) (C. M. Metzler, G. L. Elfring, and A. J. McEwen, *Biometrics* 30:562, 1974), using the CSTRIP program to determine initial parameter estimates (13). The data were fit to a one-compartment model of the format:

$$C = A (e^{-K_d t} - e^{-K_a t})$$

Where C is the concentration in milk at time t ; A is a constant coefficient or intercept; and K_d and K_a are rate constants of elimination and absorption, respectively. The fitting of the data did not require the incorporation of a lag time.

RESULTS

Distribution of ceftriaxone to the fetus. The time course of the entry of ceftriaxone into the analyzed tissues and of its disappearance from them is shown in Table 1, with derived parameters in Table 2. Ceftriaxone reached substantial concentrations in the umbilical cord blood, amniotic fluid, and placenta by 1 h of sampling, peaked at 4 to 8 h, and was eliminated from all of these tissues with half-lives of approximately 6 h. The virtual identity of the elimination half-lives from these tissues and those from maternal serum is striking.

The concentrations of ceftriaxone in the first voided urine of five of the newborns of these

TABLE 2. Distribution of ceftriaxone into fetal tissues

Distribution area	AUC ^{0-24a} ($\mu\text{g} \cdot \text{h/ml}$)	$t_{1/2}$ (h) ^b
Maternal serum	651.9	6.0
Umbilical cord serum	334.4	7.0
Amniotic fluid	256.1	6.8
Placenta	162.8 ^c	5.4

^a AUC⁰⁻²⁴, Area under the curve from 0 to 24 h.

^b $t_{1/2}$, Half-life.

^c Micrograms · hour per gram.

patients were highly variable, ranging from 6 to 92 $\mu\text{g/ml}$.

Penetration of ceftriaxone into milk. The data are presented graphically in Fig. 1, with derived pharmacokinetic parameters in Table 3. The maternal serum concentrations and the AUC in this group of patients were approximately half those of the subjects noted above, reflecting the twofold smaller dose. Ceftriaxone entered breast milk quickly and was then slowly eliminated. The amounts which gained entry, however, were small as reflected in the low concentrations in milk and the small AUC, approximately 3 to 4% of the AUC of serum ceftriaxone concentrations versus time. The concentrations of ceftriaxone in milk after intramuscular administration were consistently higher than those after

intravenous administration, whereas the concentrations in maternal serum were essentially identical with these dosing formulations.

DISCUSSION

The determinants of drug delivery to fetal tissues or milk have been studied, but presumably the drug and the physiological characteristics important for absorption, distribution, and elimination from the body in general would be applicable (11). Additional factors are operative in the fetus. For example, since fetal urine is voided into the amniotic fluid, the fetus may then be redosed with the excreted drug, effectively limiting cumulative elimination. Similarly, just as the drug reaches the fetus from the maternal circulation, the transfer undoubtedly occurs in the opposite direction. The chemical characteristics of the drug, such as protein binding, molecular size, lipid solubility, etc.; perfusion relationships between mother and fetus; and potentially a host of other factors can presumably influence this bidirectional transfer (11). Since myriad determinants are undefined, it is virtually impossible to predict a priori the distribution of the drug to the fetus.

Since ceftriaxone may be used in pregnant patients, we felt it important to explore its distribution into fetal tissues and into milk. Although it was anticipated that the high protein binding (83 to 96%) of ceftriaxone would limit its transfer to fetal tissue, substantial and probably clinically relevant concentrations were attained in all samples assessed in this study (Table 1). As noted above, our use of horse serum for assaying ceftriaxone concentrations in maternal and umbilical cord serum could have created an error in the absolute values for serum concentrations and AUCs in these samples. This flaw in experimental design notwithstanding, our observations show unequivocally the substantial penetration of fetal tissues by ceftriaxone.

The data show that the elimination rates of ceftriaxone from fetal tissues were remarkably similar, if not identical, to those from maternal serum. This observation is considerably different from findings in analogous studies of other antibiotics (3, 14), including several different cephalosporins (Table 4; 1, 2, 4, 5, 7). These data may indicate that with chronic dosing, the disproportionate accumulation of ceftriaxone in fetal tissues relative to maternal serum may not occur; this would be in contrast to findings or predictions with other drugs (1-5, 7, 8, 14) and may be clinically important. However, because of uncertainty concerning the determinants of the fetomaternal transfer of drugs, the extrapolation of our findings to chronic dosing with ceftriaxone should be cautious until further studies specifically address this point.

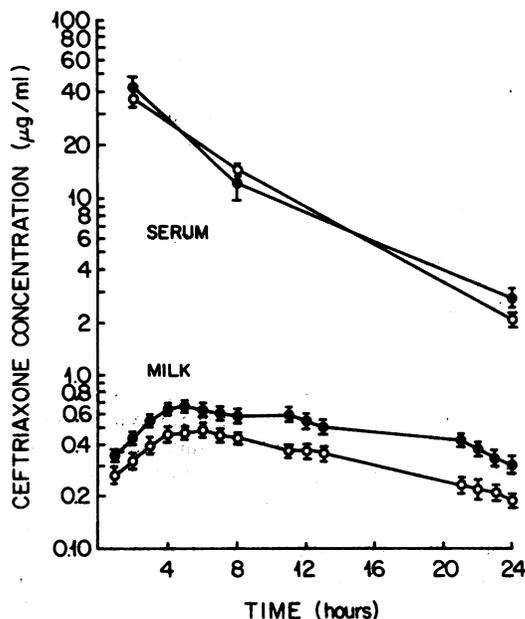


FIG. 1. Mean (\pm standard error of the mean) concentrations of ceftriaxone in maternal serum and breast milk versus time after intravenous (O) or intramuscular (●) administration of a 1-g dose. Each group comprised 10 subjects.

TABLE 3. Penetration of ceftriaxone into milk and serum

Administration route (n)	Serum		Milk		
	AUC ($\mu\text{g} \cdot \text{h/ml}$)	$t_{1/2}$ (h)	AUC ($\mu\text{g} \cdot \text{h/ml}$)	$t_{1/2ab}$ ^a (h)	$t_{1/2el}$ ^b (h)
Intravenous (10)	391.2 \pm 23.0	5.3 \pm 0.2	11.8 \pm 4.5	1.7 \pm 0.9	12.8 \pm 3.7
Intramuscular (10)	379.0 \pm 56.3	5.3 \pm 0.4	21.0 \pm 2.5	1.7 \pm 0.2	17.3 \pm 2.1

^a $t_{1/2ab}$, Half-life in absorption phase.
^b $t_{1/2el}$, Half-life in elimination phase.

Since the majority of our patients received oxytocin to facilitate delivery, the possible effect of this drug should be considered. It is conceivable that this agent may influence the distribution of the drug to the fetus as has been shown to occur when prostaglandins have been used for therapeutic abortions (3). Because of the substantial delivery that did occur to the fetus, however, a significant effect of oxytocin seems unlikely.

Because ceftriaxone is highly protein bound (9, 10), one might predict limited distribution out of maternal blood. Our finding of minimal penetration into breast milk is consistent with this postulate and similar to findings with cefotaxime (7) despite that cephalosporin's being considerably less protein bound (20 to 40%) (9). In this single-dose study, the concentrations of ceftriaxone reaching breast milk were sufficiently low (Fig. 1) that one would predict negligible clinical relevance save the possibility of altering the oral flora of the suckling infant. The prolonged elimination time of ceftriaxone from milk relative to that from maternal serum causes a disproportionate accumulation in milk with chronic dosing. Whereas steady-state maternal serum concentrations would be reached in approximately 1

day, this would not occur in milk for 1.5 to 3 days, and the steady-state concentration would probably reach values of 3 to 4 $\mu\text{g/ml}$ (6, 12). These concentrations might then attain a measure of clinical importance. Why the concentrations in milk were higher after intramuscular than after intravenous administration of ceftriaxone to the mother is unclear. The differences would not be expected to be clinically important.

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TABLE 4. Elimination half-lives of various antibiotics from maternal serum compared with fetal tissues

Antibiotic	$t_{1/2}$ ^a (h) from:				
	Maternal serum	Umbilical cord serum	Amniotic fluid	Placenta	Reference
Cefatrizine	2.4			4.4	(4)
Cefotaxime	0.7	2.3	2.8		(7)
Cephaloridine		^b			(1)
Cefazolin	1.5			4.4	(2)
Tobramycin	1.5	5.2			(3)
Azocillin	1.3	2.3	^c	^c	^d

^a $t_{1/2}$, Half-life.
^b Slower serum decline.
^c Increasing at 6 h.
^d Unpublished data.