ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 1978, p. 924-926
0066-4804/78/0014-0924$02.00/0

Vol. 14, No. 6
Printed in U.S.A.

Materno-Fetal Cephradine Transfer in Pregnancy

IAN CRAFT[1]* AND THOMAS C. FORSTER[2]

Academic Department of Obstetrics and Gynaecology, Royal Free Hospital, London N.W.3.,[1] and Squibb Institute for Medical Research, Moreton, Wirral, England[2]

Received for publication 7 July 1978

Cephradine, a semisynthetic cephalosporin, has widespread use. There is, however, a paucity of data on the transfer of this antibiotic in pregnancy. Studies were undertaken after an intravenous dose of 2 g of cephradine was given in two elective situations: (i) therapeutic abortion in the first trimester and (ii) elective cesarean section in late pregnancy. Blood and tissue levels of cephradine obtained showed that the antibiotic is rapidly transferred to the feto-placental unit throughout pregnancy after intravenous administration to the mother.

An efficient and safe antibiotic for use in obstetric practice must achieve therapeutic concentrations in maternal and fetal or neonatal serum and amniotic fluid without serious side effects and have an appropriate range of activity against likely pathogens. Cephalosporins may have advantages over other antibiotics in these respects. There is, however, incomplete information concerning their transfer characteristics.

It has been reported (1) that effective concentrations of cephaloridine could be achieved in maternal and neonatal cord serum after intramuscular doses of 1 to 2 g, with peak values appearing at 2 and 4 h, respectively. Concentrations in liquor amnii (amniotic fluid) were found to increase more gradually and were dose dependent. Other workers (3) noted that cephalothin concentrations increase in liquor after intravenous use, but similar studies (5) showed uterine tissue levels considerably lower than when cephradine was administered in the same dose and by the same route. The differences in serum protein binding of different cephalosporins also influence antimicrobial activity.

TABLE 1. *Cephradine concentrations in early pregnancy at therapeutic abortion*[a]

Patient no.	Gestation (wks)	Injection-to-evacuation time (min)	Cubital vein (μg/ml)	Liquor (μg/ml)	Placenta (μg/g)	Fetus (μg/g)
1	12	10	148	Neg	—	—
2	10	11	150	Neg	—	—
3	13	10	182	0.8[b]	—	—
4	9	7	198	14.3[b]	—	—
5	11	9	108	Neg	—	—
6	14	9	185	1.3[b]	—	—
7	8	9	161	5.2[b]	—	—
8	10	10	100	Neg	5.5	—
9	8	10	112	Neg	1.9	5.4
10	12	11	180	0.5	17.0	8.4
11	7	12	94	—	8.7	—
12	11	12	41	0.4[b]	8.7	16.2
13	8	10	96	0.4[b]	8.5	14.0
Mean ± SD	10 ± 2.2	9.9 ± 1.3	135 ± 47	1.9 ± 4.2	8.4 ± 5.0	11.0 ± 5.0

[a] SD, Standard deviation; —, no sample; Neg, negative value.
[b] Some blood contamination.

There are limited data on the transfer of cephradine in pregnancy. Borgogne-Berezin et al. (2) reported a liquor concentration of 3 μg/ml 3 h after the last oral dose of 1 g given daily for 3 consecutive days. Differences in liquor concentrations were reported (6) with the stages of pregnancy following oral doses of 500 mg given every 6 h for at least 48 h. In midpregnancy, the mean liquor value was 1.15 μg/ml, but no increase in concentration occurred with time.

However, the study was conducted during the induction of second-trimester abortion by using a dose of prostaglandin F2α that is known to increase uterine tone and alter feto-placental function. In a small group in late pregnancy, mean cord serum and liquor values were reported as 1.7 and 13.0 μg/ml, respectively, following the same oral dose regimen.

Since gastrointestinal function may be influenced by the pregnant condition, particularly during labor, and since oral intake is considered inadvisable, a study was undertaken to evaluate the concentrations of cephradine after a loading dose of 2 g given intravenously in different biological tissues and fluids in two elective situations, i.e., at therapeutic abortion in the first trimester and at elective cesarean section, by taking samples from the mother and the feto-placental unit.

All serum and tissue samples were stored at −20°C until assayed. A modified agar diffusion plate assay using *Sarcina lutea* (ATCC 9431) as the test organism was used to determine cephradine concentrations (4). Since cephradine is not known to produce biologically active metabolites, and cephralosporinase (code 31-110; Miles Laboratories) was found to inactivate the antibiotic in control samples, the assay is assumed to detect only cephradine. The lower limit of the assay was a reading of 0.4 μg/ml, beneath which negative values were recorded. Tissue samples were washed extensively in normal saline to minimize blood contamination before storage and assay using noncompensated standards.

In early pregnancy, 2 g of cephradine was injected intravenously in 13 volunteer subjects approximately 10 min before suction termination was performed. A control blood sample was taken before and at the time of evacuation of the uterus. Immediately before evacuation, an attempt was made to aspirate liquor in an atraumatic fashion. If contamination occurred, this was graded macroscopically from mild to heavy staining. In approximately half the cases studied, fetal tissues, including placenta, membrane, and fetus, were taken for assay. The time for injection to evacuation was recorded, and oxytocics were not given.

A mean cephradine concentration of 135 μg/ml was detected in the maternal serum 10 min after injection (Table 1). All control samples were negative. Significant concentrations were found in the feto-placental tissues at this short time interval and, in one patient with an empty gestation sac, high levels were detected in samples taken from the decidua (55 μg/g) and sac wall (26 μg/g). The liquor concentration, although low, is falsely high, since no detectable

TABLE 2. *Cephradine concentrations in late pregnancy at elective cesarean section*[a]

Patient no.	Injection delivery time (min)	Maternal				Feto-placental				
		Cubital vein (μg/ml)	Femoral artery (μg/ml)	Uterine vein (μg/ml)	Myometrium (μg/g)	Umbilical vein (μg/ml)	Umbilical artery (μg/ml)	Placental (μg/g)	Cord (μg/g)	Membrane (μg/g)	Liquor (μg/ml)
14	20	54	—	—	—	15	14	23	32	9.2	2.0
15	15	—	74	94	—	22	22	7.9	24	7.1	0.7
16	14	86	71	76	—	20	15	8.7	—	15	0.7
17	18	42	46	44	13	12	10	7.6	15	6.7	Neg
18	11	158	189	169	22	35	28	67	1.8	62	0.4
19	9	158	157	188	59	20	23	38	1.4	9.3	Neg
20	30	63	75	93	26	22	27	11	3.0	6.9	Neg
21	20	157	—	93	—	53	56	18	9.4	21	8.0[b]
22	12	130	100	201	—	48	35	24	7.6	23	—
23	15	87	—	—	7.9	26	—	20	1.7	7.7	Neg
24	25	110	95	107	24	40	56	11	Neg	7.8	Neg
Mean ± SD	17 ± 6	104 ± 45	101 ± 48	119 ± 54	25 ± 18	28 ± 14	29 ± 16	21 ± 18	10 ± 11	16 ± 16	1.1 ± 2

[a] SD, Standard deviation; —, no sample; Neg, negative value was recorded.
[b] Some blood contamination.

levels were found in 5 of the 12 patients sampled who had clear liquor, whereas the remainder had various degrees of blood contamination.

Cephradine was administered in the same manner to 11 patients undergoing elective cesarean section, but in this situation maternal and neonatal arterial and venous samples were taken on either side of the placenta at the time of delivery. The umbilical vessels were sampled separately from the surface of the placenta. In some instances, liquor, placenta, cord, membrane, and a sample of myometrium were also assayed. In two instances neonatal blood was taken 12 and 20 h, respectively, after delivery to confirm that neonatal excretion had occurred.

Mean cephradine concentrations were high in the maternal circulation 17 min after injection (Table 2) with a value of 104 μg/ml in the antecubital vein. Significant levels were found also at this time in the myometrium. Rapid neonatal transfer had occurred, as indicated by the cord blood values and by the tissue concentrations in the empty cord and in membrane and placenta. The mean liquor level of 1.1 μg/ml was falsely high, since one of the ten patients sampled had a blood-stained specimen with a reading of 8 μg/ml and, in the remaining nine patients with clear liquor, five were recorded as negative and the others as 0.4, 0.7, 0.7, and 2.0 μg/ml, respectively. The cephradine concentrations found in two neonatal blood samples taken 12 and 20 h after delivery were 1.0 and 0.6 μg/ml, respectively.

These results indicate that cephradine is rapidly transferred to the feto-placental unit after intravenous administration to the mother throughout pregnancy and is excreted by the neonate. In late pregnancy, high concentrations can be achieved in the fetus in a very short time. It is probable that effective liquor concentration would result within 1 to 2 h, depending upon fetal urinary production rates. The fact that cephradine is largely excreted in the urine in an unmetabolized state favors its use in obstetric practice in which both maternal and fetal tissue and liquor concentrations are desirable.

LITERATURE CITED

1. **Barr, W., and R. Graham.** 1967. Placental transmission of cephaloridine. Postgrad. Med. J. Suppl. **43**:101–104.
2. **Bergogne-Berezin, E., N. Lambert-Zechovsky, and J. L. Rouvillois.** 1975. Pharmokinetics of a new cephalosporin. Med. Malad. Infect. **5**:426–431.
3. **Corson, S. L., and R. J. Bolognese.** 1970. The behavior of cephalothin in amniotic fluid. J. Reprod. Med. **4**: 105–108.
4. **Forster, T. C.** 1976. Microbiological assay of cephradine in blood and urine, vol. 5, p. 227–230. *In* E. Reid (ed.), Methodological developments in biochemistry. North Holland Pub., New York.
5. **Michel, C. F., H. Knothe, B. Lauer, and E. Werner.** 1975. Concentration of cephradine and cephalothin in the serum and uterine musculature. Geburtshilfe Frauenheilkd. **35**:24–27.
6. **Mischler, T. W., S. L. Corson, R. J. Bolognese, M. J. Letocha, and E. S. Neiss.** 1974. Presence of cephradine in body fluids of lactating and pregnant women. Clin. Pharmacol. Ther. **15**:214.