Placental Transfer of Cefotiam Dihydrochloride
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The concentrations of cefotiam dihydrochloride (CTM) in maternal and fetal blood and in amniotic fluid were determined by bioassay in 38 women at parturition. With an intravenous infusion of 1 g of CTM, the decline in concentration of CTM in maternal blood was biphasic; CTM was not detectable at 6 h after administration. Peak levels of CTM in umbilical cord blood (13.0 to 23.9 μg/ml) were attained between 15 and 28 min after intravenous infusion; those in amniotic fluid (19.6 to 23.5 μg/ml) were attained at ca. 2.5 h.

When one considers using antibiotics for pregnant women, placental drug transfer must be taken into account. Substantial transfer to the fetus and amniotic fluid is not necessarily a disadvantage if the drug exerts minimal side effects. In fact, this may make the drug a reasonable choice for treatment of amnionitis and fetal infection. Accordingly, we studied the placental transfer of cefotiam dihydrochloride (CTM) (Pansporin; Takeda Chemical Industries, Ltd., Osaka, Japan), a cefem with a broad spectrum (6, 9), to the fetus and amniotic fluid.

Seven normal pregnant women (four primiparas and three multiparas, aged 24 to 37 years) who agreed to participate in this study were each given 1 g of CTM dissolved in 10 ml of distilled water by intravenous infusion during weeks 37 to 41 of pregnancy. Blood samples were collected at 5, 15, 30, 60, 120, 180, and 300 min after infusion.

Also, 38 normal pregnant women in labor (17 primiparas and 21 multiparas, aged 21 to 37 years) who agreed to participate in this study were each given 1 g of CTM by intravenous infusion. Maternal and fetal (umbilical cord) blood were collected at parturition. Amniotic fluid was obtained by induced rupture of membranes immediately before parturition to minimize contamination of the fluid by maternal blood. Each of the mothers delivered a normal term baby via easy labor.

The concentrations of CTM in serum and in amniotic fluid were determined by bioassay, using the cylinder-plate diffusion method (5, 9) and Proteus mirabilis ATCC 21100 as the assay organism. Sensitivity of the procedure applied to blood and amniotic fluid was 0.2 μg/ml.

The concentrations of CTM in maternal blood at various times after infusion are shown in Fig. 1. The concentration at 5 min was 112.0 ± 13.9 μg/ml. Concentrations declined rapidly to levels of 13.4 ± 4.6, 4.3 ± 1.7, 1.7 ± 0.5, and 0.5 ± 0.2 μg/ml at 1, 2, 3, and 5 h, respectively, after dosage.

The data on the concentrations of CTM in maternal blood, fetal blood, and amniotic fluid obtained from 38 women at parturition are shown in Table 1. The concentrations in fetal blood were 23.9 μg/ml at 15 min after infusion, 13.0 to 15.9 μg/ml at 20 to 30 min (4 cases), and declined gradually to levels of less than 1 μg/ml after 6 h. The ratio of the concentration of CTM in fetal blood to that in maternal blood was 0.753 to 1.302 during the period from 1 h, 10 min to 3 h after infusion.

The concentrations in amniotic fluid were less than 4 μg/ml at ca. 1 h after infusion (9 cases), 8.5 to 23.5 μg/ml at ca. 2 to 3 h (6 of 8 cases), 5.5 to 9.1 μg/ml at ca. 6 to 10 h (4 cases), and 0.3 μg/ml at ca. 28 and 31 h (2 cases).

The concentrations in amniotic fluid increased from 1 h after infusion, with concentrations of 19.6 μg/ml at 2 h, 10 min, 19.8 μg/ml at 2 h, 15 min, and 23.5 μg/ml at 2 h, 27 min; after this time the concentration began to decrease.

The results clearly show that CTM rapidly disappeared from maternal blood in the same manner as cefoxitin (3). According to Seiga et al. (8), CTM is excreted largely unchanged via the kidneys. The concentration of CTM in maternal blood is maintained at a higher level than the necessary minimal inhibitory concentration against most gram-negative bacilli from just after infusion to 5 h postinfusion (6, 9).

On the other hand, the concentration of CTM in fetal blood was 11.7 μg/ml at 5 min after infusion and rose to a peak level of 23.9 μg/ml after 15 min. The concentration then declined to less than 1.0 μg/ml at 6 h after administration. The ratio of the concentration in fetal blood to that in maternal blood was 75.3 to 130.2% at 1 h, 10 min to 3 h after infusion.

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FIG. 1. Concentrations of CTM in maternal blood after intravenous administration of 1 g to seven pregnant women. Vertical bars show ± standard deviation.
administration. From 3 h on, the level in fetal blood became much higher than that in maternal blood and remained at 0.2 to 0.5 µg/ml, i.e., at an effective concentration, even at 6 to 14 h after infusion.

The concentration in amniotic fluid was less than 4 µg/ml up to 1 h after administration, 3.9 to 17.6 µg/ml at 3 to 9 h, and 0.3 to 4.1 µg/ml even at 14 to 31 h after injection. This shows that the concentration in amniotic fluid is maintained at a higher level than the minimal inhibitory concentration necessary for most *Escherichia coli* strains for at least 24 h after a 1-g dose (6, 9). The concentration of CTM in amniotic fluid fluctuated rather greatly compared with that in maternal and fetal blood. This may be due to the great differences in the volume of amniotic fluid in individual cases. The fact that effective levels of CTM could be observed for a long period may be assumed to be derived from the storage of CTM metabolites in fetal urine and excretion into the amniotic fluid as reported for transfer of ampicillin (1, 4).

On the basis of our results, we conclude that CTM is transferred to the fetus and amniotic fluid more rapidly than intramuscular sulbenicillin as we reported previously (5). The differences in the amounts of CTM and sulbenicillin transferring to the organs and those remaining in the serum may result from the differences in the mode of administration (intravenous or intramuscular) and the drug characteristics (1, 2, 4, 5, 7).

Since CTM is characterized by a more potent antibacterial activity than some other antibiotics, intravenous administration of 1 g of CTM two or three times a day is an adequate dose for maternal infections such as urogenital tract infections, provided the immunological response of the patient is normal.

Although there is controversy regarding the administration of an antibiotic in cases with premature rupture of membranes, the intravenous infusion of CTM at 1 g per day will result in antimicrobial action in the fetus and amniotic fluid.

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**LITERATURE CITED**