Published in final edited form as:
Transplantation. 1988 September ; 46(3): 468–469.

CYCLOSPORINE AND ITS METABOLITES IN MOTHER AND BABY

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Cyclosporine (CsA) is a potent immunosuppressive agent that has significantly improved allograft survival in recipients of human organ transplants (1,2). Recently there have been a few cases of successful pregnancies in transplant patients receiving CsA alone or in combination with steroids (3,4). A general concern regarding pregnancy in transplant patients is the potential harmful effect of chronic maternal immunosuppression on the fetus. It is essential to determine the extent of exposure of the fetus to the immunosuppressive drug and its metabolites. We recently studied the concentrations of CsA and several of its metabolites in maternal and cord blood, placenta, and the umbilical cord in two patients receiving chronic CsA therapy.

The first patient was a 26-year-old woman with primary biliary cirrhosis secondary to common bile duct obstruction who received a successful liver transplantation in November 1985. Immunosuppression was achieved with CsA and steroids. During the second postoperative week she also received the monoclonal antibody OKT 3. In February 1987, she delivered a 3208 g baby boy. At the time of delivery she was receiving CsA 200 mg orally b.i.d., prednisone 10 mg, hydralazine 50 mg q.i.d., ferrous sulphate 300 t.i.d, furosemide 40 mg q.d. and multivitamin therapy. On the day of the delivery she received CsA at 10 A.M. and the baby was born at 5:45 P.M. Maternal blood was obtained at 8.5 hr after CsA administration while cord blood was obtained at 7.8 hr after CsA administration. Maternal and cord blood along with placenta and umbilical cord were analyzed for CsA and several of its metabolites using a gradient high-pressure liquid chromatographic method developed in our laboratory (5).

The second patient was a 25-year-old woman who received an orthotopic liver transplant in November 1985 for cirrhosis of unknown cause. Immunosuppression was achieved with CsA and steroids. Four weeks following the transplant, the patient developed cytomegalovirus hepatitis from which she recovered with reduction in immunosuppression. She did well for 10 months and then developed biliary obstruction that was corrected surgically. At this time she became pregnant. Pregnancy was complicated by anemia requiring blood transfusions and preeclampsia. At gestational age 36 weeks, she had a caesarean section because of fetal distress, and a live baby boy (weight 1690 g) was delivered at 8 A.M. At the time of delivery her medications included Riopan 30 ml p.o. every 4 hr, ranitidine 150 mg orally b.i.d., ferrous sulfate 300 mg orally t.i.d., prednisone 15 mg orally every day and CsA 125 mg orally every 12 hr. Maternal and fetal cord blood were drawn simultaneously at the time of delivery 10 hr after the previous oral cyclosporine dose. The baby had intrauterine growth retardation, as the weight and head circumference were below the fifth percentile. The blood samples, umbilical cord, and placenta were refrigerated at 4°C until analyzed by HPLC.

Table 1 lists the concentrations of CsA and its metabolites in blood and in different tissues. The highest concentration of CsA was seen in the umbilical cord of patient 1. The placenta contained CsA concentrations nearly five to ten times greater thon the maternal and the fetal blood, and had the highest concentrations of all the metabolites measured. While small

concentrations of M 21 were observed in the placenta and the maternal blood of patient 1, M 18 concentrations were below measurable levels in most of the specimens.

Cyclosporine is very lipid-soluble, extensively distributed in the body, and highly metabolized. Previous studies have reported the presence of CsA in cord blood, placenta, amniotic fluid, and breast milk (4). In addition to CsA, we have observed high concentrations of CsA metabolites in the placenta, indicating the presence of CsA metabolizing enzymes in this tissue and/or accumulation of these metabolites in the placenta. Very high concentrations of CsA (nearly 30 times that of the maternal blood) were also observed in the umbilical cord of one patient. Some of the metabolites, particularly M 17, appear in very high concentrations in the blood and also possess significant immunosuppressive effect (6,7). Whether the metabolites of CsA also contribute to the toxicity is not known. In this study we report for the first time the concentrations of CsA metabolites in cord blood, placenta, and umbilical cord. Of interest is the relatively high concentration of all the metabolites in the placenta.

While no specific harmful effects attributable to CsA were observed in the baby, it is clear that the fetus is exposed not only to CsA but also to its metabolites. According to the tests conducted by Sandoz Inc. (Basel, Switzerland) CsA is not mutagenic in the Ames test and did not produce any chromosomal abnormalities in animals. However, since the fetus is exposed to chronic CsA and its metabolites, the immediate septic complications and the possible long-term effects on gestationally immunosuppressed children should be investigated.

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Table 1

Cyclosporine and its metabolites in mother and child[a]

	Maternal blood (ng/ml)	Cord blood (ng/ml)	Placenta (ng/g)	Umbilical cord (ng/g)
CyA	90, 105	53, 55	506, 318	2641, <25
M-17	134, 132	159, 162	481, 184	137, 97
M-21	<25, 0	0, 0	<25, 0	0, 0
M-1	89, 63	28, 0	229, 89	28, 0
M-18	0, <25	0, 0	0, 0	0, 0

[a]The first value was observed in patient 1 and the second value was observed in patient 2.