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Exceptional Case

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Acute kidney injury in an infant of a kidney allograft recipient

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ABSTRACT

Tacrolimus has been used in pregnant organ recipients for >20 years, and the relationship between fetal complications and the amount of tacrolimus crossing the placenta is still controversial. We report the case of a kidney transplant recipient who used tacrolimus and gave birth to an offspring that developed, shortly after birth, an acute kidney injury caused by tacrolimus exposure, which was detected by measuring tacrolimus levels in the umbilical vein, as well as in maternal blood. Even if whole-blood levels of tacrolimus are within the therapeutic range throughout pregnancy, the amount of tacrolimus could reach toxic levels.

Keywords: fetal exposure, kidney transplantation, placental transfer, pregnancy, tacrolimus

BACKGROUND

Tacrolimus is used in solid organ transplant recipients as an immunosuppressive agent that blocks T cell activation during pregnancy. The incidence of major structural malformations in cases of fetal exposure to immunosuppressants during pregnancy is not much higher than that in the general population. However, intrauterine growth restriction, low birthweight, reversible renal dysfunction and hyperkalaemia have been reported in offspring of kidney transplant recipients [1].

CASE REPORT

A 31-year-old woman with a history of Goodpasture's syndrome received a living related kidney allograft. The maintenance immunosuppressive therapy comprised mycophenolate mofetil (MMF 1000 mg daily), tacrolimus (Prograf® 3 mg daily) and methylprednisolone (5 mg daily). Five years later, the patient expressed the wish to get pregnant. Her blood pressure (BP) was in the normal range. Her serum creatinine (sCr) level was 1.04 mg/dL, estimated glomerular filtration rate 71 mL/min/1.73 m^2 and urine protein:creatinine ratio (PCR) <1 g/g; graft functions had also been stable over the last 2 years. Accordingly, tacrolimus and methylprednisolone treatment were continued, but MMF was replaced with azathioprine 75 mg daily. Pregnancy was confirmed at week 6 of gestation. Tacrolimus trough levels (TTLs) were kept between 4 and 7 ng/mL, with an average tacrolimus dose of 4.57, 9.53 and 9 mg/day in early, mid and late pregnancy, respectively. The patient received regular obstetric care during the entire course of pregnancy. The gestational period was uneventful until gestational week 21 when the patient developed hypertension and proteinuria (PCR: 2.8 g/g). BP increased to 150/100 mmHg and was well controlled with α-methyldopa 750 mg daily. An elective Caesarean section (CS) was performed at week 36 of pregnancy. The patient's sCr level was 2.34 mg/dL the day before the CS. In order to assess for fetal exposure to tacrolimus, whole-blood samples were obtained from both maternal blood (4 h after tacrolimus dosing) and the umbilical cord vein at the time of delivery (Figure 1).

A female newborn weighing 2450 g was delivered. The Apgar (Appearance, Pulse, Grimace, Activity, Respiration) scores were

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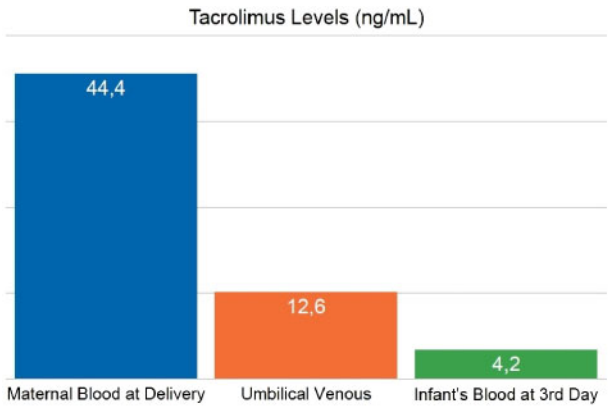

FIGURE 1: Whole-blood tacrolimus levels of maternal, umbilical cord venous and newborn blood samples.

7 and 8 at 1 and 5 min, respectively. The newborn was transferred to the neonatal intensive care unit (NICU) for close monitoring. Reduced urine output (0.3 mL/kg/h) and elevated blood urea nitrogen (BUN) and sCr levels were suggestive of acute kidney injury (AKI). Creatinine level was 1.6 mg/dL (normal range: 0.24–0.85 mg/dL) on admission to the NICU (12 h after birth). Urinalysis was negative for protein. The newborn received 60–80 mL/kg of enteral fluid and nutrition daily. Renal ultrasonography revealed two normal kidneys. On day 3 after birth, the tacrolimus level was measured to determine whether the AKI was due to drug toxicity. Whole-blood tacrolimus, creatinine and potassium levels were 4.2 ng/mL, 1.3 mg/dL and 4.9 mEq/L, respectively. On day 5 after birth, urine output increased from 0.3 to 1.6 mL/kg/h. BUN and sCr levels regressed to the normal range (BUN: 8 mg/dL; creatinine: 0.42 mg/dL). At the 6-month post-partum follow-up visit, the infant was doing well, with no proteinuria and a normal creatinine level of 0.41 mg/dL.

DISCUSSION

To date, data on maternal and fetal tacrolimus transfer kinetics and the effects of tacrolimus exposure through maternal-to-fetal transfer on fetal development are limited [1].

In the first case report on placental transfer of tacrolimus, tacrolimus levels from the umbilical vein and newborn's blood were reported to be 8.1 and 6.4 ng/mL, respectively. While the mother's TTL on hospital admission for urgent CS was 6.5–7.6 ng/mL, the TTL at the time of delivery was not stated. In addition, indometacin administration to treat patent ductus arteriosus in the neonate makes it difficult to directly associate the AKI with tacrolimus toxicity [2].

Zheng *et al.* investigated whole-blood, plasma and unbound tacrolimus concentrations in maternal and umbilical cord blood samples in eight solid organ transplant recipients. Mean tacrolimus concentrations in maternal and umbilical cord venous blood were 9.0 ± 3.4 ng/mL and 6.6 ± 1.8 ng/mL, respectively. Mean tacrolimus concentrations at the time of delivery in umbilical cord venous blood were 71% of maternal concentrations [3]. The authors suggested this decrease could be explained by several mechanisms protecting the fetus against drug toxicity, including the molecular weight of tacrolimus. Another possible mechanism is P-glycoprotein, which acts as a membrane carrier for tacrolimus on placental syncytiotrophoblasts. A further important mechanism involves molecular binding of tacrolimus to erythrocytes, accounting for 85–95% of unbound drug in blood. Since haematocrit levels in the umbilical vein are higher, the amount of free drug delivered to the fetus is reduced.

CYP3A7 is a major cytochrome P450 enzyme in the fetal liver, and its efficacy in tacrolimus metabolism is significantly less than that of CYP3A4. However, in the post-partum period, CYP3A7 is replaced with CYP3A4. Accordingly, blood levels of tacrolimus in newborns are reduced by about 15% per day [4].

In our case, the average tacrolimus dose used was 7.6 mg/day and TTLs were maintained at around 4–7 ng/mL during the entire pregnancy. Maternal tacrolimus levels at delivery across cases are hard to compare because they depend on the time interval between tacrolimus dosing and blood sampling, which, in the present case, was 4 h. Tacrolimus levels in umbilical cord venous blood were 26% of maternal levels at the time of delivery in our case. We believe this difference in levels could be explained by the various mechanisms mentioned earlier, of which the most likely could involve P-glycoprotein, which, as the drug level increases, might become hyperactive in order to protect the fetus from drug toxicity. In our report, there was no nephrotoxic exposure, except for that of tacrolimus.

As also described by Hebert *et al.*, measurement of plasma or unbound tacrolimus concentrations in pregnant transplant recipients might better reflect the active form of the drug, rather than measurement of whole-blood concentrations [5].

In conclusion, tacrolimus should be considered as a potential cause of AKI in infants of kidney transplant recipients on treatment with the immunosuppressant.

CONFLICT OF INTEREST STATEMENT

None declared.

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