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CASE REPORT

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Case report of unchanged tacrolimus clearance in a hypoxemic pediatric liver transplant recipient with hepatopulmonary syndrome

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Abstract Reductions in hepatic oxygen supply may reduce the oxidative metabolism of drugs, including tacrolimus. We encountered a patient (2.3-year-old girl) with hypoxemia [arterial oxygen tension (PaO_2) 40.9 mmHg in room air] due to hepatopulmonary syndrome who had undergone living related liver transplantation. After transplantation, tacrolimus was initially administered by continuous intravenous infusion, and her PaO_2 was maintained at more than 50 mmHg [72.8 ± 10.4 (SD) mmHg] by oxygen supplementation. Apparent clearance of tacrolimus (calculated as: the infusion rate of tacrolimus/blood concentration) in the patient (0.075 l/h per kg) was comparable to those of non-hypoxemic control pediatric cases (0.092 ± 0.014 l/h per kg, $n = 7$, mean age 2.2 years, PaO_2 149.2 ± 41.5 mmHg), except for the acute decline in the early period after transplantation. These findings suggest that the reduction in tacrolimus clearance is negligible when arterial oxygen tension is maintained at more than 50 mmHg, even in patients with hypoxemia.

Keywords Tacrolimus · Liver transplantation · Hypoxemia · Hepatopulmonary syndrome

Introduction

Severe acute hypoxemia reduces the elimination of oxidatively metabolized drugs in ex vivo studies using isolated perfused rat liver preparation [1, 2, 3]. There is a substantial acinar oxygen gradient from high concentration in the peri-portal zone (zone 1) to low concentration in the peri-central zone (zone 3) [4, 5]. There is also evidence that a microsomal drug-oxidation system predominantly exists in the centri-lobular area [5, 6, 7]. Such an enzyme system located in zone 3 is expected to be affected by hypoxia. These findings lead to the conception that reductions in hepatic oxygen supply may diminish the hepatic disposition of oxidatively metabolized drugs in vivo.

Hepatopulmonary syndrome occurs in a subgroup of patients with chronic hepatic disease associated with portal hypertension, which causes intrapulmonary vasodilatation and subsequent hypoxemia [8]. Tacrolimus, an immunosuppressant widely used after organ transplantation, is demethylated or hydroxylated by hepatic microsomal mixed-function oxidases [9], and these reactions require sufficient oxygen supply.

In patients with hepatopulmonary syndrome, who are undergoing liver transplantation, the transplanted liver is subjected to hypoxemia, which may diminish

hepatic elimination of tacrolimus and elevate its blood concentration. We report on the clearance of tacrolimus in a pediatric patient with hepatopulmonary syndrome, who had undergone living related liver transplantation, and compare it with non-hypoxemic liver-transplanted pediatric patients.

Case report

The hypoxemic case

A 2-year 4-month-old girl (11.6 kg, 87.2 cm) underwent living related liver transplantation. She had been diagnosed with biliary atresia, and hepatojejunal anastomosis was performed 49 days after her birth. Eight months after the surgery it was suspected that she had hypoxemia, because of the presence of cyanosis and clubbed fingers. Her arterial blood gas measurement in room air was 46.6 mmHg, and intrapulmonary shunting, quantified by a macro-aggregated albumin scan, was 52%. On the basis of these findings, she was diagnosed as having hepatopulmonary syndrome. Before transplantation, her room air arterial oxygen tension (PaO_2) was 40.9 mmHg, and it was corrected only to 150.3 mmHg even by 100% oxygen inhalation.

Immunosuppressive therapy after liver transplantation consisted of a combination of tacrolimus and methylprednisolone. After the transplantation, tacrolimus was administered by continuous intravenous infusion at an initial dose of 0.06 mg/kg per day. Thereafter, the infusion rate of tacrolimus was adjusted to a target level of 15 to 20 ng/ml. Tacrolimus whole-blood concentrations were measured by the microparticle enzyme-linked immunoassay (IMx tacrolimus II immunoassay; Abbott Japan, Tokyo, Japan). She remained intubated and had been under respiratory control to maintain her PaO_2 at more than 50 mmHg until post-transplantation day 8 (Table 1, Fig. 1).

Figure 1 shows the changes in apparent clearance (CLapp) of tacrolimus, calculated from the blood concentration and the infusion rate of the patient until post-transplantation day 8. In the present case, CLapp of tacrolimus acutely decreased below 0.10 l/h per kg immediately after transplantation. CLapp decreased further, to 0.05 l/h per kg, 3 and 4 days after transplantation, and gradually increased to around 0.08 l/h per kg thereafter. Averaged tacrolimus concentration was 18.9 ± 2.8 (SD) ng/ml until post-transplantation day 8. After extubation at post-transplantation day 8, CLapp of tacrolimus of the patient remained stable at around 0.08 l/h per kg (range 0.074–0.096 l/h per kg). Tacrolimus was continuously infused until post-transplantation day 20, and then it was switched to oral dosing. Oral tacrolimus was given at a dose of 2.0 mg twice daily (0.34 mg/kg per day), and the trough tacrolimus blood concentrations were 8 to 10 ng/ml (9.3 ± 1.2 ng/ml) until the day of discharge (day 47).

Non-hypoxemic cases

As non-hypoxemic controls we selected seven pediatric patients that had undergone living related liver transplantation between June and December 2002. Those patients did not have any respiratory problem before transplantation. The causes leading to liver transplantation were biliary atresia (five cases), Byler's disease (one case) and biliary cirrhosis after resection of a giant hemangioma in the liver (one case). Age, body weight, and graft size were comparable to those of the hypoxemic patient (Table 1). Four of seven patients were extubated 1 day after transplantation (mean 3.9 days; range 1–12 days) and their arterial blood gas was monitored for several days after extubation.

During the first 5 days after transplantation, PaO_2 in the non-hypoxemic controls ($n = 7$) was significantly higher than that of the present case ($P < 0.05$ by two-way ANOVA; Fig. 1). Overall averaged PaO_2 was 149.2 ± 41.5 mmHg, and the averaged arterial oxygen saturation was more than 97.8% during the observed period (average 7.7 days after transplantation; range 5–13 days) (Table 1).

Table 1 Gender, age, body weight, graft size and arterial oxygen after living related liver transplantation in non-hypoxemic patients and the patient with hepatopulmonary syndrome. Data are shown as mean ± SD. *SaO_2* arterial oxygen saturation, *POD* postoperation day

Non-hypoxemic patients	Gender	Age (years)	Body weight (kg)	Graft volume (g)	PaO_2 (mmHg)	SaO_2 (%)	Observed period (POD)
1	Male	2.7	10.8	238	122.6 ± 26.6	98.3 ± 0.6	5
2	Male	2.2	9.3	242	129.3 ± 32.6	98.3 ± 0.6	6
3	Female	1.6	10.5	278	144.6 ± 44.7	98.4 ± 0.9	7
4	Female	2.0	9.9	270	165.4 ± 57.8	98.9 ± 0.7	5
5	Male	4.8	15.5	328	141.5 ± 53.5	97.8 ± 1.3	6
6	Male	1.0	9.1	190	180.9 ± 40.8	98.9 ± 0.4	12
7	Female	0.8	9.3	212	153.0 ± 22.7	98.9 ± 0.9	13
Average		2.2 ± 1.3	10.6 ± 2.2	251 ± 46	149.2 ± 41.5	98.5 ± 0.8	7.7 ± 3.4
Present case	Female	2.3	11.2	250	72.8 ± 10.4 (45.9~118.7)	93.1 ± 3.5 (80.3~98.6)	8

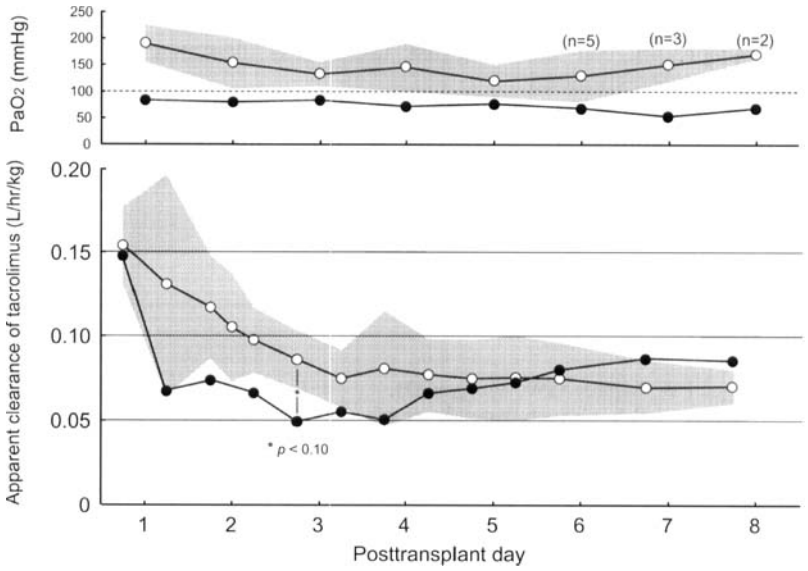

Fig. 1 Changes in arterial oxygen tension (PaO_2) and apparent clearance of tacrolimus after liver transplantation in a patient with hepatopulmonary syndrome (*solid circles*) and non-hypoxemic patients (*open circles*). *Shading* shows the area of the mean ± 1 SD of the non-hypoxemic control cases ($n = 7$ unless noted otherwise)

The initial dose of continuous intravenous tacrolimus and the target concentration in the blood were the same for both the present case and the non-hypoxemic controls. During the infusion period, averaged blood concentration of tacrolimus was 18.1 ± 1.0 ng/ml (range 17.4–19.4 ng/ml) in those patients, which was quite similar to that of the present case. Unlike that in the patient with hepatopulmonary syndrome, the CLapp of tacrolimus in the control cases gradually decreased during the 3 days after transplantation, after which it ceased decreasing (Fig. 1). CLapp in the case, from 2 to 4 days, was at the lower end of the control range presented, but it did not reach statistical significance ($P < 0.10$ by ANOVA on the morning of day 3). Overall averaged CLapp until day 8 in the control cases was 0.092 ± 0.014 l/h per kg (range 0.073–0.120 l/h per kg), which was not different from that of the case (0.075 l/h per kg, $P > 0.10$ by ANOVA). Tacrolimus was switched to the oral route 10.7 ± 3.5 days (range 7–16 days) after transplantation. The oral dose of tacrolimus was 0.32 ± 0.18 mg/kg per day (range 0.08–0.41 mg/kg per day), and the mean trough concentrations were 11.7 ± 3.2 ng/ml (range 6.4–15.6 ng/ml). Again, this was comparable to the case, where a dose of 0.34 mg/kg per day yielded concentration of tacrolimus in whole blood of 9.3 ± 1.2 ng/ml.

Discussion

We found that the apparent clearance of tacrolimus in a hypoxemic patient with hepatopulmonary syndrome was comparable to that of non-hypoxemic cases after liver transplantation. Our patient with hepatopulmonary syndrome had a lower PaO_2 and arterial oxygen saturation than did the control cases. However, she did not have an obvious alteration in the clearance of tacrolimus, except for the apparent decline in the early period after transplantation.

Tacrolimus clearance rapidly decreased and remained low for 4 days after transplantation in this patient. Thereafter, the clearance of tacrolimus increased to a level comparable with that of the non-hypoxemic controls, even with the persistence of hypoxemia. The biphasic changes of tacrolimus clearance observed in this case might be a reflection of an initial response to acute hypoxia and an adaptive change to hypoxia in the later period. As in our case, an initial decrease and a recovery in hepatic CYP3A4 activity has been reported in subjects exposed to high altitude-induced hypoxia [10]. The effect of hypoxia on CYP enzymes depends on oxygen level, and hypoxia is able to mediate both inhibition [11, 12] and induction [13] of CYP enzymes. The recovery of tacrolimus clearance in the later period, therefore, could be related to induction of drug metabolism by persistent hypoxia. Alternatively, perfusion of the liver, shifting the tacrolimus to the peri-central regions, may be increased in the transplanted liver.

The precise mechanism of the recovery of tacrolimus clearance is unclear, but it is likely that the degree of hypoxemia in the patient was too mild to impair hepatic drug metabolism, especially during the later period. Indeed, hypoxemia (PaO_2 48.5 mmHg) in dogs did not affect hepatic disposition of theophylline, another oxidatively metabolized drug [14]. Hepatic oxidative metabolism might be strongly blunted by a more severe hypoxemia. The limitation of the study resides in the method of tacrolimus measurement. The microparticle enzyme-linked immunoassay overestimates tacrolimus concentration due to the non-specific binding of the

antibody in this assay [15]. Thus, one should be careful in interpreting our data because tacrolimus clearance may be underestimated.

In conclusion, we reported on a hypoxemic patient with hepatopulmonary syndrome, who had undergone liver transplantation and had a clearance of tacrolimus comparable to that of non-hypoxemic liver transplant patients. These findings suggest that a reduction in the clearance of tacrolimus may be negligible when PaO_2 is maintained at more than 50 mmHg in patients with hypoxemia.

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