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CASE REPORT

Tacrolimus trough levels before, during and after jejunostomy in a liver transplant patient: A case report

Juliane Preuss[a,d], Mathieu Gazon[b,d], Jean-Yves Mabrut[c,d], Serge Duperret[b,d], Salim Mezoughi[c,d], Michel Tod[a,d], Christian Ducerf[c,d], Bruno Charpiat[a,*,d]

[a] *The departments of pharmacy, Croix-Rousse hospital, hospices civils de Lyon, 103, Grande-Rue de la Croix-Rousse, 69317 Lyon cedex 04, France*
[b] *The departments of anesthesiology and critical care, Croix-Rousse hospital, hospices Civils de Lyon, 103, Grande-Rue de la Croix-Rousse, 69317 Lyon cedex 04, France*
[c] *The departments of surgery and liver transplantation, Croix-Rousse hospital, hospices Civils de Lyon, 103, Grande-Rue de la Croix-Rousse, 69317 Lyon cedex 04, France*
[d] *Université Claude-Bernard Lyon 1, 43, boulevard du 11-Novembre-1918, 69622 Villeurbanne cedex, France*

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Summary Although the feasibility of oral tacrolimus administration in the presence of jejunostomy has already been reported, few studies monitoring tacrolimus trough blood levels have been analyzed in detail, either during or after a jejunostomy closure. We report on our experience with a 34-year-old patient who underwent liver transplantations, with a proximal jejunostomy constructed a few days prior to the second transplantation. He was administered tacrolimus by a predominantly oral route, and less frequently received it by jejunostomy. The aim of this paper is to discuss this administration strategy and whether a different method could have been more suitable. This case report highlights that during the jejunostomy period, the tacrolimus doses that were required to maintain trough concentrations within the therapeutic range were four times higher than those administered after the closure of the jejunostomy. We observed an increase in the Dose-Normalized Trough Concentration (DNTC) values when tacrolimus was administered for 4 consecutive days by jejunostomy as compared to oral administration, indicating that the relative bioavailability of tacrolimus increased. Moreover, when returning to oral administration, the subsequent DNTC value was halved, highlighting a reduction in the tacrolimus bioavailability. Thus, in such a case, administration by jejunostomy could be more appropriate.
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* Corresponding author. Department of pharmacy, Croix-Rousse hospital, hospices civils de Lyon, 103, Grande-Rue de la Croix-Rousse, 69317 Lyon cedex 04. Tel.: +33 4 72 07 18 88; fax: +33 4 72 07 18 94.
E-mail address: bruno.charpiat@chu-lyon.fr (B. Charpiat).

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Introduction

A large variability in the rate of absorption and the absolute bioavailability of orally administered tacrolimus has been previously reported [1]. Generally, the bioavailability is poor (approximately 25%), but it can range from 5% to 93% [2]. Although the feasibility of oral tacrolimus administration in the presence of jejunostomy has already been reported, few studies monitoring the tacrolimus trough blood levels have been analyzed in detail, either during or after jejunostomy closure, and there has not yet been a report on tacrolimus intake by jejunostomy that evaluates the trough blood levels [3—7].

We report on our experience with a 34-year-old patient who underwent two liver transplantations, with a jejunostomy constructed a few days before the second transplantation. He was administered tacrolimus by a predominantly oral route. The aim of this paper is to discuss the administration strategy applied and to question whether another method could have been more suitable.

Case report

On February 27th 2002, a 26-year-old male patient underwent a liver transplantation because of the development of progressive liver failure caused by erythropoietic protoporphyria. Immunosuppression was achieved with a low dose of corticosteroids and tacrolimus adjusted to maintain trough blood levels within the range of 5—15 ng/ml. From February 2002 to February 2010, the graft functioned well. In March 2010, the 34-year-old patient presented with an alteration of his clinical status, and a chronic rejection was diagnosed. On April 23rd 2010, a mesenteric ischemia associated with lactic acidosis was suspected (lactic acid 19.4 mmol/L, lipase 4160 UI/L, pH = 7.07) but was disproved by a laparotomy. Nevertheless, a proximal jejunostomy and a caecostomy were performed to monitor the status of the digestive mucous membrane. His renal function worsened, and he was dialyzed. He was then registered on the liver transplantation waiting list. On April 29th 2010, a second transplantation was achieved. The following day, he was reoperated because of perihepatic hematoma anemia and hepatic cytolysis. A severe acute respiratory syndrome followed by recurrent pneumopathies caused by multiresistant *Klebsiella pneumoniae* and atelectasis resulted in tracheotomy and in slow, difficult mechanical respiratory weaning. Although his clinical status improved in the days following the transplantation, biological results showed a chronic anemia. One month after the transplantation, he required repeated blood transfusions, and his liver function deteriorated. In addition, active cytomegalovirus (CMV) infection occurred. In June, the patient underwent an operation for a new perihepatic hematoma and for draining of the peritoneal cavity. On July 28th, the caecostomy was closed, and on August 30th, he underwent closure of the jejunostomy. On September 13th 2010, he began feeding orally, without residue, and was weaned from parenteral and enteral nutrition 5 days later. After the transplantation, immunosuppression was begun, with tacrolimus at 0.01 mg/kg per day, mycophenolate mophetil at 1 g/day and low-dose steroids.

The administration route was recorded daily, and all but 20 of the tacrolimus doses were administered orally. The remaining doses were given through the jejunostomy. For different infectious episodes, he received successively fluconazole and caspofungine until the 21st of July, and simultaneously or successively oral valganciclovir and intravenous ganciclovir, tigecycline and fosfomycine. Erythromycin was added as a prokinetic agent from May 11th until May 25th. Tacrolimus trough blood levels were measured before the morning administration of tacrolimus by the Enzyme-Multiplied Immunoassay Technique (EMIT). To evaluate the relative bioavailability of tacrolimus, we used the Dose-Normalized Trough Concentration (DNTC), which is calculated as follows: DNTC (ng/day per mg/mL) = trough blood level (ng/mL)/oral dose (mg/day).

After the first liver transplantation, the patient was discharged with a daily tacrolimus dose of 8 mg/day (0.13 mg/kg); the DNTC ranged from 1.07 to 1.81 ng/day per mg/mL from March 12th to 26th 2002 (average DNTC: 1.43 ng/day per mg/mL).

The evolution of the daily tacrolimus dose that was administered after the second transplantation from April to September 2010 and the subsequent measured trough levels are shown in Fig. 1. Tacrolimus was administered through jejunostomy at six occasions. The length of each occasion was 1 day ($n = 4$), 2 days ($n = 1$) and 4 days ($n = 1$). Table 1 shows the DNTC values that were calculated the days before, during and after the administrations by jejunostomy.

From the second transplantation until discharge, we distinguished three periods. The first (from April 29th to June 22nd) was an unstable period, characterized by infectious episodes, renal dysfunction requiring dialysis and altered liver function with low doses of tacrolimus and high corresponding trough blood levels. During this period, the daily tacrolimus doses varied from 1.5 mg to 14 mg, and the trough concentrations exceeded 20 ng/mL twice. The first instance was due to a drug-drug interaction with erythromycin. The second instance was ascribed to transitory liver dysfunction due to CMV infection and perihepatic hematoma removal. During the second period, from June 23rd to August 30th, the patient's general status improved. He required progressively increasing daily dosages, up to 30 mg. He was stabilized the month before the closure of the jejunostomy with 22 mg per day. The third period began with the closure of the jejunostomy. We observed a rapid increase in the trough levels, which necessitated the withholding of tacrolimus for 3 days during the week after the closure of the jejunostomy. The doses were tapered up to 5 mg/day, corresponding to a 77% reduction as compared with the daily doses that were administered before the closure. The patient was discharged with a daily dose of 5 mg (0.11 mg/kg per day), and his DNTC ranged from 0.85 to 2.71 ng/day per mg/mL from September 7th to 20th (average DNTC: 1.40 ng/day per mg/mL). Both the daily dose and the DNTC were similar to those obtained at discharge after the first transplantation.

Discussion

This case report highlights that during the jejunostomy period, the tacrolimus doses that are required to maintain trough concentrations within the therapeutic range

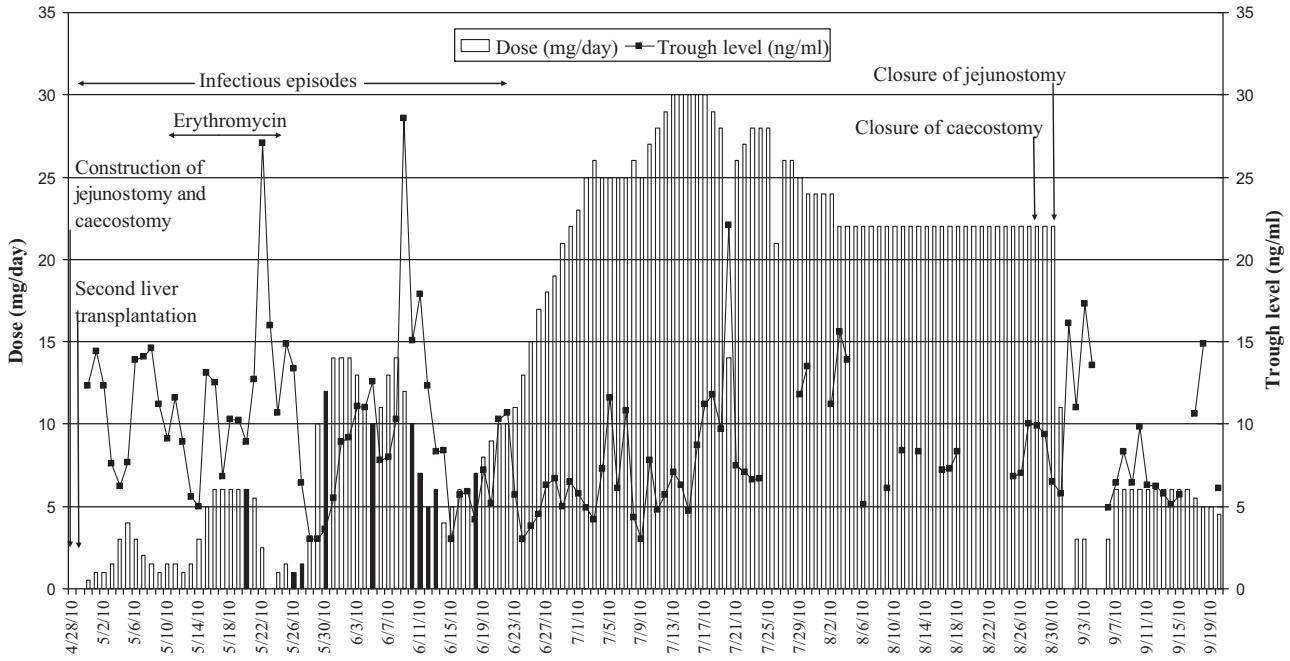

Figure 1 Daily oral dose and trough level of tacrolimus after the second liver transplantation. Open bars indicate that tacrolimus was administered by the oral route, and closed bars indicate administration by jejunostomy.

were four times higher than those administered after the closure of the jejunostomy. Similarly, Jain et al. observed in two small bowel transplant patients that the oral absorption of tacrolimus was lower when the proximal stoma was open. The percent absorption increased from 10% to 29% for the first patient and from 5% to 50% in the second when the stoma was closed [4].

Table 1 Calculated Dose-Normalized Trough Concentration (DNTC) and the corresponding trough blood level when tacrolimus was administered either by the jejunostomy or by the oral route the day prior and after.

Date (2010)	Oral dose (mg/day)	Dose by jejunostomy (mg/day)	Measured trough blood level (ng/mL)	DNTC (ng/day per mg/mL)
19 May[b]	6		8.9	1.48
20 May[a]		6	12.7	2.11
21 May[b]	5.5		27.1	4.93
25 May[b]	1.5		13.4	8.93
26 May[a]		1	6.4	6.4
27 May[a]		1.5	3	2
28 May[b]	3		3	1
29 May[b]	10		3.6	0.36
30 May[a]		12	5.5	0.46
31 May[b]	14		8.9	0.64
4 June[b]	11		12.6	1.15
05 June[a]		10	7.8	0.78
6 June[b]	11		8	0.73
9 June[b]	12		15.1	1.26
10 June[a]		10	17.9	1.79
11 June[a]		7	12.3	1.76
12 June[a]		5	8.3	1.66
13 June[a]		6	8.4	1.4
14 June[b]	4		3	0.75
17 June[b]	6		4.2	0.7
18 June[a]		7	7.2	1.03
19 June[b]	8		5.2	0.65

[a] Administered by the jejunostomy.
[b] Administered by the oral route.

Hasewaga et al. reported similar results in a 10-month-old girl after liver transplantation with an oral administration in the presence of jejunostomy. They observed a decrease in the bioavailability in the presence of a jejunostomy, and the dose required before the closure was 2.3 to 2.7 times the dose required after the closure [3].

Previously published data provide some explanations for this observation. In humans, the pre-systemic metabolism of tacrolimus by gastrointestinal CYP3A4 isoenzymes and its removal in the gut lumen by P-glycoprotein transport are extensive [8]. The upper small intestine is the major site for CYP3A4-mediated first-pass metabolism [9]. CYP3A4 expression is highest in the duodenum and in the jejunum and decreases toward the more distal regions [10,11]. All of these data suggest that increasing the dose is necessary to overcome the pre-systemic metabolism of tacrolimus and allow for passive diffusion through the upper small intestine.

With regard to the decision making process, the information given in Table 1 appears to be unequally informative. The variations that were observed during the five occasions when tacrolimus was administered for 1 day and for 2 days lack reliability when taking into account the patient status, the precision of the EMIT and the intraindividual variability. The administration of tacrolimus for 4 consecutive days through the jejunostomy may be more reliable. The increase in the DNTC values indicates that the relative bioavailability of the tacrolimus increased in the absence of drug interactions. When the oral route was begun again, the subsequent DNTC value was halved, highlighting a reduction in the tacrolimus bioavailability.

This observation raises the question of whether the adopted strategy of administering tacrolimus by an oral route was the optimal one. The analysis of previously published animal studies [12,13] and human case reports [7,14] suggests that administration by jejunostomy may be more appropriate and cost effective. Administering a drug by jejunostomy can be considered to bypass the proximal small intestine and consequently reduce the surface area available for absorption. However, because the CYP content is greater in the proximal small intestine [15], the bypass of this segment will also result in a relatively large reduction in the overall gastrointestinal metabolic activity and may increase the bioavailability of drugs that are subject to first-pass metabolism in the intestine. These two opposing processes may, to different degrees, affect the bioavailability of orally administered drugs, depending on the drug and the individual patient characteristics. In patients with a low gastrointestinal metabolic capacity who are therefore likely to achieve a high systemic exposure, a restriction of the absorption area could potentially reduce the bioavailability. In patients with a high gastrointestinal metabolic activity, a restriction of the absorption area could potentially increase the bioavailability [16,17]. This speculation is supported by previously described case reports [7,14,18]. All of these data, together with the fact that after 4 days of tacrolimus administration by jejunostomy in this study, the DNTC values were higher than were those obtained with the previous and subsequent tacrolimus doses administered by the oral route, suggest that for our patient, administering tacrolimus by the oral route was likely not the optimal strategy.

In conclusion, if the administration of tacrolimus by the oral route in a patient with a jejunostomy necessitates increasing the doses by two to four-fold over those administered before, this suggests that the patient is presenting with a high pre-systemic metabolic activity of the upper small intestine. In such a case, administration by jejunostomy could be more appropriate. Further studies are warranted to confirm this hypothesis.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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