Letter

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LETTER TO THE EDITOR

Adequate exposure to tacrolimus with sublingual administration in pediatric liver transplant patients

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Sir, – Very young children have difficulties in swallowing capsules due to their age, mechanical ventilation, and/or sedoanalgesia immediately post liver transplantation. In these specific situations, administrations of syrup or intravenous (IV) formulations are rarely used because of their instability, costs, and adverse events [1]. Thus, sublingual (SL) administration of tacrolimus is an interesting alternative in these cases because of its ease of administration besides its adequate exposure achieved [2]. Limited information of tacrolimus performance after SL administration is available [3, 4], and specifically there are no reports in pediatric patients. Therefore, we aimed to describe the dosage, exposure, drug-drug interactions, clinical, and safety parameters of tacrolimus SL administration in pediatric liver transplant patients in a retrospective observational study (Project #889).

Included patients were transplanted in 2014 – 2015 secondary to biliary atresia, and were followed-up during hospitalization at the ICU (intensive care unit). Enteric route was impaired due to mechanical ventilation, sedoanalgesia, or difficulties in swallowing the capsule. Patients with re-transplantation were excluded.

Tacrolimus was administered at an initial dose of 0.1 mg/kg b.i.d. and titrated according to blood concentrations targeted at 7 – 8 ng/mL, and also based on infectious disease and renal/liver function [5]. Patients received basiliximab at the day of transplantation and after 4 days along with prophylaxis treatment with ganciclovir, amphotericin, and trimethoprim/sulfamethoxazole.

After oral hygiene with chlorhexidine 0.12%, tacrolimus powder was placed under the tongue in the fasted state for 1 hour. Blood samples were obtained before the next tacrolimus morning dose (C_0) and tacrolimus concentrations were determined using CMIA (Architect® Abbott, Chicago, IL, USA). Drug-drug interactions (DDI) with known impact on the pharmacokinetics of tacrolimus were evaluated including azoles, macrolides, and steroids [6].

Daily dose-normalized trough concentrations (DNC, (ng/mL)/(mg/kg)) of tacrolimus were registered. Also, the number of dosage adjustments necessary to achieve the target tacrolimus C_0 during the first 14 days after transplantation was recorded.

Biopsy-proven acute rejection (AR), serum creatinine, and adverse events were registered as described in a previous report [7]. Re-operations and intervention therapy were considered as severe surgical complications.

DDIs were evaluated using Wilcoxon matched pairs test (GraphPad Prism v.5, GraphPad Software, San Diego, CA, USA, www.graphpad.com).

In total, 22 pediatric liver transplant patients who could not swallow tacrolimus capsules due to their age, mechanical ventilation, and/or sedoanalgesia were included (Table 1). The median (range) dosage and C_0 levels was 0.11 mg/kg (0.02 – 0.31) and 6.4 ng/mL (2.0 – 23.2), respectively, as shown in Table 1. The number of dosage adjustments was 7 (5 – 11) during the first 2 weeks after transplantation, as described by other authors [8].

Three patients (13.6%) presented an interaction with clarithromycin, nifedipine, or high doses of steroids (treatment for AR). The interaction was confirmed by the change in DNC, which increased in the presence of the interacting drug. Specifically, the median (range) DNC before and during concomitant clarithromycin administration in patient A was 38.1 ng/mL (24.6 – 69.9) and 76.8 ng/mL (16.0 – 88.0), respectively ($p < 0.05$, Figure 1A). Patients B and C showed an increase in the median DNC before and during

Table 1. Study group characteristics and tacrolimus exposure.

Liver transplant patients (n = 22)	
Male/female	9/13
Age (years)	0.9 (0.6 – 6.3)[a]
Weight (kg)	7.2 (5.2 – 20.0)[a]
Follow up (days)	22 (6 – 68)[a]
Mechanical ventilation (days)	10.5 (2 – 36)[a]
Immunosuppression treatment	Number of patients
Basiliximab	21
Tacrolimus	22
Steroids	5
Azathioprine	1
Single therapy with tacrolimus	17
Number of drawn trough levels	17 (3 – 58)[a]
Daily dose of tacrolimus (mg/kg)	0.11 (0.02 – 0.31)[a]
Tacrolismus blood levels (ng/mL)[b]	6.4 (2.0 – 23.2)[a]
Serum creatinine (mg/dL)[b]	0.3 (0.2 – 0.6)[a]
Urea (mg/dL)[b]	30.2 (17.3 – 90.3)[a]
Type of donor	Number of patients
Deceased donor	12
Complete liver	5
Split liver	7
Living donor	10
Severe surgical complications[c]	8
Infections	Number of patients
Viral infection:	
Citomegalovirus	11
Epstein-Barr virus	3
Bacterial infections	12
Tacrolimus exposure variability in the first 2 weeks[d]	
Number of dose adjustments	7 (5 – 11)[a]
Number of drawn trough levels	11 (9 – 12)[a]
Time to achieve the therapeutic FK level (days)[e]	3 (1 – 8)[a]
C0%CV[f]	49.8 (27.7 – 89.3)[a]

C_0 = tacrolimus trough levels; FK = tacrolismus; %CV = coefficient of variation (%). [a]Data is expressed as median (range); [b]Data from all patients, obtained during the follow-up period; [c]Severe surgical complications were recorded according to Clavien et al. [9] definition, considering re-operations and intervention therapy; [d]Exposure variability was defined as the coefficient of variation of tacrolimus trough levels and number of dose adjustments required to reach the tacrolimus target level of 7 – 8 ng/mL; [e]Time to achieve the therapeutically accepted tacrolimus target of 7 – 8 ng/mL; [f]Drug-drug interactions were excluded of this value, which was obtained during the first 2 weeks after transplantation.

the interaction with nifedipine or steroids, respectively, without statistical significance ($p > 0.05$, Figure 1B, C). No patient received more than one interacting drug simultaneously.

Three patients (13.6%) experienced an AR and one of those occurred in the context of low tacrolimus C_0 (3.9 ng/mL, SD 1.8) due to a high rate of infections and severe surgical complications [9] (36.4%) that altogether justified the low tacrolimus doses received.

Furthermore, 3 patients (13.6%) experienced neurotoxicity (n = 1), nephrotoxicity (n = 1) in the context of a high tacrolimus C_0 of 14.2 ng/mL, and hypomagnesemia (n = 1) after a C_0 of 23.2 ng/mL but also in the context of a nifedipine-tacrolimus interaction. Two patients died secondary to surgical complications without AR episodes or adverse events during the study period.

Data presented here demonstrated acceptable tacrolimus concentrations in 22 pediatric liver transplant patients with SL administration during the hospitalization at ICU. Although the dosage described here was lower to that used for oral administration [9], tacrolimus C_0 were comparable between both routes. The main reason of this is that lipophilic drugs are absorbed into the sublingual venous circulation coming directly to cardiovascular circulation and from there, into the systemic circulation bypassing the gastrointestinal and first-pass metabolism [4, 10].

The present efficacy and safety profiles of tacrolimus early after pediatric liver transplantation are in line with published results on oral administration [8]. Furthermore, special attention should be paid when administering nifedipine and high doses of steroids simultaneously with tacrolimus [6]. Sublin-

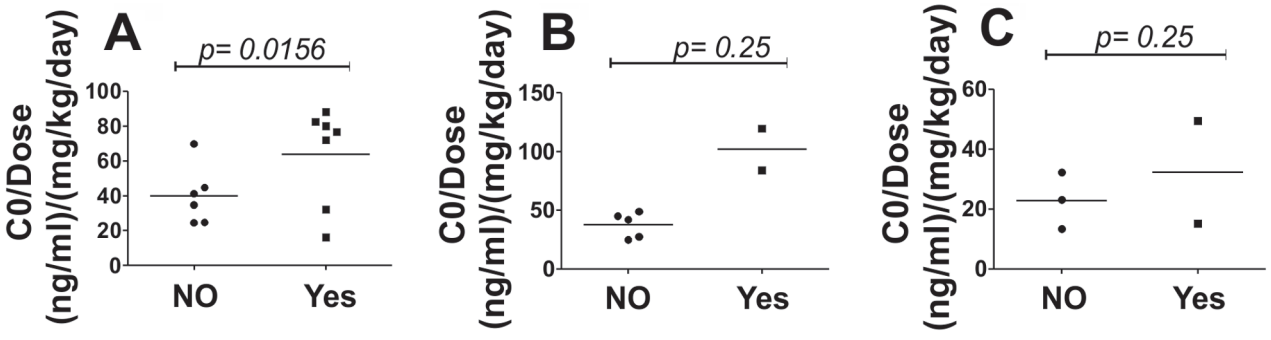

Figure 1. Tacrolimus exposure increased in presence of a drug-drug interaction after sublingual administration. C_0: tacrolimus trough concentrations; Dose = tacrolimus daily dose corrected by body weight; NO = C_0/Dose without concomitant administration of interacting drugs; YES = C_0/Dose in presence of interacting drugs; A = Concomitant administration of clarithromycin in patient 4; B: Concomitant administration of nifedipine in patient 6; C: concomitant administration of high doses of steroids in patient 9.

gual tacrolimus is a viable alternative when oral administration is unavailable. It may result in potential clinical improvements and cost savings. Further investigation is needed to characterize the pharmacokinetics of sublingual tacrolimus administration. Besides utilization of sublingual tacrolimus, this study highlights the role of therapeutic drug monitoring to maintain tacrolimus C_0 within the therapeutic range, with special emphasis on drug safety.

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Conflict of interest

None of the authors have any potential, perceived, or real conflicts of interest.

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