Clinical Pharmacokinetics of Oral Versus Sublingual Administration of Tacrolimus in Adult Liver Transplant Recipients

Zahra Nasiri-Toosi,[1] Simin Dashti-Khavidaki,[2] Mohsen Nasiri-Toosi,[3] Hossein Khalili,[2] Ali Jafarian,[3] Hamideh Irajian,[3] Alireza Abdollahi,[4] Sima Sadrai[2]

Abstract

Objectives: **Oral tacrolimus administration is the common route of drug delivery. Recent studies suggest sublingual administration of tacrolimus as an alternative route may produce comparable drug trough levels with similar or even lower doses than the oral route, especially in lung transplant recipients; however, most of this research does not encompass intraindividual variations compared between the 2 routes. This study sought to compare the bioavailability and blood trough concentrations of orally and sublingually administered tacrolimus in adult liver transplant recipients by considering intraindividual variations in tacrolimus pharmacokinetics properties.**

Materials and Methods: **Six adult liver transplant recipients received their tacrolimus either orally or sublingually within 2 consecutive days. Blood samples to determine tacrolimus concentrations were gathered at 0, 0.5, 1, 2, 4, 6, and 12 hours after oral and sublingual tacrolimus administration. Mean data values were used to calculate the pharmacokinetics parameters via the feathering or residual method, using the 1-compartment, first-order elimination pharmacokinetics model. Compared pharmacokinetics parameters included drug bioavailability, maximum blood concentration (C_{max}), time to reach maximum blood level (T_{max}), and trough blood concentrations.**

Results: **Trough whole blood levels, area under the concentration-time curve, T_{max}, and C_{max} after oral and sublingual administration of tacrolimus were not significantly different (10.4 ± 7.4 vs 11.2 ± 11.3 ng/mL for trough blood concentration, 181.5 ± 114.1 vs 160.8 ± 115.9 ng.h/mL for AUC, 1.9 ± 1.2 vs 1.4 ± 0.7 h for T_{max}, and 19.9 ± 10.8 vs 17.2 ± 11.7 ng/mL for C_{max}). A double-peak phenomenon was observed in some concentration-time profiles.**

Conclusions: **Sublingual tacrolimus administration does provide therapeutic drug concentrations in adult liver transplant recipients. Therefore, sublingual tacrolimus may confidently be considered as an alternative route to oral administration in patients who are unable to swallow their drugs.**

Key words: *Oral, Sublingual, Tacrolimus, Pharmacokinetics, Liver transplant*

Introduction

Calcineurin inhibitors, including tacrolimus (TAC), have been used as the cornerstone of immunosuppressive therapy in solid organ transplant recipients. The intravenous route of TAC administration is rarely used in the clinic owing to high rates of nephrotoxicity, neurotoxicity,[1] rare cases of anaphylactic reactions,[2] or near-fatal cardiac

From the [1]Tehran University of Medical Sciences; the [2]School of Pharmacy, Tehran University of Medical Sciences; and Nephrology Research Center, Tehran University of Medical Sciences, Imam Khomeini Hospital Complex; the [3]Liver Transplantation Ward, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences; and the [4]Valie-Asr Hospital, Tehran University of Medical Sciences. Tehran, Iran

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Corresponding author: *Simin Dashti-Khavidaki, Associate Professor of Clinical Pharmacy, School of Pharmacy, Tehran University of Medical Sciences, and Nephrology Research Center, Tehran University of Medical Sciences, Tehran, Iran ZIP code: 141761-4411 PO Box: 14155/6451*

Phone: *+98 912 247 1998* ***Fax:*** *+98 21 6695 4709* ***E-mail:*** *dashtis@sina.tums.ac.ir*

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arrhythmias.[3] Oral TAC administration is the common route of drug delivery. After oral administration of TAC, gut and hepatic metabolism by cytochrome P450 microsomal enzymes (CYP3A), and P-glycoprotein (P-gp) efflux at the gut, result in low TAC bioavailability.[4] Sublingual administration of TAC, bypassing gut processes, may provide comparable drug bioavailability and desired trough blood concentrations compared to the oral route even with lower drug dosages.

For drugs with sublingual absorption, this route of drug administration provides faster onset of action, and additionally, reduced drug dosage to achieve similar target levels compared with oral administration; this may result in lower medical costs. Therefore, sublingual administration might be an alternate route, especially in patients who cannot swallow the oral dose form—for example, intubated liver transplant recipients, and those with postoperative ileus, which prohibits oral drug administration. A few studies have compared oral and sublingual administration of TAC,[5-7] and their results showed achievement of acceptable TAC blood concentrations in patients who received sublingual TAC. Previous studies assessed the pharmacokinetics parameters of orally administered TAC;[8-14] however, there has not been any study that assesses the pharmacokinetics parameters of sublingual TAC in adult liver transplant recipients. This study sought to comparethe bioavailability and trough blood concentrations of orally and sublingually administered TAC in adult liver transplant recipients.

Materials and Methods

Six adult patients who underwent a liver transplant were included in this study. All patients received TAC as a component of their triple immunosuppressive regimen, which included prednisolone and mycophenolate mofetil.

All included patients were within the first week after liver transplant, white, took TAC twice daily 1 hour before a meal, and were clinically stable regarding liver function. Patients with any medical or gastrointestinal disorders that could interfere with absorption, distribution, metabolism, or excretion of TAC were excluded. The research protocol was approved by the ethics committee of Tehran University of Medical Sciences and conformed with the ethical guidelines of the 1975 Helsinki Declaration. All patients signed an informed consent form.

Blood samples for determining whole blood TAC concentrations were collected 4 to 5 days after TAC initiation or any dosage change to be sure of achieving steady-state drug concentrations. At this time, patients received their morning TAC doses orally and sublingually on 2 consecutive days.

Four patients received their morning dose of TAC orally on the first day of sampling and sublingually on the second day, and vice versa for the 2 other subjects. According to Goorhuis'study,[6] we prepared a TAC suspension in a 0.5-mg/mL concentration using TAC capsules. In this study, TAC capsules were opened, and the powder was dispersed in water to a concentration of 1 mg/mL to reduce the volume that would be used for sublingual administration. The prepared suspension was placed under the patients tongue drop by drop during 10 minutes. During administration, patients were instructed not to swallow the oral solution. The sublingual administered liquid was 2 mL in five patients and 3 mL in one patient. To ensure patient compliance, oral or sublingual TAC was administered to patients directly by 1 of the researchers. All patients were notified of the importance of immunosuppressive drugs in maintaining their transplanted liver. Blood samples were taken before administration of the morning dose of TAC (C_0) and at 0.5, 1, 2, 4, 6, and 12 (C_{trough}) hours after the morning dose via oral or sublingual routes. Tacrolimus whole blood concentrations were determined using an available method, Enzyme Multiplied Immunoassay (Dade Behring EMIT 2000 TAC assay kit; Siemens AG, Munich, Germany).

Mean data values were used to calculate the pharmacokinetics parameters via the feathering or residual method. Pharmacokinetics parameters were calculated through a 1-compartment, first-order elimination pharmacokinetics model using the formula $Cl=k_e \times Vd$, $T_{1/2}=0.693/k_e$, $Vd=F \times k_a \times dose/(k_a - k_e) \times C$, in which Cl, k_e, Vd, $T_{1/2}$, F, k_a, and C were TAC clearance, elimination rate constant, apparent volume of distribution, half-life, bioavailability, absorption rate constant, and Y-intercept of the concentration-time curve. Area under the concentration-time curve (AUC) was estimated by the trapezoid method. F was considered to be 0.25, as reported by other researchers.[1] A paired

2-sample *t* test was used to compare oral and sublingual AUC and TAC trough concentration levels. A *P* value < .05 was considered significant. Owing to the absence of a decline elimination phase in 5 of the 12 concentration-time profiles, data parameters also were estimated by using a nonlinear mixed effect model program, Monolix, version 3.1 (available at http://www.monolix.org/sdoms/software/index.php?/download-monolix31beta.html).[15] Parameters were estimated by minimizing the "maximum likelihood estimator" of the parameters. A constant model was used to describe the residual variability.[16]

Results

Six adult patients (3 men, 3 women; mean age, 37.5 ± 11.9 y; range, 22-51 y) completed the study. The study was performed between December 2009 and December 2010. These patients required transplants because of liver cirrhosis caused by autoimmune liver disease (3 patients), hepatitis C infection (2 patients), and cryptogenic liver cirrhosis (1 patient). Patients' demographics are summarized in Table 1. The ratio of sublingual to oral TAC concentration at each time point was calculated, and the mean of these ratios was 0.96 ± 0.29 (range, 0.73-1.54). Table 2 shows the mean pharmacokinetics parameters of orally and sublingually administered TAC. Because both the AUC and trough blood concentrations of TAC are of higher clinical values, these parameters have been presented in Table 3 for both routes of drug administration in all subjects. The ratio of sublingual to oral route AUC was 0.89 ± 0.41 (range, 0.61-1.67). As shown in Figures 1 to 3, the time to maximum drug concentration (T_{max}) after oral TAC administration was equal to sublingual administration in 1 patient, nonsignificantly higher than sublingual administration in 2 patients, and lower in 3 patients. The AUCs after oral TAC administration were not significantly higher than those of the sublingual route in 5 patients. Differences between the sublingual and oral TAC concentration, at each time point, in patient 1 and patient 2 were lower than in the other patients. As seen in Table 2, there were no statistically significant differences between achieved AUC, T_{max}, C_{max}, and C_{trough} after orally and sublingually administered TAC. Nevertheless, apart from a few odd points, the concentration-time profiles for 5 patients showed the same trend. As shown in Figures 1 to 3, the double-peak phenomenon was observed in 7 of 12 concentration-time profiles. Three of 12 sublingual

Table 1. Recipient Demographics Data

Patient Data	Values
Age (y) (mean ± SD*)	37.5 ± 12
Sex (male/female)	3/3
Weight (kg) (mean ± SD*)	70 ± 5.2
Height (cm) (mean ± SD*)	167.5 ± 7.3
Underlying disease leading to liver transplant	
Autoimmune liver disease	3
Hepatitis C infection	2
Cryptogenic liver cirrhosis	1

*Standard deviation

Table 2. Mean TAC Pharmacokinetics Parameters After Oral and Sublingual Administration

Parameters	Sublingual Administration	Oral Administration	*P*
AUC*(ng.h/mL)	160.8 ± 115.9	181.5 ± 114.1	.19
k_e† (h^{-1})	0.05	0.03	
$T_{1/2}$‡ (h)	14.8	24.6	
k_a§ (h^{-1})	0.9	2.2	
Vd¶/F# (L)	222.2 ± 41.8	220.4 ± 45	
Cl**/F (L/h)	10.4 ± 1.9	6.2 ± 1.3	
C_{trough}†† (ng/mL)	11.2 ± 11.3	10.4 ± 7.4	.37
T_{max}‡‡ (h)	1.4 ± 0.7	1.9 ± 1.2	.21
C_{max}§§ (ng/mL)	17.2 ± 11.7	19.9 ± 10.8	.3

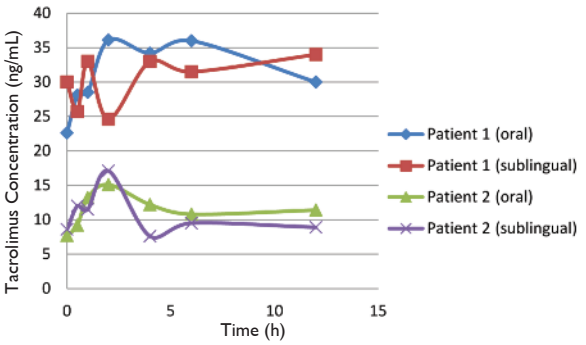
Abbreviations:*, area under the concentration-time curve; †, elimination rate constant; ‡, half-life; §, absorption rate constant; ¶, apparent volume of distribution; #, fraction of dose absorbed (bioavailability factor); **, clearance; ††, trough concentration; ‡‡, time of occurrence for maximum drug concentration; §§, maximum concentration; TAC, tacrolimus

Table 3. AUC and TAC Trough Concentration After Oral and Sublingual Administration of the Drug in Each Patient

Patient No.	Sublingual Administration		Oral Administration		Ratio of Sublingual to Oral TAC Parameters	
Patient	AUC (ng.h/mL)	C_{trough} (ng/mL)	AUC (ng.h/mL)	C_{trough} (ng/mL)	AUC (ng.h/mL)	C_{trough} (ng/mL)
1	376	34.0	397.6	22.6	0.95	1.5
2	122.3	8.9	140.9	7.7	0.87	1.16
3	138.8	7.0	219.7	14.7	0.63	0.48
4	194.7	5.5	116.7	3.6	1.67	1.53
5	64.4	4.4	100.8	3.1	0.64	1.42
6	68.9	7.6	113.7	10.4	0.63	0.73

Abbreviations: AUC, area under the concentration-time curve; TAC, tacrolimus

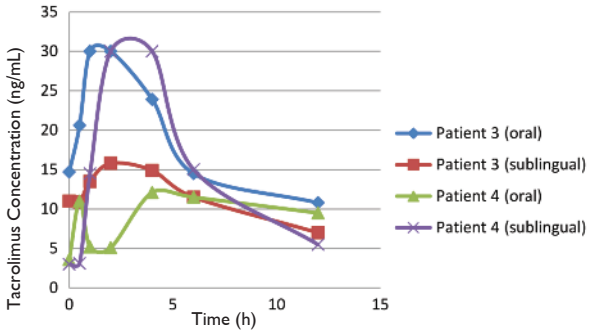
Figure 1. Profiles of TAC Concentrations After Oral and Sublingual Administration in the First and Second Patients on 2 Consecutive Days



Abbreviations: TAC, tacrolimus

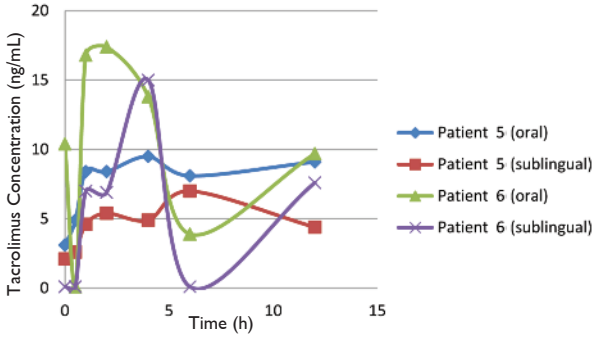
concentration-time profiles showed a lag time of up to one-half hour. Table 4 shows the TAC pharmacokinetics parameters estimations by Monolix for pooled oral and sublingual data.

Figure 2. Profiles of TAC Concentrations After Oral and Sublingual Administration in the Third and Fourth Patients on 2 Consecutive Days



Abbreviations: TAC, tacrolimus

Figure 3. Profiles of TAC Concentrations After Oral and Sublingual Administration in the Fifth and Sixth Patient on 2 Consecutive Days



Abbreviations: TAC, tacrolimus

Table 4. Tacrolimus Pharmacokinetics Parameters After Pooled Data of Oral and Sublingual Administration by Monolix 3.1

Parameters	Parameter Value	SE # (Linear)	RSE**(%)
K_a*(h^{-1})	0.5	0.3	68
Vd†/F‡(L)	129.0	57.0	44
K_e§(h^{-1})	0.09	0.04	49
Cl¶/F(L/h)	11.0	2.5	26

*Abbreviations:**, absorption rate constant; †, apparent volume of distribution; ‡, fraction of dose absorbed (bioavailability factor); §, elimination rate constant; ¶, clearance; #, standard error; **, relative standard error

Discussion

This study compared the clinically valuable pharmacokinetics parameters of orally and sublingually administered TAC (AUC, C_{max}, C_{trough}, and T_{max}) in adult Iranian liver transplant recipients. Tacrolimus absorbs poorly after oral administration, with large interindividual variation in bioavailability from 4% to 89%.[8] When oral administration is not practical, particularly during the first week after transplant, when some patients are intubated or have postoperative ileus, sublingual administration might be an alternate route. Therefore, all patients included in this study were in their first week after transplant. The results of this study showed that sublingual administration of TAC provides therapeutic drug concentration and comparable drug bioavailability in dosages similar to oral dosages in adult liver transplant recipients.

Reams[5] has reported achieving desired therapeutic TAC concentrations by administrating sublingual TAC at dosages similar to those of the oral route in 22 lung transplant recipients with cystic fibrosis within the first few months after surgery. Also, a preliminary study by Goorhuis[6] in pediatric liver transplant recipients showed that buccal administration of TAC is well tolerated, with similar resultant TAC trough levels compared with drug levels after TAC delivery through nasogastric tube. Collin[17] reported the potential safety of sublingual TAC as an alternative to the intravenous route in 16 patients with thoracic transplant: 90.4% of their TAC concentration samples were within the therapeutic range. In Collin's study, the powder content of the capsules was put directly under the patient's tongue; but in our study, to enhance drug absorption, the powder content of the capsules was dispersed in water before administration.

Based on the findings of these studies and also owing to the TAC first-pass effect that happens after oral administration, we suggest that TAC bioavailability via oral mucosa maybe higher after sublingual administration. However, the concentration-time profile of our patients, and the mean T_{max} of 1.4 hours, proposed that TAC absorption probably occurs in the lower gastrointestinal tract rather than being absorbed through the oral mucosa. This result agrees with those of Romero[18] and van de Plas.[19] Therefore, sublingual dispersion of TAC is really simply oral administration of a liquid, and although the liquid is placed under the tongue drop by drop over several minutes, eventually, the patient swallows the liquid rather than absorbing the drug via the oral mucosa. Contrary to our results, Hanger[7] reported a 50% reduction in TAC sublingual dose to achieve similar blood levels of oral TAC in 34 lung transplant recipients.

This study showed no difference in AUC, C_{trough}, T_{max}, and C_{max} between the 2 routes of TAC

administration; however, the sample size was not large enough to demonstrate equivalence in exposure, and further studies with more patients are required to confirm our findings. On the other hand, sublingual to oral AUC ratio ranges widely, from 0.61 to 1.67, in the same patients. With a narrow therapeutic index drug like TAC, this difference and variability seems clinically unacceptable, and it is not recommended to switch patients between 2 modes of drug administration frequently. The most-important point about TAC is interindividual and intraindividual pharmacokinetics variation. To escape intraindividual variation in this study, both routes of drug administration were assessed in all subjects, which has not been considered in previous studies.[5-717-19]

The rationale for the double-peak phenomenon has been attributed to variability in stomach emptying, variable intestinal motility, presence of food, enterohepatic recycling, or failure of dosage form. In this study, a double peak was seen in both routes of drug administration; therefore, failure of capsules to open can be ruled out. All of our patients received TAC 1 hour before a meal, so the possible effect of food presence on double-peak concentration would be minimized. To undergo enterohepatic recycling, the drug must be secreted in the bile either as is, or as a metabolite that can be converted to the parent drug; this does not happen with TAC.

Double-peak phenomena, especially in the early postoperative period, are more likely due to altered gastric emptying and dissolution issues. Post-transplant reduced gastric emptying time may be a suggested mechanism for the double-peak phenomena of TAC. However, there are some reports that TAC may exhibit prokinetic properties owing to its macrolide structure,[20] and a short lag phase of solid gastric emptying was reported with TAC compared with cyclosporine in renal transplant recipients.[21] Therefore, the real effect of slowed gastric emptying on the observed double peak requires more study.

Some animal studies have suggested regional differences in CYP3A activity and P-gp expression level in the small intestine that could account for the site-dependent absorption of TAC. Differences in P-gp function at various intestinal sites in a subject, or at a given intestinal site in various subjects, may lead to large intraindividual and interindividual variability in the bioavailability of orally administered TAC.[22,23] CYP3A and P-gp polymorphisms may have some role in double-peak phenomena after TAC administration.

Jusko[14] showed a brief absorption lag time (T_{lag} 0.39 h) after oral administration of TAC. In our study, we found a comparable absorption lag time in the sublingual concentration-time profile. As seen in Table 3, estimation of the parameters by Monolix is comparable with classic parameter calculations except for the absorption phase. This may be due to the lag time and the double-peak phenomena seen in some patients.

The major limitations of this study were the low number of patients and unavailability of a more-specific dosage form for sublingual TAC administration. Because the concentration-time profiles of all 6 patients who engaged in this study were similar, and because of high cost of whole-blood TAC assessment, especially for 14 subsequent samples, inclusion of more patients was stopped with these results. However, further studies with more patients, and also, a more-suitable prepared dosage form for TAC sublingual administration, are recommended to confirm or reject our findings.

Conclusions

This study revealed that sublingual administration of TAC suspension prepared from its available capsules does provide therapeutic drug concentration and may be considered confidently for those patients who are unable to swallow their drugs.

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