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Comparison of Oral, Sublingual and Enteral Route of Tacrolimus Administration in Adult Transplant Recipients Hospitalized in A Critical Care Unit

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Abstract

After the early post-operative stage of solid organ transplant (SOT), oral administration of immunosuppressive drugs such as tacrolimus may be compromised, due to gastrointestinal problems or surgical complications.

The study aimed to compare the consistency and variability of tacrolimus blood concentrations after administering tacrolimus orally, sublingually and by nasogastric tube in critical adult transplant recipients, as well as to analyze which factors might affect this variability.

A retrospective observational study was performed, including seventy-nine lung, liver and kidney SOT patients. Tacrolimus was administered by different routes. The coefficient of variation (CV) was used to quantify the intrapatient variability of tacrolimus blood concentrations.

Mean tacrolimus blood levels were significantly higher when using nasogastric and sublingual routes, versus the oral one ($p<0.001$). The variability observed was higher in nasogastric tube administration, CV 45.8% (20.2), compared to the oral, CV 32.9% (19.6), and sublingual routes, CV 37.2% (11.0) ($p= 0.013$). The role of potential influencing factors on the

consistency of tacrolimus therapy, including drug-drug interactions, showed in the multiple analysis of variance design that the inhibitor (p=0.008) and metabolic factors (p= 0.016) are influencing factors.

There is a high variability of tacrolimus blood concentrations during intensive care unit admission, which is higher when the nasogastric tube is used. Nevertheless, considering the characteristics of each route of administration, sublingual and nasogastric routes could be viable alternatives to the oral route for short-term use in patients who are unable to receive medications orally and need to maintain effective blood concentrations of immunosuppressive medications.

Keywords: Tacrolimus; transplant; administration; concentration; variability

Introduction

Solid organ transplantation (SOT) can increase survival rate and improve the quality of life in patients with end-stage organ disease. After the transplant, it is important to maintain effective blood concentrations of immunosuppressive medications to prevent allograft rejection and adverse events [1]. Tacrolimus is an immunosuppressive drug characterized by a narrow therapeutic index, a large side-effect profile and a high pharmacokinetic variability [2]. Oral tacrolimus administration is the most common route of drug delivery. Nevertheless, different routes of tacrolimus administration – such as intravenous, sublingual or by nasogastric tube – are available to conduct viable therapy in any clinical circumstances after SOT. More particularly in the early post-operative stage, oral administration may be compromised due to nausea, vomiting, mechanical ventilation, decreased absorption secondary to gastroparesis or ileus, surgical complications and oropharyngeal dysphagia (risk of aspiration) [3,4].

The intravenous route is rarely used, as tacrolimus administration requires careful technical management for this drug's dilution and infusion rate. Moreover, it contains castor oil derivates associated to anaphylactic reactions and it is related with a high rate of nephrotoxicity and neurotoxicity [5–8]. The sublingual route may be a true alternative in patients who cannot swallow the oral dose for tacrolimus administration [9–11], such as intubated patients or patients with postoperative ileum. Apparently, sublingual administration bypasses gut processes and provides comparable trough blood concentrations compared to the oral route, even with lower drug dosages [12]. Last, the nasogastric administration of tacrolimus would not substantially affect the pharmacokinetic profile of tacrolimus, if compared to intact capsules [13, 14], and could be a viable option to ensure appropriate tacrolimus exposure in transplant recipients with a functional oral tube.

Various studies have compared oral, sublingual and nasogastric tube tacrolimus administration and, generally, their results showed that acceptable mean tacrolimus blood concentrations were attained [15, 16]. Nevertheless, and on top of that, it is widely known that high intrapatient variability of tacrolimus – especially in an early post-operative stage – is related to a worse outcome in transplant recipients [17]. This would cause a worsening in graft and patient survival rates [18, 19], both compromising efficacy and safety. A higher variability in tacrolimus exposure implies, first, a higher risk for developing a composite endpoint of graft loss [20], acute or late acute rejections and an independent risk factor for novo donor-specific antibodies (dnDSA) development [21]. Secondly, it entails an increased risk of toxicity manifested in a decline in the kidney function or in a higher risk of infections [4]. It has been reported that subject variability (defined as the coefficient of variation) is considered to be high if it is 30% or greater in one or more of the bioequivalences measurements [22].

All things considered, out of mean values, data on the reproducibility and variability of tacrolimus blood levels and the influence of the tacrolimus administration route are really scarce. Moreover, post-operative, severe or critical patients are under hemodynamic instability – e.g., changes in hematocrit – or altered kidney function – e.g. changes in serum creatinine –, or are subjected to intensive complementary drug treatment that is able to generate interaction – e.g. metabolic influence on tacrolimus [17]. Given the importance of this issue, the aim of this study is to compare the consistence and the variability of tacrolimus blood

concentrations administered orally, sublingually and by nasogastric tube in critically ill transplant patients, as well as to analyze which factors might affect this variability.

Materials and Methods

Study Design

Retrospective observational study performed from May to December 2017. The patients were identified from pharmacy drug prescription records. The inclusion criteria included immediate SOT patients (lung, liver and kidney) – who had undergone transplant surgery – or SOT patients who had acute complications that required intensive care unit (ICU) admission. That's because it's the case in which patients have more problems with the oral administration of tacrolimus. Patients treated with oral, sublingual or by nasogastric tube tacrolimus for a minimum of two consecutive days and those with at least three tacrolimus blood concentrations were included in the study. Nevertheless, patients with either only one day of follow-up, two or less samples of tacrolimus blood levels or incomplete clinical records were excluded.

Immunosuppressive Treatment

Tacrolimus was administered twice daily as follows:

Oral Tacrolimus Administration was performed by using Prograf® oral capsules, which were administered with approximately 100 ml of water.

Sublingual Tacrolimus Administration was performed by using Prograf® oral capsules, either capsule was opened and their powder content was placed under the patients' tongue, which dissolved completely after 15 minutes [9]. As for the dose administered orally or by nasogastric tube, 50% of the tacrolimus dose was administered by sublingual route to patients with digestive motility troubles and intolerance to oral and nasogastric tube routes and 100%, in the same way, to patients who needed higher tacrolimus blood concentrations.

Nasogastric Tube Tacrolimus Administration was performed by using Prograf® oral capsules, which were administered by dissolving them in water. Water was injected before and after tacrolimus administration through the nasogastric tube. Enteral feeding was stopped at least 1 hour before and 0.5 hour after tacrolimus administration. Tacrolimus dosage was adjusted according to the physician criteria in order to maintain tacrolimus trough concentrations within the targeted therapeutic range

Tacrolimus Blood Concentration Assessment

Full blood samples were routinely drawn just before each dose and were collected with EDTA venous blood collection as an integral part of the therapeutic follow-up during hospitalization. Blood levels were analyzed by enzyme-multiplied immunoassay being 1ng/mL as the limit of quantitation. And finally, the coefficient of variation (CV) was used to quantify the intrapatient variability (IPV) of tacrolimus blood concentrations.

Collected Data

The patients' demographic, clinical and analytical data were gathered from the hospital's clinical records. The collected data were: type of transplant, demographics, analytical parameters (creatinine, glomerular filtration rate and hematocrit), tacrolimus route of administration and drug blood levels. If patient had been using tacrolimus on more than one route of administration, the administration period for each route was collected separately. The concomitant drugs administered during ICU admission were also registered and possible pharmacologic interactions with tacrolimus were evaluated.

Drug-Drug Interactions

Tacrolimus presents significant pharmacokinetics and pharmacodynamics drug drug interactions (DDI) with many drugs, so concomitant pharmacotherapy must be considered. All treatments were analyzed for potential drug interactions by using Lexicomp® drug interactions [25], online software for DDI checking. This software provides a risk rating scale (A, B, C, D or X), the reliability rate and it also identifies factors that may influence the occurrence or severity of the interaction (e.g., metabolizer phenotype). DDI were classified in 5 risk rating scales: A (no known interaction; evidence have not demonstrated interactions between the specified drugs), B (no action needed; there isn't any evidence of its clinical relation), C (monitor therapy; dosage adjustments of some drugs may be needed), D (consider therapy modification; drugs may interact in a clinically significant way) and X (avoid combination; risks associated with concomitant drugs use usually outweigh the benefits). All DDI were analyzed,collected, classified, quantified and integrated in a single variable ('metabolic factor'), as follows:

Metabolic factor (value) = Σ ((Metabolic induction [+], inhibition [-]; C (1), D (2), X (3) DDI1) + (…. DDIn))

In DDI analysis, azoles antifungal agents were selected and its impact on tacrolimus blood levels was analyzed in more detail. Those agents are known for inhibiting the first-pass metabolism, primarily via cytochrome P450 3A (CYP3A) enzymes in the intestine and liver of tacrolimus [26]. This results in an increase of tacrolimus levels, due to an improvement in oral absorption rates and a decrease of total body clearance [27,28]. The specific prescription of these drugs resulted in a new variable: the 'inhibitory factor'.

Statistical Analysis

Analytical consistency of tacrolimus therapy was defined by parameters derived from patient blood concentrations. For each case, mean and standard deviation of tacrolimus blood concentrations (ng/ml), coefficient of variation (%) [CV], coefficient of variation >30%19 (yes/no) [CV30], percentage of tacrolimus blood concentrations under 5 ng/ml (%) [p5], percentage of tacrolimus blood concentrations under 7 ng/ml (%) [p7] and percentage of blood concentrations over 15 ng/ml (%) [p15] were calculated. Concrete cut points were selected, as therapeutic concentrations of tacrolimus were defined as 5/7–15 ng/ml[29] through concentrations. The influence of the administration route (oral, sublingual and by nasogastric tube) on mean tacrolimus blood concentrations, the variability and the risk of therapeutic failure or toxicity were therefore evaluated.

For descriptive purposes, continuous data were expressed in mean (standard deviation) or median (range), whereas categorical data were expressed in absolute value and percentage. Clinical and demographic data of the patients were described and compared for the three routes of treatment. Comparison of continuous variables was performed using the student-Fisher's t-test and categorical variables were compared using the chi-squared test (plus the Fisher's exact test, when necessary).

Analysis of variance (ANOVA) was used, for analytical purposes, to evaluate differences in the analytical consistency parameters among the three tacrolimus administration routes. The role of potential influencing factors – such as hematocrit and creatinine serum levels, the metabolic factor and the inhibitory factor – was also evaluated by including them in the analysis. All statistical analysis were performed by using the IBM SPSS statistics software (version 18.0). It was deemed that a P value below 0.05 has a statistical significance.

Results

Patient Characteristics

A total of 79 patients were included -104 courses of treatment-, who had undergone solid organ transplant or had acute complications that required ICU admission. There were 60 patients with lung transplant (56 early transplants), 13 with liver

transplant (12 early transplants) and 6 with kidney transplant (4 early transplants). Their mean age was 51.0 (SD 14.0) and 48 were men (60.8%). Median follow-up was 6.0 days (SD 4.6). According to the hospital protocol, initial tacrolimus dosage was: tacrolimus 0.05 mg/kg twice daily in lung transplant, tacrolimus 0.06 - 0.07 mg/kg twice daily in kidney transplant and tacrolimus 0.025 - 0.04 mg/kg twice daily in liver transplant. Routes of tacrolimus administration in our patients' cohort were distributed as follows: orally in 29 patients, sublingually in 26 patients and by nasogastric tube in 49 patients.

(Table 1) describes the baseline demographic characteristics, analytical parameters (hematocrit and serum creatinine), and tacrolimus administration routes with their argumentation, for our SOT patients. Lung transplant patients were the ones who needed the largest number of alternative routes: 49 patients needed nasogastric tube and 26 patients sublingual administration. The main reason for using sublingual route was for gastroparesia – in 16 patients (61.5%) – and that for nasogastric tube was for orotracheal intubation and sedoanalgesia – 48 patients (97.9%).

Table 1: Baseline demographic, analytical and clinical parameters, according to tacrolimus route of administration, in SOT patients.

SOT	Lung (N= 60)	Liver (N= 13)	Kidney (N= 6)
Type of transplant depending on the time passed since transplantation (N)	Early transplant: 56	Early transplant: 12	Early transplant: 4
Demographics			
Age (y), Mean (SD)	49.2 (13.5)	59.7 (8.8)	53.9 (21.3)
Gender (Female, %)	22 (36.7)	6 (46.2)	3 (50.0)
Analytical parameters during ICU admission			
Hematocrit (%), Mean (SD)	28.4 (8.3)	27.7 (2.9)	29.1 (3.2)
Creatinine (mg/dl), Mean (SD)	0.7 (0.7)	0.9 (0.7)	2.0 (1.4)
Routes of tacrolimus administration			
Oral TAC administration SL TAC administration NSG TAC administration	27 28 49	6 1 8	5 - 2
Clinical purpose justifying SL route			
Digestive motility troubles:Gastroparesia Intestinal occlusion ImproveTAC bioavailability Gastrointestinal hemorrhage	16 4 8 -	- - - 1	- - - -
Clinical purpose justifying NSG route			
Digestive motility troubles: Incompletely oral tolerance (immediate postoperative) Intestinal occlusion Orotracheal intubation and sedoanalgesia Gastrointestinal hemorrhage	 1 - 48 -	 6 - 2 -	 - 1 - 1

SOT, solid organ transplant; TAC, tacrolimus; SL, sublingual; NSG, nasogastric tube; SD, standard deviation; NA, not available.

Tacrolimus Blood Concentration

The mean number of determinations of tacrolimus blood concentrations considering the route of administration were 5.4 (4.9) by oral route, 15.6 (13.4) by sublingual and 9.7 (8.0) by nasograstric tube. Consistency of tacrolimus therapy according to the route of administration is described in Table 2.

Table 2: Mean and variability of tacrolimus blood concentrations depending on the administration route.

Administration route	Oral	Sublingual	Nasogastric tube	Total	P
Number of patients	29	26	49	104	-
Blood samples (n/patient)	5.4 (4.9)	15.6 (13.4)	9.7 (8.1)	10.0 (9.7)	-
Tacrolimus blood concentrations (ng/ml)	8.9 (2.8)	11.9 (2.7)	12.4 (3.8)	11.3 (3.6)	<0.001
CV (%)	32.9 (19.6)	37.2 (11.0)	45.8 (20.2)	40.4 (18.8)	0.013
CV >30% (%)	50.0 (51.1)	68.0 (47.6)	80.9 (39.8)	69.8 (46.2)	0.026
p5 (ng/ml) (%)	12.0 (32.6)	3.9 (8.5)	10.5 (30.7)	8.2 (27.4)	<0.001
p7 (ng/ml) (%)	24.7 (42.3)	13.1 (33.8)	20.6 (40.4)	18.3 (38.7)	<0.001
p15 (ng/ml) (%)	13.9 (34.7)	21.5 (41.1)	26.2 (44.0)	22.5 (41.8)	0.005

Data are expressed as Mean (SD). p5, percentage of tacrolimus blood levels under 5 ng/ml; p7, percentage of tacrolimus blood levels under 7 ng/ml; p15, percentage of blood levels over 15 ng/ml; CV, coefficient of variation.

Mean tacrolimus blood concentrations were significantly higher by following nasogastric and sublingual route, compared to the oral one (p<0.001). The variability observed was higher in nasogastric tube administration, CV= 45.8% (20.2), compared to the oral, CV= 32.9% (19.6), and sublingual routes, CV= 37.2% (11.0) (p= 0.013). Furthermore, CV30 was 80.9% (39.8) by nasogastric tube administration, which was significantly higher than in the other routes (p= 0.026). The difference found in p5 and p7 resulted in being significantly higher by oral route (p< 0.001, in both cases), with a percentage of patients of 12.0% and 24.7% respectively. Last, p15 was higher in nasogastric tube administration, accounting for 26.2% of cases (p= 0.005).

Drug-Drug Interactions Analysis

At least one potential drug–drug interaction (DDI) was observed in all patients. DDI analysis is summarized in Table 3.

Table 3: Drug-drug interactions observed in the treatment of patients included during the period of the study.

Drug interaction level	Number of patients	Drug involved	Effect in blood tacrolimus	Number of interactions
B	79	Mycophenolate	Increase	72
		Fentanyl	Increase	59
C	86	Amiodarone	Increase	23
		Amlodipine	Increase	15
		Azithromycin	Increase	8
		Erythromycin	Increase	12
		Ertapenem	Increase	2
		Everolimus	Decrease	1
		Levofloxacin	Increase	1
		Corticosteroids*	Decrease	86
		Metoclopramide	Increase	52
		Nifedipine	Increase	3
		Tigecycline	Increase	2

D	17	Fluconazole	Increase	16
		Voriconazole	Increase	3
X	2	Sirolimus	Decrease	2
Total	89	-	-	268

*Methylprednisolone and prednisone.

The number of drugs that potentially increased tacrolimus blood concentrations was 13 and those that potentially decreased them was 3. The total number of interactions that increased tacrolimus concentrations during ICU hospitalization was 267 and those that decreased them were 89. It's worth mentioning that a drug could be involved in more than one DDI. Mycophenolate [72 (26.9%)] and fentanyl [59 (22.0%)] were the most frequent drugs involved in interactions that increase tacrolimus concentrations, and corticosteroids [86 (32.1%)] in those that decrease them.

Influencing Factors

The role of potential influencing factors (Table 4)

Table 4: Factors that can significantly influence the intrapatient variability of tacrolimus blood levels, considering the administration by different routes.

Administration route	Oral	Sublingual	Nasogastric tube	Total	P
Number of patients	29	26	49	104	-
Inhibitor factor (Value)	20.7 (41.2)	38.5 (49.6)	26.5 (44.6)	27.9 (45.1)	0.333
Metabolic factor (Value)	2.7 (3.3)	6.5 (3.9)	4.7 (3.9)	4.6 (4.0)	<0.001
Hematocrit (%)	29.3 (4.0)	28.4 (2.2)	29.3 (2.6)	29.1 (3.0)	0.435
Creatinine (mg/dl)	0.8 (0.5)	0.6 (0.3)	0.9 (0.5)	0.8 (0.5)	0.029

Data are expressed as Mean (SD).

On the consistency of tacrolimus therapy showed, in the multiple analysis of variance design, that the inhibitor factor (p=0.008) and the metabolic factor (p= 0.016) are influencing factors, whereas hematocrit (p= 0.557) and creatinine (p= 0.205) are not. Estimated consistence parameters for tacrolimus considering the influencing factors are shown in Table 5.

Table 5: Estimated mean values for tacrolimus consistence variables, after multiple analysis of the variance that included the influencing factors[a].

Parameter	Administration route	Mean	CI 95%
Tacrolimus blood concentrations (ng/ml)	Oral	9.3	7.9 – 10.6
	Sublingual	11.5	10.1 – 12.8
	Nasogastric tube	12.7	11.8 – 13.6
	Total	11.1	10.5 – 11.8
CV (%)	Oral	34.0	26.4 – 41.5
	Sublingual	37.1	29.5 - 44.7
	Nasogastric tube	45.4	40.1 – 50.7
	Total	38.8	34.9 – 42.6
CV >30% (%)	Oral	52.8	34.5 – 71.1
	Sublingual	69.1	50.8 – 87.4
	Nasogastric tube	78.8	66.0 – 91.7
	Total	66.9	57.6 – 76.2
p5 (ng/ml) (%)	Oral	15.6	7.7 - 23.5
	Sublingual	5.8	2.2 – 13.7
	Nasogastric tube	8.2	2.7 – 13.8
	Total	9.9	5.8 – 13.9
p7 (ng/ml) (%)	Oral	32.5	23.0 – 42.1
	Sublingual	19.2	9.7 – 28.8
	Nasogastric tube	17.0	10.3 – 23.4
	Total	22.9	18.1 – 27.8
p15 (ng/ml) (%)	Oral	9.6	0.8 – 18.3
	Sublingual	20.4	11.6 – 29.2
	Nasogastric tube	33.4	27.2 – 39.5
	Total	21.1	16.6 – 25.6

[a] Values taken for influencing covariables: Creatinine 0.84 mg/dL; Hematocrit 29.1 %; Metabolic factor 4.8; Inhibitor factor 0.29. p5, percentage of tacrolimus blood levels less than 5 ng/ml; p7, percentage of tacrolimus blood levels less than 7 ng/ml; p15, percentage of blood levels over 15 ng/ml; CV, coefficient of variation.

Nevertheless, the differences and significance found on the tacrolimus therapy adjusted analysis of consistency, according to the route of administration, remained unaltered (Mean, $p < 0.001$; CV, $p = 0.033$; p7, $p = 0.032$; and p15, $p < 0.001$) in relation to the primary univariate analysis, with the exception of CV30 ($p = 0.074$) and p5 ($p = 0.198$), which were not significant.

In the specific case of the influence of the inhibitor factor presence (Table 6) on the consistence of tacrolimus therapy, it was found to be significant in values of CV, 15.5 (IC95% 12.1-18.9) vs 38.7 (IC95% 29.5-47.9) and CV30= 0.0 (IC95% 0.0-28.9) vs 66.7 (IC95% 43.9-89.5) in oral route. On the other hand, p15 values were 21.0% (IC95% 13.6-28.4) vs 36.3 (IC95% 27.1-45.5) in nasogastric tube administration. Finally, and taking into account the three routes of administration, the inhibitor factor presence was significant in CV30, 53.6% (IC95% 33.6- 73.6) vs 76.5 (IC95% 66.5-86.5) and in p15, 16.2% (IC95% 10.8- 21.6) vs 25.8 (IC95% 19.6-32.0).

Table 6. Comparison of mean levels of tacrolimus, CV, CV30%, p15 (ng/ml) and p5 (ng/ml), depending on the route of administration and the presence of the inhibitor factor.

Administration route	Oral route		Sublingual route		Nasogastric tube		Total	
Inhibitor factor (Presence)	No	Yes	No	Yes	No	Yes	No	Yes
Tacrolimus blood concentrations (ng/ml)	9.1 (8.0-10.2)	8.1 (5.4-10.8)	12.1 (10.7-13.5)	11.5 (10.1-12.9)	12.9 (11.5-14.3)	11.2 (9.6-12.8)	11.6 (10.8-12.4)	10.7 (9.5-11.9)
CV (%)	38.7 (29.5-47.9)	15.5 (12.1-18.9)*	37.3 (31.1-43.5)	37.0 (30.8-43.2)	46.4 (39.0-53.8)	44.1 (35.1-53.1)	42.4 (37.6-47.2)	35.5 (29.5-41.5)
CV >30% (%)	66.7 (43.9-89.5)	0.0 (0.0-28.9)**	80.0 (58.0-100.0)	50.0 (16.0-84.0)	80.0 (66.2-93.8)	83.3 (60.9-100.0)	76.5 (66.5-86.5)	53.6 (33.6-73.6)
p5 (ng/ml) (%)	17.4 (5.0-29.8)	16.7 (0.0-50.1)	4.5 (0.0-9.5)	2.9 (0.0-6.9)	9.0 (3.6-12.4)	6.1 (0.0-12.5)	10.6 (5.8-15.4)	7.2 (0.0-14.4)
p15 (ng/ml) (%)	9.6 (3.0-16.2)	6.1 (0.0-14.9)	25.7 (13.7-27.7)	16.0 (10.0-22.0)	36.3 (27.1-45.5)	21.0 (13.6-28.4)$	25.8 (19.6-32.0)	16.2 (10.8-21.6)

*p= 0.009; **p= 0.003; $p= 0.069; p= 0.026; p= 0.068. Data are expressed as Mean (CI 95%). p5, percentage of tacrolimus blood levels under 5 ng/ml; p7, percentage of tacrolimus blood levels under 7 ng/ml; p15, percentage of blood levels over 15 ng/ml; CV, coefficient of variation.

Discussion

Tacrolimus is an immunosuppressant drug with a narrow therapeutic window that cannot be suspended from the treatment of transplant patients, as this would lead to a graft rejection [30]. Patients admitted to ICU might present unpredictable tacrolimus absorption, due to gastrointestinal complications – such as nausea, vomiting, gastroparesis or ileus –, orotracheal intubation or sedoanalgesia, making the oral route not optimal or viable [10, 15, 31]. For those situations, the tacrolimus administration by sublingual [16, 32] and nasogastric tube [13] was explored as potentially complementary routes to the oral one, with the main goal of not altering the consistency of the immunosuppressive treatment. The consistency of tacrolimus blood concentrations after using different routes of administration of tacrolimus – such as oral, sublingual and nasogastric tube – in a cohort of critical transplant recipients has been compared in this study. More concretely, our results showed that the main reason for using sublingual route was gastroparesis and for nasogastric tube was orotracheal intubation.

It was previously suggested that a higher degree of tacrolimus IPV was associated with graft rejection and worse long-term outcomes after SOT [33–35]. More specifically, a high IPV means that the patients are exposed to episodes of subtherapeutic and supratherapeutic drug concentrations and it was associated with a high immunological risk recipient, which entails a risk for both acute rejection and graft loss, plus a risk of toxicity [19, 36–38]. Our results have shown a high IPV if we analyze the results obtained in any of the 3 routes. However, considering the study period right after transplantation for most of the patients – early transplants who were admitted to ICU –, these results could be justified by the characteristics of the patients included and their variability in bioavailability [17]. Nevertheless, the results obtained from tacrolimus administration by nasogastric tube have shown higher values of CV and CV30 variables, compared with sublingual and oral routes. That is associated to the nasogastric tube having a higher IPV. Mean values of tacrolimus blood concentrations also were analyzed by taking into account the administration route. The results obtained of p5 and p7 showed a lower percentage of patients with considered infra-therapeutic blood concentrations in oral and sublingual routes, compared to the nasogastric tube. The sublingual route was also associated with a percentage of p15 that is lower than the nasogastric tube's, which could indicate that it may not increase the risk of toxicity

as much as the nasogastric administration. Those findings have not been described yet by other authors. Similar results of tacrolimus blood concentrations were obtained with sublingual route after comparing it to the oral one of some of the authors reviewed [23, 39].

The presence of variables that can significantly influence the value of tacrolimus blood concentrations was also analyzed. Tacrolimus is a strong immunosuppressant that displays numerous drug interactions that can significantly modify blood concentrations of tacrolimus and, consequently, its IPV puts the patient at high risk of either toxicity or transplant rejection [29]. Patients admitted to ICU – which were the type of patients included in the study – are frequently highly polymedicated, so the presence of drug interactions or other factors that modify blood concentrations of tacrolimus are higher [17]. Hence, the importance of analyzing possible pharmacological interactions defined in our study as the metabolic factor. An algorithm to quantify DDI with tacrolimus has been developed by the authors of this study based on DDI severity. This algorithm had not been previously referenced in the reviewed literature. It has shown that DDI have a significant influence on tacrolimus blood concentrations considering or not the tacrolimus administration route. These observations make sense, given that drug-drug interactions of tacrolimus occur due to its metabolism by the cytochrome P450 (CYP) 3A, which is also responsible for the metabolism of many other drugs [2], regardless of the route of administration.

More specifically, we have also analyzed the pharmacological group of azoles, considering the severity of the interaction, which is classified under the DDI scale as having a D risk. As we observed in our study and as other authors have described it [26, 27], this therapeutic group has a significant impact on the pharmacokinetics of tacrolimus through the inhibition of tacrolimus metabolism, resulting in an increase in tacrolimus blood concentrations. This is of great interest, since, once those variables are detected, we can assume that their presence can modify the tacrolimus blood concentrations.

Hematocrit and creatinine serum levels were evaluated because their correlation with tacrolimus blood concentrations. Hematocrit has a significant effect and predicts variability in tacrolimus blood concentrations, because tacrolimus distributes into erythrocytes and binds to them – up to 98.8% of tacrolimus is bound inside red blood cells [40–42]. In addition, in the clinically unstable transplant patient, erythrocyte counts may fluctuate highly due to bleeding, red blood cell transfusions, dilution or bone marrow depression. That said, hematocrit concentrations are a key factor in the interpretation of tacrolimus blood concentrations. Calcineurin inhibitors are also a known cause of acute and chronic nephrotoxicity. Researchers reported a significant correlation between the tacrolimus high blood concentrations and the increase of creatinine serum levels p [4, 43, 44]. Nonetheless, our results didn't show a significant influence of hematocrit or creatinine on the consistency of tacrolimus blood concentrations. In terms of hematocrit, it is probably due to the fact that, although the patients had low hematocrit values, these values remained stable during the study period.

Our study has some limitations that should be considered when interpreting the results. Firstly, we only have information for including in the study for a short period of time, due to lacking a data collection system. In any case, the results obtained with the available information may be sufficient to obtain a first set of conclusions, on which we will have to continue working. Secondly, a sublingual formulation is not commercially available for tacrolimus, so the dissolution of tacrolimus formulation administered sublingually depends on the liposolubility properties and the duration of the exposure to the mucosal surface. In addition to this, for sublingual administration describes erratic absorption, potential for ingestion, less predictable drug–drug interactions than oral route, unknown correlation between trough concentration and exposure and no consistent dose conversion or method of administration was elucidated. Thirdly, the experience described in the evidence with the sublingual administration of tacrolimus is mainly based on patients with lung transplantation, but there is very little information on its use in other types of transplantation, such as kidney or liver. Most of the publications are retrospective, not comparative and reflect individual experiences in health centers with small numbers of patients. Fourthly, the dose of tacrolimus administered sublingually was calculated depending on the purpose of that route. The conversion ratio from oral to sublingual route was not the same in patients for whom the sublingual route was used, due to poor absorption of the drug at the gastrointestinal tube, compared to patients who

wanted to achieve higher blood concentrations of tacrolimus.

Nevertheless, as in our study we only focused on the study of the variability of the blood concentrations of the drug, it's not necessary to know the exact dose that is administered to the patient. Fifthly, a small sample size was included in some specific organ groups, as liver and kidney transplant. However, taking into account the objective of the study, it reflects the reality of an ICU in which alternative routes of administration to the oral route are needed for any type of patient. Finally, the severity of the illness, the indication for transplantation, the time after organ transplant and the genomic testing information couldn't be obtained, so that could have an impact on the variability.

Conclusions

During ICU admission, tacrolimus blood concentrations showed a high IPV in SOT patients. Additionally, this IPV of tacrolimus blood concentrations is selectively different when nasogastric tube, sublingual or oral route is used. Thus, IPV is higher when nasogastric tube is used, followed by the sublingual route and the oral route. A smaller number of infra- therapeutic tacrolimus values were observed when the sublingual route or the nasogastric tube was used, compared to the oral route.

Nevertheless, once the differences between the mean blood concentrations of tacrolimus and its IPV for each route of administration have been evaluated and, taking into account the characteristics of each of them, both the sublingual and nasogastric routes could be deemed as viable alternatives to the oral route for short-term use in patients who are unable to receive medications orally.

Contrary to the hematocrit and creatinine values, the metabolic and inhibitory factors demonstrated to be variables that could influence the consistency of tacrolimus therapy.

In future studies, it would be interesting to evaluate the correlation between the concentrations and drug exposure in all routes of administration used for the administration of tacrolimus, particularly in the immediate post-transplant period – as it's the case of most patients in our study –, which it's when adequate tacrolimus exposure is crucial.

Study Highlights

Tacrolimus is characterized by a narrow therapeutic index, a large side-effect profile and a high pharmacokinetic variability. Solid organ transplant (SOT) patients admitted to Intensive Care Unit (ICU) might present unpredictable tacrolimus absorption making the oral route not optimal or viable. For those situations, in which the efficacy and safety may be compromised, tacrolimus administration by sublingual and nasogastric tube was explored as potential complementary routes to the oral one. During ICU admission, tacrolimus blood concentrations showed a high intrapatient variability (IPV) in SOT patients and it was selectively different when nasogastric tube, sublingual or oral route was used. Nevertheless, once the differences between the mean blood concentrations of tacrolimus and its IPV for each route of administration have been evaluated, both the sublingual and nasogastric routes could be deemed as viable alternatives to the oral route for short-term use in patients who are unable to receive medications orally.

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Author contribution statement

S.G-G., L.D-M, JB. M-R participated in research design and writing the article. JB.M-R, S.G-G., L.D-M, C.D-T, M.L-G and I.B participated in data analysis. S.G-G., L.D-M, C.D-T, I.B-A, V.M-T, IB.T-R, M.L-G and JB.M-R critically reviewed the article.

Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Snell GI, Westall GP, Paraskeva MA (2013) Immunosuppression and allograft rejection following lung transplantation: Evidence to date. Drugs. 73:1793-1813.

2. Iwasaki K (2007) Metabolism of tacrolimus (FK506) and recent topics in clinical pharmacokinetics. Drug Metab Pharmacokinet. 22:328-35.

3. Berkowitz N, Schulman LL, McGregor C, Markowitz D (1995) Gastroparesis after lung transplantation: Potential role in postoperative respiratory complications. Chest. 108:1602-07.

4. Sikma MA, Van Maarseveen EM, Van De Graaf EA, et al. (2015) Pharmacokinetics and Toxicity of Tacrolimus Early after Heart and Lung Transplantation. Am J Transplant. 15:2301-13.

5. Nakamura Y, Takeuchi H, Okuyama K, et al. (2005) Evaluation of appropriate blood level in continuous intravenous infusion from trough concentrations after oral administration based on area under trough level in tacrolimus and cyclosporine therapy. Transplant Proc. 37:1725-7.

6. Shank BR, Deaver M, Baker A, et al. (2018) Interdisciplinary implementation of tacrolimus intravenous standard concentration in hematopoietic stem cell transplantation recipients. J Oncol Pharm Pract. 24:365-70.

7. Hirano Y, Sugimoto S, Mano T, et al. (2017) Prolonged administration of twice-daily bolus intravenous tacrolimus in the early phase after lung transplantation. Ann Transplant. 22:484-92.

8. Snell GI, Ivulich S, Mitchell L, Westall GP, Levvey B (2013) Evolution to twice daily bolus intravenous tacrolimus: Optimizing efficacy and safety of calcineurin inhibitor delivery early post lung transplant. Ann Transplant. 18:399-407.

9. Watkins KD, Boettger RF, Hanger KM, et al. (2012) Use of sublingual tacrolimus in lung transplant recipients. J Hear Lung Transplant. 31:127-32.

10. Reams BD, Palmer SM (2002) Sublingual tacrolimus for immunosuppression in lung transplantation: A potentially important therapeutic option in cystic fibrosis. Am J Respir Med. 1:91-8.

11. Van De Plas A, Dackus J, Christiaans MHL, Stolk LML, Van Hooff JP, et al. (2009) A pilot study on sublingual administration of tacrolimus. Transpl Int. 22:358-9.

12. Collin C, Boussaud V, Lefeuvre S, et al. (2010) Sublingual tacrolimus as an alternative to intravenous route in patients with thoracic transplant: A retrospective study. Transplant Proc. 42:4331-7.

13. Undre N, Baccarani U, Britz R, Popescu I (2019) Pharmacokinetic profile of prolonged-release tacrolimus when administered via nasogastric tube in de novo liver transplantation: A sub-study of the DIAMOND trial. Ann Transplant. 24:268-72.

14. Undre N, Dickinson J (2017) Relative bioavailability of single doses of prolonged-release tacrolimus administered as a suspension, orally or via a nasogastric tube, compared with intact capsules: A phase 1 study in healthy participants. BMJ Open. 7:1-7.

15. Nasiri-Toosi Z, Dashti-Khavidaki S, Nasiri-Toosi M, et al. (2012) Clinical pharmacokinetics of oral versus sublingual administration of tacrolimus in adult liver transplant recipients. Exp Clin Transplant. 10:586-91.

16. Hanger KM, Boettger RF, Watkins KD, et al. (2010) A Pharmacokinetic Analysis of Oral vs Sublingual Administration of Tacrolimus in Lung Transplant Recipients. Chest. 138:542A.

17. Sikma MA, Hunault CC, Van Maarseveen EM, et al. (2020) High Variability of Whole-Blood Tacrolimus Pharmacokinetics Early After Thoracic Organ Transplantation. Eur J Drug Metab Pharmacokinet. 45:123-34.

18. Del Bello A, Congy-Jolivet N, Danjoux M, et al. (2018) High tacrolimus intra-patient variability is associated with graft rejection, and de novo donor-specific antibodies occurrence after liver transplantation. World J Gastroenterol. 24:1795-1802.

19. Rodrigo E, Segundo DS, Fernández-Fresnedo G, et al. (2016) Within-Patient Variability in Tacrolimus Blood Levels Predicts Kidney Graft Loss and Donor-Specific Antibody Development. Transplantation. 100:2479-85.

20. Rahamimov R, Tifti-Orbach H, Zingerman B, et al. (2019) Reduction of exposure to tacrolimus trough level variability is associated with better graft survival after kidney transplantation. Eur J Clin Pharmacol. 75:951-8.

21. Mendoza Rojas A, Hesselink DA, van Besouw NM, Baan CC, van Gelder T (2019) Impact of low tacrolimus exposure and high tacrolimus intra-patient variability on the development of de novo anti-HLA donor-specific antibodies in kidney transplant recipients. Expert Rev Clin Immunol. 15:1323-31.

22. Davit BM, Chen ML, Conner DP, et al. (2012) Implementation of a reference-scaled average bioequivalence approach for highly variable generic drug products by the us food and drug administration. AAPS J. 14:915-24.

23. Al Sagheer T, Enderby CY (2019) Determining the conversion ratios for oral versus sublingual administration of tacrolimus in solid organ transplant recipients. Clin Transplant 33.

24. Al Sagheer T, Enderby CY (2019) Determining the conversion ratios for oral versus sublingual administration of tacrolimus in solid organ transplant recipients. Clin Transplant 33: e13727.

25. Lexicomp. Lexi-Interact Monograph Description. 2001. Accessed Jan 1, 2022.

26. Dusit Lumlertgul MD* KNM, Noppamas Rojanasthien MD**, Kittika Kanchanarattanakorn MD***, Suparoek Jittikanont MD*, Amara Manoyot MD*, et al. (2006) Pharmacokinetic Study of the Combination of Tacrolimus and Fluconazole in Renal Transplant Patients. J Med Assoc Thai 89:73-8.

27. Hairhara Y, Makuuchi M, Kawarasaki H, et al. (1994) Effect of Fluconazole on Blood Levels of Tacrolimus 1345:8457294.

28. North-lewis PJ, Gonde CE, Mowat AP, Heaton NJ (1997) Tacrolimus (FK506) malabsorption : management with fluconazole coadministration. Transpl Int 10:331-4.

29. Brunet M, Gelder T Van, Åsberg A, et al. (2019) Therapeutic Drug Monitoring of Tacrolimus-Personalized Therapy : Second Consensus Report. Ther Drug Monit. 41:261-307.

30. Staatz C, Taylor P, Tett S (2001) Low tacrolimus concentrations and increased risk of early acute rejection in adult renal transplantation. Nephrol Dial Transplant 16:1905-9.

31. Kuypers DRJ (2020) Intrapatient Variability of Tacrolimus Exposure in Solid Organ Transplantation: A Novel Marker for Clinical Outcome. Clin Pharmacol Ther. 107:347-58.

32. Pennington CA, Park JM (2015) Sublingual tacrolimus as an alternative to oral administration for solid organ transplant

recipients. Am J Heal Pharm. 72:277-84.

33. Mendoza Rojas A, Hesselink DA, van Besouw NM, Baan CC, van Gelder T (2019) Impact of low tacrolimus exposure and high tacrolimus intra-patient variability on the development of de novo anti-HLA donor-specific antibodies in kidney transplant recipients. Expert Rev Clin Immunol 15:1323-31.

34. Rayar M, Tron C, Jézéquel C, et al. (2018) High Intrapatient Variability of Tacrolimus Exposure in the Early Period after Liver Transplantation Is Associated with Poorer Outcomes 102.

35. Rodrigo E, Segundo DS, Fernández-fresnedo G, Cos M De, Arias M (2015) Within-Patient Variability in Tacrolimus Blood Levels Predicts Kidney Graft Loss and Donor-Specific Antibody Development. Transplantation 00:1-7.

36. Whalen HR, Glen JA, Harkins V, et al. (2017) High Intrapatient Tacrolimus Variability Is Associated with Worse Outcomes in Renal Transplantation Using a Low-Dose Tacrolimus Immunosuppressive Regime. Transplantation 101:430-6.

37. Goodall DL, Willicombe M, McLean AG, Taube D (2017) High Intrapatient Variability of Tacrolimus Levels and Outpatient Clinic Nonattendance Are Associated With Inferior Outcomes in Renal Transplant Patients. Transplant Direct. 3: e192.

38. Seibert SR et al. (2018) Tacrolimus Trough and Dose Intra-Patient Variability and CYP3A5 Genotype: Effects on Acute Rejection and Graft Failure in European American and African American Kidney Transplant Recipients. Clin Transplant. 32: e13424.

39. Federico S, Carrano R, Sabbatini M, et al. (2016) Sublingual administration improves systemic exposure of tacrolimus in kidney transplant recipients: comparison with oral administration. Eur J Clin Invest. 46:651-7.

40. Minematsu T, Sugiyama E, Kusama M, et al. (2004) Effect of hematocrit on pharmacokinetics of tacrolimus in adult living donor liver transplant recipients. Transplant Proc 36:1506-11.

41. Sikma MA, Hunault CC, Huitema ADR, De Lange DW, Van Maarseveen EM (2020) Clinical Pharmacokinetics and Impact of Hematocrit on Monitoring and Dosing of Tacrolimus Early After Heart and Lung Transplantation. Clin Pharmacokinet. 59:403-8.

42. Wallemacq P, Armstrong VW, Brunet M, Haufroid V, Holt DW, et al. (2009) Opportunities to optimize tacrolimus therapy in solid organ transplantation: report of the European consensus conference. Ther Drug Monit. 31:139-52.

43. P. Sheiner, E. Silver, C. Swales, C. Rochon, A. Lally MB (2011) Direct Correlation Between Tacrolimus Levels and Serum Creatinine Seen Only Early After Transplant 995.

44. Bentata Y (2020) Tacrolimus: 20 years of use in adult kidney transplantation. What we should know about its nephrotoxicity. Artif Organs 44:140-52.