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Pharmacokinetics of Tacrolimus in Kidney Transplant Recipients: Twice Daily Versus Once Daily Dosing

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Tacrolimus a macrolide immunosuppressant that is routinely given in two equally divided doses every 12 h. However, the time-dependent pharmacokinetics of tacrolimus suggest that once daily morning administration of tacrolimus may produce appropriate drug exposure. The purpose of this pilot study was to compare the pharmacokinetics and safety of twice vs. once daily administration of tacrolimus in stable kidney transplant recipients. Steady-state tacrolimus pharmacokinetic parameters were estimated on two occasions in an open-label, three-arm, two-period sequential study: twice daily dosing (Phase I) and once daily dosing (Phase II). In phase II, 18 patients were assigned to one of three arms: those taking 67%, 85% and 100% of their total twice daily dose once in the morning. In phase I, the mean area under the blood concentration–time curve (AUC) was higher after the morning dose, AUC_{0-12} 117 ± 40 vs. AUC_{12-24} 97 ± 30 ng/h/mL, p = 0.012. In the 85% Group, the mean AUC ratio between twice and once daily was 1.0 (95% CI, 0.9–1.1) which predicted the best conversion ratio. Tacrolimus given once daily in the morning, at 85% of the twice daily dose, provides safe and equivalent drug exposure to twice daily dosing. This convenient dosing schedule may help to increase compliance and lower costs.

Key words: Dosing interval, pharmacokinetics, tacrolimus

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Introduction

The availability of calcineurin inhibitors has revolutionized the practice of transplantation by lowering acute rejection rates and improving short-term graft survival. Available calcineurin inhibitors include tacrolimus (Prograf®, Fujisawa Healthcare, Inc., Deerfield, IL, USA) and cyclosporine that are both Food and Drug Administration (FDA) approved for administration in two equally divided doses every 12 h. Routinely, tacrolimus and cyclosporine doses have been titrated based on blood trough concentrations and clinical assessments of rejection and tolerability.

Although cyclosporine trough level is routinely used in therapeutic monitoring due to convenience, it correlates poorly with systemic drug exposure and clinical outcomes (1–4). In contrast, tacrolimus trough concentrations (C_{min}) have been found to correlate well with the area under the blood concentration–time curve (AUC) which reflects total body exposure to the drug (5). Also, a good correlation between clinical outcomes and the tacrolimus C_{min} has been observed in clinical trials (6–9). A 2-h post-dose cyclosporine level (C2) has been proposed as a more reliable tool to monitor cyclosporine therapy because C2 has a better correlation with AUC than cyclosporine trough level (10–12). However, unlike cyclosporine C2 levels, tacrolimus peak concentration ($C_{max.}$) has not been routinely utilized to predict rejection or toxicity (9).

Transplant clinicians generally assume that equivalent peak concentrations and AUC's are obtained after each dose of cyclosporine or tacrolimus, although many medications exhibit chronopharmacokinetics (13). The time-dependent pharmacokinetics of tacrolimus suggest that once daily morning administration of tacrolimus may produce appropriate drug exposure to prevent organ rejection without significantly increasing toxicity (14). These variations in tacrolimus absorption suggest that once daily dosing may be possible at a lower total dose when given in the morning. Furthermore, taking fewer medications less frequently may help transplant patients to better manage their drug therapy, increase compliance and lower medication costs. Therefore, the purpose of this pilot study was to compare pharmacokinetics and safety

of twice daily vs. once daily oral administration of tacrolimus in stable kidney transplant recipients.

Materials and Methods

Patients

Inclusion criteria consisted of kidney transplant recipients (18 years or older) at Washington University/Barnes-Jewish Hospital taking tacrolimus-based immunosuppression with stable kidney function (greater than 6 months post-transplantation, serum creatinine <2 mg/dL, no history of rejection) and stable immunosuppression (therapeutic tacrolimus concentrations 5–10 ng/mL, no change in tacrolimus dose within 1 month prior to the study). Exclusion criteria consisted of pregnant women, nursing mothers, patients unwilling or unable to comply with the study protocol, patients with significant liver impairment (serum transaminases or total bilirubin greater than two times the upper limit of normal), patients with a hematocrit <30%, use of concomitant cytochrome P450 3A4/P-glycoprotein inducers or inhibitors, or patients with diabetes mellitus unable to fast overnight. This study was approved by the Human Studies Committee of Washington University (protocol number 01–0884).

Study protocol

Steady-state tacrolimus pharmacokinetic parameters were estimated on two occasions in an open-label, three-arm, two-period, sequential study. Twenty-four hour pharmacokinetic studies were conducted at the end of each period (Phase I and II). In phase I of the study, patients were asked to take their maintenance tacrolimus dose twice daily in equally divided doses. In phase II, patients were divided into three groups based on their phase II dosing regimen: those taking 67% of their total twice daily dose once daily (67% Group), those taking 85% of their total twice daily dose once daily (85% Group) and those taking 100% of their total twice daily dose once daily in the morning (100% Group).

In phase I, patients were asked to self-administer their maintenance tacrolimus at 08.00 and 20.00 hours daily in equally divided doses and to record the time of intake. On the last day of phase I (day 6), patients were admitted to the General Clinical Research Center (GCRC) and given their morning tacrolimus dose with 120 mL of water at approximately 08.00 hours and their evening dose 12 h after the morning dose at approximately 20.00 hours. Serial blood samples (3 mL each) were collected from the indwelling catheter into EDTA-containing tubes at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 9, and 12 h after the morning dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 9, and 12 h after the evening dose. Throughout the study, aliquots of blood were frozen and stored at −20 °C until analyzed by microparticle enzyme immunoassay (MEIA; IMx, Abbott Laboratories, Abbott Park, IL, USA) for tacrolimus concentration.

In phase II, the tacrolimus dose was calculated based on group assignments (Group 67%, 85% or 100%) and rounded to commercially available dosage forms (0.5 mg, 1 mg, and 5 mg capsules). For example, if a patient was taking tacrolimus 4 mg orally twice daily and assigned to the 67% Group, then the once daily dose was 5.5 mg (8 mg per day × 67% = 5.36 mg, rounded to 5.5 mg). Patients were instructed to self-administer their once daily dose at 08.00 hours. On the last day of phase II (day 14), patients were admitted to the GCRC and given their daily tacrolimus dose with 120 mL of water at approximately 08.00 hours. Serial blood samples 3 mL each) were collected from the indwelling catheter into EDTA-containing tubes at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 16, 20, and 24 h after the dose.

Diet

Patients were asked to abstain from alcohol and caffeine for 48 h prior to and during the pharmacokinetic studies. To control for the effects of food on tacrolimus pharmacokinetics (15,16), patients were asked to fast from 22.00 hours on days 5 and 13, prior to the admission to the GCRC. The exact same diet was given at the same times on both tacrolimus study days (days 6 and 14). Breakfast was provided 2 h after the morning dose of tacrolimus at 10.00 hours, lunch at noon, and dinner at 17.00 hours (3 h prior to the evening dose in phase I). Patients were allowed 30 min for food consumption. Food and beverage intake was monitored and recorded.

Endpoints

Area under the blood concentration time curve was calculated using the trapezoidal rule for ascending concentrations and logarithmic trapezoidal rule for descending concentrations. The primary endpoint was the ratio of AUC_{0-24} between the twice daily and once daily tacrolimus drug exposure. Secondary endpoints included tacrolimus peak concentration (C_{max}.), time to reach C_{max}. (T_{max}.), tacrolimus trough concentration (12 h after each dose on day 6, C_{12} and C_{24}; 24 h after dose on day 14, C_{24}). Safety assessment included adverse events as assessed by patient interview and laboratory parameters which were obtained at baseline and upon completion of the study.

Statistical analysis

Paired *t*-tests were used for continuous variables. Pearson's analysis was used to assess correlation between AUC and tacrolimus concentration. A p-value of <0.05 was considered significant.

Results

Eighteen renal transplant recipients were recruited for the study and equally divided into three groups. Most patients were female (78%) and Caucasian (90%). The mean age was 43 ± 14 (range 20–62) (Table 1). There were no differences in characteristics between the groups.

Table 1: Characteristics of patients

Patient characteristic	(n = 18)
Mean age (years)	43 ± 14 (20–62)*
Male	4 (22%)
Female	14 (78%)
Caucasian	16 (89%)
African-American	2 (11%)
Weight (kg)	91 ± 18 (55–123)*
Height (cm)	169 ± 10 (141–189)*
Time from transplant (years)	1.8 ± 1.2 (0.5–5)*
Disease leading to transplant	
Polycystic kidney disease	4 (22%)
Glomerulonephritis	4 (22%)
Hypertensive nephrosclerosis	2 (11%)
Reflux nephropathy	2 (11%)
Congenital nephropathy	1 (6%)
Interstitial nephritis	1 (6%)
Chronic pyelonephritis	1 (6%)
Other	1 (6%)
Unknown	2 (11%)
Immunosuppression	
Tacrolimus + azathioprine + prednisone	8 (44%)
Tacrolimus + mycophenolate +prednisone	5 (28%)
Tacrolimus + prednisone	5 (28%)

*Mean ± SD (range).

Table 2: Summary of pharmacokinetic parameters

	Group 67%		Group 85%		Group 100%	
Parameter	BID	QD	BID	QD	BID	QD
Daily dose (mg)	3.8 ± 2.2	2.8 ± 1.5	6.7 ± 3.2	5.7 ± 2.8	6.3 ± 3.9	6.3 ± 3.9
Daily dose (mg/kg)	0.04 ± 0.02	0.03 ± 0.01	0.07 ± 0.01	0.06 ± 0.03	0.08 ± 0.07	0.08 ± 0.07
C12 (ng/mL)	6.6 ± 2.5	4.6 ± 1.9	5.6 ± 1.0	6.5 ± 1.9	5.9 ± 1.8	7.9 ± 2.4
C24 (ng/mL)	5.9 ± 2.3	3.4 ± 1.1	6.0 ± 0.8	4.6 ± 1.3	5.9 ± 2.2	5.6 ± 2.1
Trough ratio (BID/QD)	0.7 ± 0.3		0.8 ± 0.2		1.0 ± 0.2	
$C_{max.0–24}$ (ng/mL)	18.1	17.0	17.7	23.4	19.0	24.1
$T_{max·0–24}$ (h)	2.0	1.0	1.5	1.5	1.5	2.0
$C_{max.12–24}$ (ng/mL)	9.1	–	7.7	–	8.5	–
$T_{max·12–24}$ (h)	15.0	–	21.0	–	18.0	–
$AUC_{0–24}$ (ng/h/mL)	212 ± 81	145 ± 55	201 ± 39	206 ± 56	206 ± 80	242 ± 86
AUC ratio (BID/QD)	0.7 ± 0.1		1.0 ± 0.1		1.2 ± 0.3	
$AUC_{0–12}$ (ng/h/mL)	118 ± 44	95 ± 37	118 ± 29	141 ± 39	116 ± 50	141 ± 83
$AUC_{12–24}$ (ng/h/mL)	96 ± 38	50 ± 18	83 ± 11	68 ± 18	112 ± 32	79 ± 29
Mean difference (%) $AUC_{0–12}/AUC_{12–24}$	23%	89%	41%	116%	4%	77%

BID: twice daily administration; QD: once daily administration in the morning.
Mean ± SD.

Twice daily dosing

In phase I, in all three groups combined, there was a shorter time to the $T_{max.}$ (1.5 vs. 3.0 h) and a higher $C_{max.}$ (17.8 vs. 8.4 ng/mL) with morning vs. evening administration, although C_{12} and C_{24} were similar (Table 2, Figure 1). The mean AUC was higher after the morning dose compared with the evening dose, $AUC_{0–12}$ 117 ± 40 vs. $AUC_{12–24}$ 97 ± 30 ng/h/mL, respectively, $p = 0.012$. C_{24} had a strong correlation with $AUC_{0–24}$ ($R^2 = 0.80$, Figure 2).

Once daily dosing

In phase II, C_{12} and C_{24} increased as the percentage of the twice daily dose given once daily dose increased (Table 2). Likewise, the $C_{max.}$ and $AUC_{0–24}$ were higher in the 85% and 100% Groups when compared with the 67% Group (Figure 1). The higher $C_{max.}$ did not translate into adverse events. The once daily C_{24} had a strong correlation with $AUC_{0–24}$ ($R^2 = 0.77$, Figure 2).

Twice daily vs. once daily dosing

In the 67% Group, the AUC ratio between twice daily and approximately 67% of the twice daily dose given once daily was 0.7 (95% CI, 0.6–0.7) (Table 2) suggesting lower once daily exposure to tacrolimus. In the 100% Group, the AUC ratio between the twice daily dose and 100% of the twice daily dose given once daily was 1.2 (95% CI, 0.9–1.5) suggesting higher exposure with once daily tacrolimus. In the 85% Group, the mean AUC ratio was 1.0 (95% CI, 0.9–1.1) between the twice daily and once daily exposure which predicted the best conversion ratio between once and twice daily dosing. The mean trough ratio between twice daily dosing and once daily dosing increased as the percentage of the once daily dose increased. In the 67% Group, the mean trough ratio was 0.7 (95% CI, 0.4–1.0), in the 85% Group 0.8 (95% CI, 0.6–1.0), and in the 100% Group 1.0 (95% CI, 0.8–1.2).

Safety

No adverse events occurred and patients did not report side-effects to the new dosing strategy. The mean serum creatinine was statistically lower on Day 14 with once daily administration (1.34 ± 0.33 mg/dL, Day 6 vs. 1.26 ± 0.35 mg/dL, Day 14, $p = 0.011$).

Follow-up

Most (16/18) patients have been maintained on once daily tacrolimus for at least 6 months (range 6–18 months). The average maintenance conversion dose was 85% of the twice daily dose, 5.8 ± 3.4 mg/day before conversion vs. 4.9 ± 2.7 mg/day after conversion. No rejection episodes have occurred during this time period and the mean serum creatinine has been maintained, 1.27 ± 0.29 mg/dL, at 6 months post-conversion.

Discussion

The results of this study demonstrate that tacrolimus given once daily at 85% of the twice daily dose provides safe and equivalent drug exposure to twice daily dosing. Furthermore, the tacrolimus concentration 24 h (C_{24}) after the dose provides a strong marker for once daily drug exposure.

In phase I of the study, evening absorption of tacrolimus was impaired, as exhibited by the lower evening $C_{max.}$ and AUC seen in twice daily dosing. One explanation for the lower evening AUC is the decreased oral bioavailability of tacrolimus when taken with food. Several studies have reported that the oral bioavailability of tacrolimus is

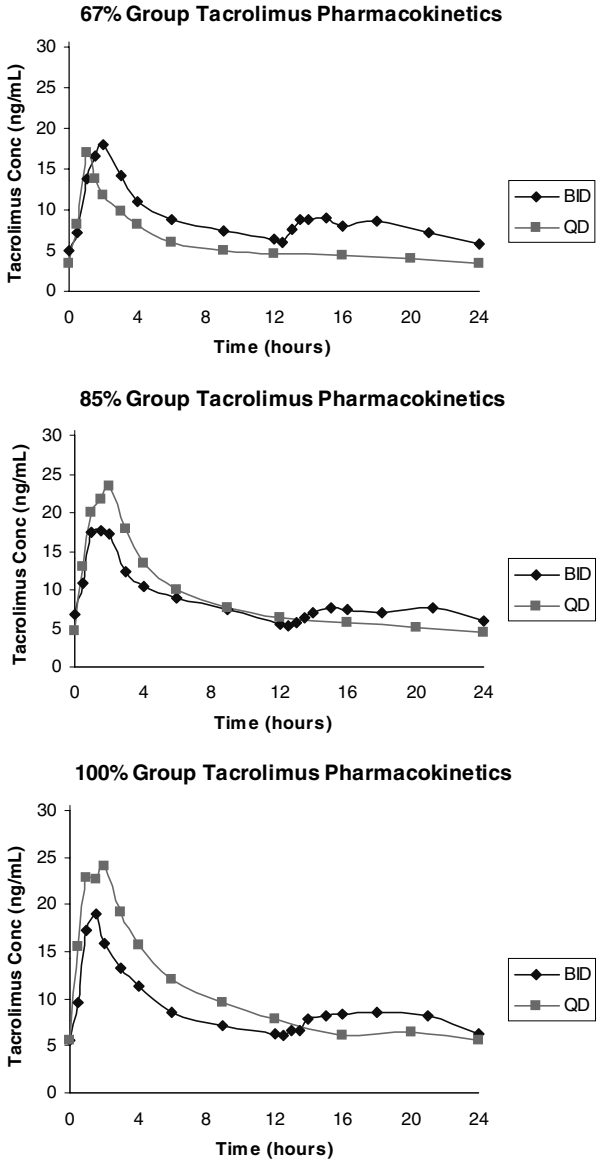

Figure 1: Tacrolimus blood concentration–time profile of a representative subject from each dosing regimen. In the 67% Group, the area under the blood concentration-time curve (AUC) ratio between twice daily and once daily was 0.680. In the 100% Group, the AUC ratio between twice daily dose and once daily was 1.227. In the 85% Group the mean AUC ratio was 1.025 between the twice daily and once daily exposure, thus predicted the best conversion ratio between once and twice daily dosing.

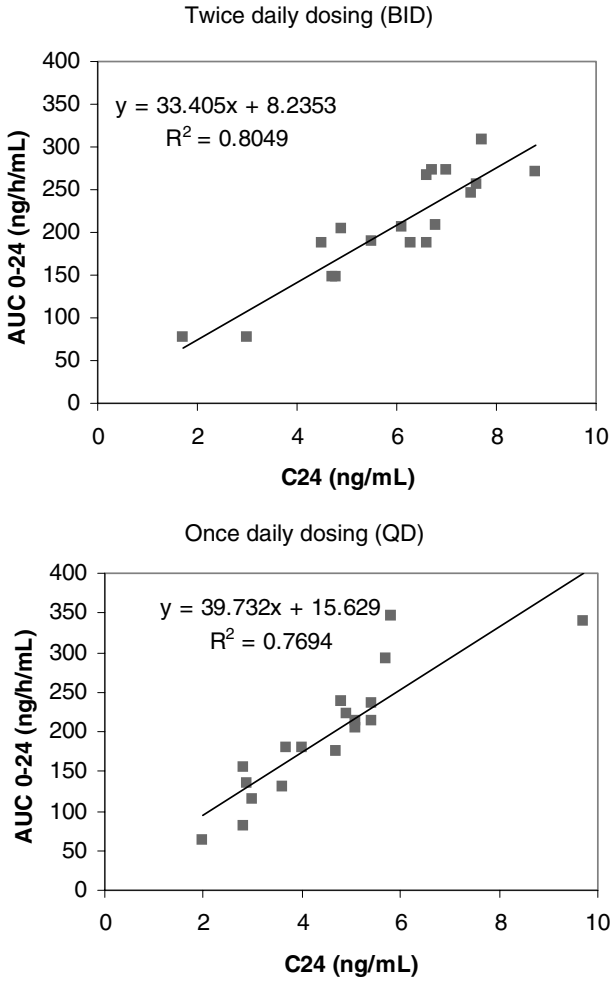

Figure 2: Correlation between tacrolimus concentration and area under the concentration-time curve (AUC). C_{24} has a strong correlation with drug exposure (AUC_{0-24}) with both twice daily ($R^2 = 0.80$) and once daily ($R^2 = 0.77$) dosing.

altered after food consumption (15–17). An increase in C_{max}. (15–40%) and AUC (2–12%) have been reported in a fasting state vs. a nonfasting state (15–17). Furthermore, the time of tacrolimus administration with respect to a meal has been reported to effect bioavailability of tacrolimus (15,16). It is possible that in Phase I of the trial the evening dose of tacrolimus had altered bioavailability because food was allowed from 2.5 to 3 h prior to the evening dose, whereas for the morning dose patients were asked to fast for 10 h prior to administration. The manufacturer recommends that tacrolimus be taken 1 h before or 2 h after a meal, but it is possible that even minimal food retention in the gastrointestinal tract altered the evening absorption of tacrolimus.

Additionally, circadian variations in absorption and disposition of oral tacrolimus may help to explain our results (14). In a study of 12 stable liver transplant recipients, mean AUC after the morning dose was greater than after the evening dose (219 ± 54 ng/h/mL vs. 188 ± 57 ng/h/mL, $p = 0.004$). Likewise, the mean C_{max}. was higher after the morning dose than after the evening dose (32.2 ± 9.1 ng/mL vs. 21.6 ± 8.3 ng/mL, $p = 0.008$). However, the mean C_{min}. was similar between the doses (13.5 ± 4.7 ng/mL vs.

13.3 ± 5.2 ng/mL, p = 0.9). It is noteworthy that 7 out of 12 patients (58%) showed no apparent peak in tacrolimus concentrations with the evening dose. Our trial confirms these findings.

Similar drug exposure with once daily dosing in the morning was achieved in our study without added toxicity. Furthermore, the higher C_{max}. achieved in the 85% and 100% Groups did not correlate with adverse events. This is supported by a phase III trial in kidney transplant recipients that evaluated the correlation of tacrolimus C_{max}. and toxicity. Of 205 study patients, 181 had at least one peak concentration reported within the first year of the trial. For patients with more than one peak drawn, the highest value was used in the analysis. No correlation was found between C_{max}. and neurotoxicity, tremor, diarrhea, nephrotoxicity, increased serum creatinine, hyperglycemia, diabetes, or biopsy-confirmed acute rejection (P. Blahunka, Fujisawa, Deerfield, IL, USA, personal communication, 12/01).

Whether it was due to the effect of food on tacrolimus bioavailability or circadian variations in absorption, this pilot study of stable renal transplant recipients demonstrates that the superior absorption of tacrolimus in the morning allows tacrolimus to be taken once daily at a lower dose. Furthermore, this pharmacokinetic analysis demonstrates that tacrolimus given once daily is safe and effective in select patients that are at low risk of rejection (no history of acute rejection, stable renal function, at least 6 months from transplant, Caucasian recipients) under controlled circumstances (nondiabetic patients, restricted food consumption, no interacting medications). Lastly, this study demonstrated that a 24-h trough concentration (C_{24}) was a good marker for total drug exposure (AUC). Although, this dosing strategy was safe and effective in this pilot trial of select patients, further study is warranted. This convenient dosing schedule may allow transplant patients to better manage their drug therapy, increase compliance and lower medication costs.

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