Population pharmacokinetics of tacrolimus in adult kidney transplant recipients

Objectives: The aims of this study were to investigate the population pharmacokinetics of tacrolimus in adult kidney transplant recipients and to identify factors that explain variability.

Methods: Population analysis was performed on retrospective data from 70 patients who received oral tacrolimus twice daily. Morning blood trough concentrations were measured by liquid chromatography-tandem mass spectrometry. Maximum likelihood estimates were sought for apparent clearance (CL/F) and apparent volume of distribution (V/F), with the use of NONMEM (GloboMax LLC, Hanover, Md). Factors screened for influence on these parameters were weight, age, gender, postoperative day, days of tacrolimus therapy, liver function tests, creatinine clearance, hematocrit fraction, corticosteroid dose, and potential interacting drugs.

Results: CL/F was greater in patients with abnormally low hematocrit fraction (data from 21 patients only), and it decreased with increasing days of therapy and AST concentrations (P < .01). Average parameter estimates were as follows: CL/F = 31.8 L/h (hematocrit <0.33), CL/F = 24.2 L/h (hematocrit >0.33), and V/F = 2080 L. Marked interindividual variability (42% to 111%) and residual random error (3.7 ng/mL) were observed. On the basis of the derived model, a patient with normal AST (20 U/L) or high AST (200 U/L) concentrations 7 days after commencement of therapy would require a tacrolimus dose of 4.6 mg or 4.0 mg, respectively, to achieve a steady-state trough concentration of 10 ng/mL.

Conclusions: The population pharmacokinetics of tacrolimus in adult kidney transplant recipients showed wide variability. Thus it is not possible to use a standard tacrolimus dose as an empiric predictor of concentration in this population. An understanding of factors that influence the pharmacokinetics of tacrolimus may assist in drug dosage decisions. (Clin Pharmacol Ther 2002;72:660-9.)

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Tacrolimus, a potent immunosuppressive agent, has emerged as a valuable therapeutic alternative to cyclosporine (INN, ciclosporin) after adult kidney transplantation.1 Similar to cyclosporine, tacrolimus has a narrow therapeutic window.2 Continuous adequate immunosuppression is imperative for maintenance of the graft, whereas overimmunosuppression can lead to serious toxicities and infections and increased risk of lymphoproliferative disease. Tacrolimus displays considerable interindividual and intrindividual variability in its pharmacokinetics, with poor correlation between drug dosage and blood concentrations.2 These factors make defining an optimal dosing schedule for this agent difficult.3

Some studies have evaluated the pharmacokinetic properties of tacrolimus.2 The oral bioavailability of this agent is generally low (approximately 25%) but can vary from 4% to 93%. Tacrolimus binds extensively to erythrocytes and in plasma to α1-acid glycoprotein and albumin. It is extensively metabolized by the cytochrome P450 system and is subject to P-glycoprotein counter-transport.3 Greater than 95% of tacrolimus is eliminated by the biliary route, with renal excretion of the parent drug accounting for less than 1% of total body clearance.

To date, pharmacokinetic studies in adult kidney transplant recipients have used a classic approach to
data generation, with multiple concentration-time measurements taken over a single dosing interval or a relatively short time period.\textsuperscript{5, 9} Kinetic information has been obtained only in small, relatively homogeneous patient groups, in the immediate posttransplant period. Different factors that may alter drug pharmacokinetics have not been investigated simultaneously. Such studies provide little information on interindividual and intrindividual pharmacokinetic variability. Furthermore, kinetic information has been based on immunoassay analysis of tacrolimus blood samples. Such assays are not specific for the parent drug, with reports of significant and variable cross-reactivity of assay antibody with some tacrolimus metabolites.\textsuperscript{3} Assay techniques that provide specific tacrolimus concentration measurement with greater sensitivity, such as liquid chromatography-tandem mass spectrometry, are now available.\textsuperscript{10}

On the basis of clinical experience to date, it has been recommended that the target tacrolimus whole-blood trough concentrations are as follows: 15 to 20 ng/mL during the first 2 weeks after kidney transplantation, 10 to 15 ng/mL during weeks 3 and 4, 5 to 10 ng/mL thereafter for the first year, and 5 to 7 ng/mL after the first year.\textsuperscript{11} Dosing of tacrolimus in adult kidney recipients involves trial and adjustment before a desired target concentration is achieved. Individualization of dosage to achieve target drug concentrations more quickly would further improve tacrolimus therapy.

The information necessary for dosage individualization can be obtained through population pharmacokinetic analysis.\textsuperscript{12} In such an approach, a picture of the concentration-time profile of a drug is generated from “sparse” data pooled from a large group of subjects.\textsuperscript{13} During modeling, typical population values for kinetic parameters are estimated, together with interindividual and residual (unexplained) variability. The influence of multiple covariates (covariates) on pharmacokinetic parameters can also be examined. Population pharmacokinetic information can be used in a Bayesian dosage prediction program to assist with dosage individualization.\textsuperscript{12} Tacrolimus population databases, however, are not included in Bayesian computer programs and, as such, must first be generated. To date, no information on the population pharmacokinetics of tacrolimus in adult kidney transplant recipients has been published.

The aims of this study were to investigate the population pharmacokinetics of tacrolimus in an adult kidney transplant cohort, with the use of routine drug monitoring data, and to identify factors that explain pharmacokinetic variability.

METHODS
Patients and data collection
The Princess Alexandra Hospital (Brisbane) and Queen Elizabeth Hospital, Royal Adelaide Hospital, and Flinders Medical Centre (Adelaide) were identified as major institutions in Australia that cared for adult kidney transplant recipients. All patients from these sites, aged 15 years or greater, who had undergone a kidney transplant and who had previously received or were currently receiving tacrolimus were eligible. Written permission to collect data, available as part of routine care or clinical trial reporting, was obtained from the drug’s manufacturer (Janssen-Cilag Ltd, Sydney, Australia), ethics committees at each of the aforementioned hospitals, and the University of Queensland Medical Research Ethics Committee. Pharmacokinetic, demographic, and covariate data were collected retrospectively from patient medical records, clinical trial case folders, and a therapeutic drug monitoring database.

Drug administration
Patients received oral tacrolimus therapy as part of a triple immunosuppressive regimen, which also included azathioprine or mycophenolate mofetil and corticosteroids. Therapy was generally initiated at a dosage of 0.075 mg/kg twice daily. Subsequent doses were adjusted empirically on the basis of clinical evidence of efficacy and toxicity and to maintain tacrolimus trough blood concentrations between 10 and 20 ng/mL in the first 3 months after transplant and between 2 and 15 ng/mL thereafter. Patients were instructed to take the tacrolimus dose at the same time each morning and evening, on an empty stomach.

Therapeutic drug monitoring
In the immediate posttransplant period, blood samples were collected daily (before the morning dose) for the determination of whole-blood 12-hour trough concentrations of tacrolimus until the concentrations were stabilized and within the predefined concentration range. Subsequent sampling occurred at each outpatient visit. Trough samples were also taken if signs and symptoms of rejection were observed or as needed to manage any suspected adverse event. Tacrolimus blood concentrations were measured by a validated liquid chromatography-tandem mass spectrometry assay.\textsuperscript{10, 14}

Population modeling
Fixed effects. Population pharmacokinetic modeling was performed with NONMEM (version 5.1.1; Globomax LLC, Hanover, Md).\textsuperscript{15} Maximum likelihood es-
timates were sought for apparent clearance (CL/F) and apparent volume of distribution (V/F). As the majority of concentration-time data collected came from the end of the dosing interval, the choice of absorption rate constant (kₐ) was likely to have little influence on modeling and it was fixed to a literature value of 4.48 h⁻¹.¹⁶ A baseline model (CL/F = 0.1, V/F = 0.2) was developed with the use of all patients. Candidate covariates were then screened statistically by adding these, in turn, according to a slope-intercept model (centered where physiologically appropriate) (eg, CL/F = 0.1 + 0.2 ∗ [WT - WTᵥ], in which WT is total body weight and WTᵥ is the average weight of the population), with the use of indicator variables (eg, CL/F = 0.1 ∗ GEN + 0.2 ∗ [1 - GEN], in which GEN [gender] = 1 for male subjects and 0 for female subjects), expressing them in inverse relationships (eg, CL/F = 0.1 + 0.2/AST) and exponential relationships (eg, CL/F = 0.1 ∗ [WT/WTᵥ]⁰.⁵).

The covariates screened were as follows: weight, age, gender, postoperative day, days of tacrolimus therapy, liver function test results (bilirubin, alkaline phosphatase, AST, γ-glutamyltransferase, and ALT), creatinine clearance, hematocrit fraction, current corticosteroid dose, and concurrent therapy with potential metabolic inducers and inhibitors of tacrolimus.¹⁷⁻¹⁹

The difference in the objective function value (a NONMEM-calculated global goodness-of-fit indicator equal to −2 log-likelihood value of data) between a full and reduced pair (eg, CL/F = 0.1 + 0.2 ∗ WT and CL/F = 0.1) approximates the χ² value with 1 df.¹⁵ The level of significance (α) was set at .01, which corresponds to a required change in the objective function value of 6.6. Changes in the objective function value and plots of residuals and weighted residuals (weighted in NONMEM by the standard deviation [SD]) versus model-predicted concentrations of tacrolimus were recorded.

Random effects. Deviations of CL/F and V/F of the jth individual from the estimated population average values were modeled with the use of an exponential interindividual variability error model.¹⁵

\[ PK_j = TVPK ∗ e^{\eta_{PK}} \]

in which PKᵢ is the required pharmacokinetic parameter in the jth individual and η_{PK} is a random variable distributed with zero mean and variance of \(σ_{PK}^2\) about the average value (TVPK) in the population. NONMEM also estimated the residual variance among pairs of observed and model-predicted data. The following additive residual random error model was used:

\[ C_{ij} = C_{predj} + e_{ij} \]

in which Cᵢj is the jth observed concentration for the jth individual, C_{predj} is the concentration of tacrolimus in the blood predicted by the pharmacokinetic model, and eᵢj (the difference between Cᵢj and C_{predj}) is a randomly distributed variable with zero mean and variance of \(σ_{e}^2\). Such error arises from factors such as assay variability, model misspecification, inaccurate recording of dosing or sampling times, and intrapatient kinetic variability.

The uncertainty (coefficient of variation) in estimating fixed and random parameter values was determined by expressing the standard error of estimation (calculated in NONMEM) as a percentage of the estimated value.¹⁵

RESULTS
Patients and data collection

Data were collected retrospectively from 70 kidney transplant recipients. The characteristics of the patients are presented in Table I. Patients received tacrolimus within a period from November 1994 to March 2000. A total of 1060 tacrolimus blood concentration-time measurements were collected. Concentrations ranged from 0.6 ng/mL to 50.9 ng/mL, with the majority between 2 ng/mL and 15 ng/mL (90%). The number of concentrations available per subject ranged from 1 to 57 samples with most lying between 3 and 30 concentrations (71%). The majority of samples were drawn near the trough at 10 to 14 hours after dose (91%) (Fig 1). Initial examination of the data showed no linear relationship between dose and tacrolimus steady-state trough concentration (\(r^2 = 0.06\)).

Population modeling

A 1-compartment model with first-order absorption and elimination was optimal for modeling the data. In the model-building phase, 6 covariates (hematocrit, days of therapy, enzyme inhibitors, creatinine clearance, AST, and bilirubin) reduced the objective function value by 6.6 or more (\(P < .01\)) when tested against the baseline model. At this stage, hematocrit fraction appeared to be the most important of these factors. A hematocrit level of less than 0.33 was considered to be abnormally low in our investigation, with 0.33 as the lower limit of each hospital pathology department's normal range. Patients displaying abnormally low hematocrit levels (<0.33) had significantly increased CL/F compared with patients with higher hematocrit levels (>0.33) (31.8 L/h versus 24.2 L/h). Unfortunately, hematocrit data were only available for 21 of 70
Table I. Characteristics of study patients (N = 70)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Data</th>
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<tbody>
<tr>
<td>Demographic data</td>
<td></td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>43/27</td>
</tr>
<tr>
<td>Age (y)</td>
<td>43.6 ± 14.0 (15-71) (44.6)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73.5 ± 15.9 (39.2-141.8) (73.4)</td>
</tr>
<tr>
<td>Duration of tacrolimus therapy (d)</td>
<td>218 ± 249 (2-1475) (128)</td>
</tr>
<tr>
<td>Patients receiving enzyme inhibitors (No.)</td>
<td>41</td>
</tr>
<tr>
<td>Patients receiving enzyme inducers (No.)</td>
<td>3</td>
</tr>
<tr>
<td>Pharmacokinetic data</td>
<td>1060</td>
</tr>
<tr>
<td>Samples (No.)</td>
<td></td>
</tr>
<tr>
<td>Concentration (ng/mL)</td>
<td>9.4 ± 5.0 (0.6-50.9) (8.7)</td>
</tr>
<tr>
<td>Samples per patient (No.)</td>
<td>15.1 ± 15.6 (1-57) (7.5)</td>
</tr>
<tr>
<td>Sampling time after dose (h)</td>
<td>12.3 ± 1.4 (1.3-20.3) (12.3)</td>
</tr>
<tr>
<td>Dose (ng/kg, twice daily)</td>
<td>0.063 ± 0.036 (0.01-0.234) (0.058)</td>
</tr>
</tbody>
</table>

Results are presented as number or mean ± standard deviation (SD), range, and median.

patients, and hence the likely importance of this covariate could not be tested further.

In a (forward) modeling building step, the cumulative inclusion of days of tacrolimus therapy, AST, and bilirubin reduced the objective function value by more than 6.6 at each addition. Finally, in the (backward) elimination step, days of tacrolimus therapy, AST, and bilirubin exceeded the objective function cutoff value when they were omitted individually from the model. Although inclusion of bilirubin was significant during development of the regression models and the back-elimination step (reduced CL/F with increasing bilirubin level), the uncertainty in estimating the coefficients (θ) and interindividual variability in CL/F in this model was high. Consequently, this covariate was removed. CL/F decreased with increasing days of therapy and AST concentrations. No covariates significantly explained the variability in V/F.

Consideration of the above two covariates during modeling also improved the relationship between model-predicted and observed concentrations (objective function value decreased from the baseline model, 4087 to 4027) and weighted residuals versus model-predicted concentrations and reduced interindividual variability and residual error when compared with the baseline model. A plot of model-predicted versus observed concentrations for the final model based on population parameter estimates is shown in Fig 2. A plot of model-predicted versus observed concentrations for the final model based on individual parameter estimates is shown in Fig 3. A plot of weighted residuals versus days of therapy is shown in Fig 4. The vast majority of the weighted residuals lay within 2 units of perfect agreement and were symmetrically distributed around the zero ordinate for the duration of treatment.

A summary of results from the final model, including AST concentration and days of tacrolimus therapy, is presented in Table II. Interindividual variability associated with CL/F and V/F was considerable (42% to 111%). Residual random error associated with the final model was 3.7 ng/mL. Individual Bayesian estimates for the pharmacokinetic parameters are given in Table III. The median values were 23.5 L/h for CL/F, 898 L for V/F, and 18.6 hours for the elimination half-life (t₁/₂). Whereas the median values for CL/F, V/F, and t₁/₂ were reasonable compared with previous studies, individual estimates for V/F (and hence t₁/₂) were un-
reasonably high in 7 patients (\(\text{V/F} \) values greater than 2000 L, with one huge estimate of 33,298 L). It appears that there was insufficient information to characterize

V/F (and \( t_{1/2} \)) in these 7 patients. It should be noted that these 7 unreasonably large estimates of V/F caused skewing of estimates (mean ± SD) of V/F and \( t_{1/2} \) to the right.

Table IV shows the results of simulated studies in
Table III. Individual Bayesian estimates of pharmacokinetic parameters determined with use of final population model

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean ± SD</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL/F (L/h)</td>
<td>33.0 ± 11.3</td>
<td>33.5</td>
<td>15.3–68.6</td>
</tr>
<tr>
<td>V/F (L)</td>
<td>1974 ± 4752</td>
<td>898</td>
<td>217–33,298</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>48.1 ± 127.1</td>
<td>18.6</td>
<td>4.6–939</td>
</tr>
</tbody>
</table>

which the final population model was used to calculate a 12-hour maintenance dose to achieve an average steady-state trough concentration of 10 ng/mL in recipients at various times during therapy and when AST concentrations were normal or high.

DISCUSSION

This is the first time the population pharmacokinetics of tacrolimus has been described in adult kidney transplant recipients. Days of therapy, hematocrit fraction, and AST concentration were identified as the most important factors influencing the pharmacokinetics of this agent. CL/F decreased with increasing days of tacrolimus therapy and was reduced with increasing AST concentrations. For 21 patients with hematocrit data available, when hematocrit fraction was abnormally low (<0.33), CL/F was significantly increased.

To date, 3 traditional intensive blood sampling studies have reported pharmacokinetic parameters for tacrolimus in kidney transplant recipients, with 2 additional studies providing parameter estimates immediately before transplant. All five studies used nonspecific enzyme immunoassays (rather than the more appropriate liquid chromatography-tandem mass spectrometry assay) to measure tacrolimus concentrations. Mean estimates of CL/F, V/F, and t½ were ranged from 17.0 to 30.4 L/h, 518 to 646 L, and 8.0 to 32.5 hours, respectively. Median individual Bayesian estimates for CL/F, V/F, and t½ obtained in this study (Table III) are in reasonable agreement.

A previous study of 303 kidney transplant recipients reported a statistically significant correlation between relative clearance and both hematocrit (r = 0.81, p = .017) and albumin concentrations (r = 0.74, p = .047) over the first 12 weeks after kidney transplantation. In blood, tacrolimus binds extensively to erythrocytes and plasma proteins. Hematocrit and plasma protein concentrations are generally low immediately after transplant and increase significantly as the patient recovers. Because tacrolimus concentration is measured in whole blood, low hematocrit and albumin concentrations should theoretically result in a reduction in the total concentration of tacrolimus in the whole blood. In such a situation, whole-blood drug clearance appears to increase. In reality, however, unbound drug clearance remains the same.

In the final population model in this study, tacrolimus CL/F decreased with increasing days of therapy. As days of therapy increased, the influence on CL/F was reduced, such that the effect was minimal by approximately 90 days. In this study, values from early days of therapy are likely to correspond to periods of low hematocrit and albumin concentrations, with initiation of tacrolimus immediately after transplant or conversion to tacrolimus because of rejection or poor renal function. It is possible that CL/F of tacrolimus was reduced notably with time until around day 90 as a result of significant increases in hematocrit and albumin concentrations during this period. The possibility that the bioavailability of tacrolimus might be increasing in these first 3 months, however, should also be considered.

This study was conducted retrospectively with the use of data that were available as part of routine patient care recorded in medical notes and transplant flowcharts. Unfortunately, at the beginning of this study,
hematocrit and albumin data were not parameters monitored by the study nurses or transplant physicians. Recording of hematocrit (but not albumin) data occurred toward the end of this study. Complete hematocrit data were only available for 21 patients, and no albumin data were available. CL/F was found to be greater in patients with abnormally low hematocrit fraction on the basis of data from these 21 patients.

As tacrolimus concentrations are measured relative to total drug concentration in the blood, in low hematocrit and albumin concentration situations, a lower whole-blood therapeutic range may be required. Results from this study (though incomplete) provide evidence supporting a previous suggestion that hematocrit fraction be monitored and reported to clinicians along with tacrolimus trough concentrations. Although we had no data on albumin concentrations and minimal data on hematocrit fraction, both may be important covariates to consider in future prospective population studies.

Previous studies in adult liver transplant recipients have reported that hepatic dysfunction can decrease tacrolimus clearance by up to two thirds and increase elimination half-life 3-fold. AST a marker of acute liver damage was identified as an indicator of CL/F in this study. Differences in tacrolimus dosage requirements in patients with normal and abnormally high AST concentrations, however, were small, and probably of minor clinical significance (Table IV), although very few of the patients had greatly impaired hepatic function. This may reflect the fact that none of the liver function tests are particularly accurate or sensitive indicators of metabolic function and do not take into account the effect of P-glycoprotein activity.

Corticosteroid dose and potential metabolic inducers and inhibitors of tacrolimus were not found to be important covariates in this investigation. Patients were generally followed up for periods of greater than 3 months, by which time the daily prednisone dose was tapered down to only 5 or 10 mg. These doses may be too low for the induction effect to be significant. The relatively small number of subjects who received drugs that are known metabolic inducers of tacrolimus may explain why this covariate did not prove significant (n = 3).

Past studies have reported no significant correlation between serum creatinine concentration and clearance of tacrolimus (r = 0.36). Patient gender has been shown to have no influence on tacrolimus dose. These observations were reaffirmed in this investigation.

During modeling, there was some difficulty in obtaining reasonable individual Bayesian estimates of V/F for all patients. In the final population model, estimated interindividual variability in V/F was greater than would normally be expected. The majority of concentration-time data collected in this study represented trough values. It appears that given such a sampling situation there was insufficient information available to accurately characterize V/F in all patients.

Some previous work has been done in which computer simulations were used to evaluate and compare designs of sparse data experiments. With the use of an intravenous monoclonal model, if only 2 samples could be taken, sampling as early and as late as possible was found to provide the most precise parameter estimates. Adding a third sample to the best 2-sample design mainly improved estimation of the population random effects. Compared with fixed sampling times, randomization of sampling times in all individuals results in higher robustness to model misspecification. If data to be analyzed do not contain information on absorption, then there will be no adverse effect (such as bias appearing in other parameters) if kₐ is fixed to a value similar to the true value. Better estimates of volume of distribution will be obtained when samples taken cover a large part of the elimination phase, not just trough concentrations. If only trough samples are available for analysis, estimates of clearance will be more precise and less biased compared with volume of distribution.

As reported for other transplant populations, tacrolimus dosage correlated poorly with drug blood concentrations (r² = 0.06). It is not possible to use a standard tacrolimus dose, even if adjusted for weight, as an empiric predictor of concentration in kidney transplant recipients. On the basis of the derived model, tacrolimus CL/F for a typical adult kidney transplant recipient with normal AST concentrations at 1 week after transplant is estimated to be 32.0 L/h. Such a patient should receive a maintenance dose of tacrolimus of 4.6 mg twice daily for achievement of a steady-state trough concentration of 10 ng/mL. In contrast, CL/F in a typical adult kidney transplant recipient with abnormally high AST concentrations at 1 year after transplant is estimated to be 24.1 L/h. Such a patient should receive a maintenance dose of tacrolimus of 3.3 mg twice daily for the achievement of a steady-state trough concentration of 10 ng/mL. The most important aspect of Table IV is how relative drug dosage changes with changing AST concentrations and days of therapy. If a different value of V/F was used (such as a value from the previously published literature), the relative difference between drug doses at different AST concentrations and days of therapy would not change.
Residual random error associated with the final model was 3.7 ng/mL. As the liquid chromatography-tandem mass spectrometry technique used in this study is highly specific for tacrolimus and has low imprecision across the analytic range (coefficient of variation < 8%), assay error is not expected to contribute greatly to this. A significant proportion of this error, however, may result from intrindividual variability in pharmacokinetic parameters. Previous studies of cyclosporine in adult kidney and heart transplant recipients and of tacrolimus in pediatric liver transplant recipients have reported population models with similar large residual random error. It has been suggested that a significant portion of the variability associated with the pharmacokinetics of cyclosporine may result from intrindividual variability in cytochrome P450 3A gut and liver metabolism and gut P-glycoprotein countertransport. Whether such large variability will limit the usefulness of these population pharmacokinetic data for individualized dosage prediction of tacrolimus is yet to be determined.

The pharmaceutical industry and drug regulatory bodies such as the Food and Drug Administration (United States) and the Therapeutic Goods Administration (Australia) are increasingly recognizing the importance of population pharmacokinetic studies for the development and evaluation of new drug therapies and for optimal dosing of existing drugs in specific groups of patients. The software program NONMEM is specifically designed for population modeling and uses well-established statistical methods. It is regarded as the criterion standard program in this area. The patient group included in this study is representative of “real-life” adult kidney transplant recipients. The dosage of tacrolimus given to different subjects and also during the course of each individual’s therapy) varied considerably. Data collected characterized that which is normally available for transplant recipients. Thus findings from this study should be applicable to the larger kidney transplant community.

In conclusion, results from this study extend the amount of pharmacokinetic data on tacrolimus that exist for adult kidney transplant recipients. The feasibility of applying a population approach to sparse data generated during routine clinical care, by using a 1-compartment population pharmacokinetic model in NONMEM, has been established. CL/F estimates, necessary for tacrolimus maintenance dose calculations during dosage individualization, were greater when hematocrit fraction was abnormally low and decreased with increasing days of tacrolimus therapy and with increasing AST concentrations. A prospective evaluation of the clinical utility of these observations needs to be undertaken to assess dosage prediction.

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References


