# Cyclosporine (Equoral®) Population Pharmacokinetics and Bayesian Estimation in Tunisian Renal Transplant Recipients

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## Abstract

### Objectives

Equoral® is a generic formulation of cyclosporine widely used in Tunisian renal transplant patients. The purposes of this study were to explore the pharmacokinetic variability of Equoral® in Tunisian renal transplant, to develop a population pharmacokinetic model and a MAP-BE of Equoral® PK parameters and global exposure.

### Methods

Full-PK profiles were obtained from 17 renal transplant patients given Equoral® twice-daily. Measurements were performed using an FPIA technique. To estimate popPK parameters of cyclosporine, a non linear mixed effects approach was used and the popPK parameters were used as priors to develop a MAP-BE for estimation of Equoral® PK parameters and AUC using three blood concentrations. Predictive performances were tested by calculating mean predicted error between estimated and reference AUC. The validation of these PK tools was performed using jackknife approach, visual predictive check and bootstrapping method.

### Results

Equoral® exhibited a high inter-patient variability: $C_0 = 90\pm57$ ng/mL, $C_{max} = 762\pm343$ ng/mL and $AUC_{0-12} = 2460\pm1240$ ng.h/mL. A two compartment model with Erlang distribution best described the data: residual proportional error was 26.8% and imprecision parameter estimate was less than 26%. None of the tested covariates significantly affected cyclosporine pharmacokinetics. Using this model and cyclosporine concentrations measured at 0.30 and 180min post-dose, MAP-BE could accurately estimate cyclosporine AUC, mean bias between estimated and reference AUC was 5.47 ± 29% with 82% of the patients with AUC bias < 20%. The doses proposed by the BE were similar to those proposed using all concentrations in 14 out of 17 patients.

### Conclusion

A popPK model for Equoral® when given to Tunisian kidney recipients. A MAP-BE using only three blood concentrations that estimates accurately Equoral® exposure in these patients was developed and could allow dose adjustments based on the AUC in clinical setting.

## Introduction

Cyclosporine, an immunosuppressant introduced in 1980 for the management of organ transplantation. Its pharmacokinetics is characterized by a large inter and intra individual variability and a narrow therapeutic window. This can lead to an insufficient immunosupression or toxic side effects [1,2]. Various factors may explain variability of cyclosporine pharmacokinetic, such as drug absorption, gastrointestinal motility, and liver and pancreatic function. The development the micro emulsion formulation of cyclosporine Néoral® ameliorates significantly the absorption of cyclosporine compared to the original oil-based formulation sandimmune [3]. However, pharmacokinetics of cyclosporine remains influenced by demographic factors, time after transplantation and drug interaction. Equoral® is a generic formulation of cyclosporine widely used as an alternative treatment to Neoral® in Tunisian renal transplant patients. Population pharmacokinetic data of cyclosporine Equoral® was not reported elsewhere.

The purposes of this study were:

• To explore the pharmacokinetic variability of Equoral® in Tunisian renal transplant patients.
• To develop a population pharmacokinetic (popPK) model and a Bayesian estimator (MAP-BE) for the estimation of Equoral® PK parameters and global exposure (ie, AUC).

## Methods

### Patients and Data Collection

Data were obtained from 17 adult patients who underwent renal transplantation from 2006 to 2010 at the department of Urology in the Charles Nicolle Hospital of Tunis, Tunisia. Data collection was approved by the hospital ethic comity. Patients received the generic formulation of cyclosporine (Equoral®) twice a day with doses varying between 0.66 and 4.06 mg/kg/d. All patients received concomitantly mycophenolate mofetil.

### Blood Collection

Full pharmacokinetic profiles were collected in EDTA tubes at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 hours post-dose. Blood samples were stored at -20°C until analysis.

### Cyclosporine Assay

All whole-blood samples were analyzed by fluorescence polarization immunoassay (FPIA-Axym) in Laboratory of Clinical Pharmacology of the National Center of Pharmacovigilance. Precision data of immunoassay was demonstrated previously by comparison of the two methods for CsA therapeutic monitoring HPLC and AxSYM. Result showed that the correlation coefficient is 0.99 [4]. The lower limit of quantification the assay was 23ng/ml. The method was linear between 0 and 800ng/ml.

## Population Pharmacokinetic Analysis

The population pharmacokinetic analysis was conducted by the nonlinear mixed-effects modeling (NONMEM version VI) software (GloboMax LLC, Ellicott City, MD, USA) using Wings for NONMEM version 614 (developed by N. Holford, available from http://wfn.sourceforge.net/) [1]. All population pharmacokinetic analyses were carried out using the first-order conditional estimation method (FOCE).

One, two and three structural compartment models were tested. Models with Erlang distribution (ADVAN5 SS5), which is a particular case of the gamma distribution [5] and was previously used for cyclosporine in renal transplant recipients [6], were also tested. Erlang distribution explain the transition of the drug through a linear chain of n identical transit compartments placed upstream from the deposit to the central compartment and connected by an identical exiting rate constant (ktr).

Between subjects variability (BSV) was described using exponential models. The covariance of the parameters was studied during the modeling process. Additive, proportional and combined (i.e. additive and proportional) error models were tested to describe the residual variability.

## Covariates Analysis

The screening and selection of covariates were performed as part of population pharmacokinetic analysis following a classic stepwise approach [7]. In the first step, a covariate free population pharmacokinetic model was analyzed. The potential covariates considered were the demographic characteristics [bodyweight (BW), age] and laboratory test results (bilirubin, AST, ALT). Gender was not considered as a potential covariate in our study because we have a sex ratio M/F of 13/4. The influence of continuous covariates on pharmacokinetic parameters was tested systematically via a generalized modeling approach according to an allometric function. For example, the effect of bodyweight on the central volume of distribution (VC) was tested using the following equation: $VC = TV (VC) \times (BW / medcov)^{\theta BW}$.

Where TV (VC) is the typical value of the central volume of distribution for a patient with the median covariate value (medcov) and $\theta BW$ is the estimated influential factor for bodyweight.

Covariates were introduced individually and one by one in the base model. A covariate was considered as influencing the pharmacokinetic model when its adjunction to the base model induce (i) a decrease of the objective function value (OFV) by 6.6 between the two models, and / or (ii) an improvement of parameter estimation precision and / or (iii) a reduction in Between subject variability (BSV).

## Evaluation of the Model

The final population pharmacokinetic model was evaluated using bootstrap, jackknife methods and visual predictive check (VPC). The bootstrap resampling was applied to assess the stability of the final parameter estimates and to confirm the robustness of the final model [8,9]. The bootstrap procedure was performed using Wings for NONMEM in order to compare the mean and median values of the pharmacokinetic parameters estimated using at least 1000 populations of 17 patients, with the population parameters obtained from the original data set [9]. The Jackknife method consists at a 20% at-a-time omission applying to the original data set and then reanalyzed by NONMEM. The 95% CI for parameter estimates obtained by Jackknife procedure were compared with those of the final model using the mean and SE of the NONMEM estimation [10].

## Building of a Bayesian Estimator

PopPK parameters where then used as priors to develop a Bayesian estimator (MAP-BE) for the estimation of cyclosporine AUC using a limited sampling strategy (LSS). The best LSS among the combinations of a maximum of three sampling times was selected on the basis of the D-optimality criterion (implemented in Adapt II Pharmacokinetic / Pharmacodynamic Biomedical Simulations Resource, Los Angeles, CA, USA) computed Systems Analysis Software; on the population pharmacokinetics parameters. The predictive performance of the MAP-BE were tested (i) by means of the bias (mean error) and the root mean square error (RMSE) comparing the estimated AUC to that obtained by the trapezoidal rule [11]; and (ii) by its ability to provide similar dose adjustments to those obtained using all the available time-points.

## AUC-Guided Dosing

After each AUC-assessment, dose adjustments were made to reach the predefined target.

$AUC_{0-12}$ which is 3800ng.h/mL. According to the model there was a linear correlation between dose and AUC. Dose adjustment was made by the model according to the formula $D_{new} = D_{current} \times AUC_{target}/AUC_{current}$.

## Results

A total of 17 full pharmacokinetics profiles were analyzed in this study. Patient characteristics were summarized in (Table 1).

Cyclosporine exhibited a high inter-patient variability (Figure 1): trough concentration= $90.38 \pm 65.84$ng/mL, $C_{max} = 762 \pm 343$ng/mL, time to reach the $C_{max} = 1.61 \pm 0.37$ and $AUC_{0-12} = 2457 \pm 1.24$ng.h/mL, CV values are 62.89%, 44.98%, 22.96 % and 50.68% respectively (Table 2).

## Population Pharmacokinetics

Cyclosporine pharmacokinetics was well described by a two-compartment model combined with an Erlang distribution to describe the absorption phase. Five delay compartments gave the best improvement to the model. This model showed a residual proportional error equal to 26.8% and imprecision parameter estimate less than 26% (8.7 - 25.6%). Models tested with one, two, three and four delay compartments and models with only a central compartment did not show improvement. Among the investigated covariates, no one affected significantly cyclosporine pharmacokinetics (Figure 2,4,5).

The scatter plot of predicted (PRED) and individual model-predicted (IPRED) concentrations versus observed concentrations showed no major bias (Figure 3-a,b,c,d), and 94.5% of weighted residuals were homogenously distributed over the sampling time period and within an acceptable range (-2 to 2). The population pharmacokinetic parameters obtained with the final model are summarized in (Table 3).

Table 1: Characteristics and laboratory test results of patients

| Patients Characteristics | Value[a] |
|---|---|
| CsA daily dose (mg) | 175 (50 – 300) |
| AGE (yrs) | 45 (28 – 65) |
| weight (Kg) | 77 (43 - 99) |
| Sex (M/F) | 14/3 |
| Laboratory test results | |
| Bilirubin (mg/l) | 64.85 (33.2 – 134.5) |
| Alkaline Phosphatase (UI/L) | 4.72 (4.35 – 10.2) |
| AST (UI/L) | 32.7 (23 – 62) |
| ALT (UI/L) | 4 (3.6 – 4.8) |
| a: Values are expressed as median (range) | |

Table 2: Pharmacokinetics parameters for the measured PK profiles

| Parameter | Mean (Range) | SD | CV (%) | 95% CI |
|---|---|---|---|---|
|  |  |  |  |  |
| T1/2 (h) | 8.27 (1.61 – 16.52) | 4.5 | 54.5 | [5.54 – 10.99] |
| CL (L/h) | 44.18 (22.16 – 193.3) | 40.49 | 91.66 | [23.36 – 65] |
| VD (L) | 213.7 (37.33 – 988.9) | 244.4 | 114.34 | [88.08 – 339.4] |
| $AUC_{0-12}$ (ng*h/ml) | 2457 (517.2 – 5107) | 1245 | 50.68 | [1817 – 3097] |
| Trough concentration (ng/ml) | 90.38 (15.80 – 225.5) | 56.84 | 62.89 | [61.16 – 119.6] |
| $C_{max}$ (ng/ml) | 762.2 (177.6 – 1508.6) | 342.8 | 44.98 | [585.9 – 938.5] |
| Tmax (h) | 1.611 (1 – 2) | 0.37 | 22.96 | [1.38 – 1.79] |

Table3: Finales estimates of population pharmacokinetics parameters (OFV= 1604)

| Parameter | ME | SE | RSE% | BSV (%) | 95% CI |
|---|---|---|---|---|---|
| Ktr ($h^{-1}$) | 5.28 | 0.86 | 16.28 | 24.47 | [3.59 – 6.96] |
| Q (L/h) | 25.4 | 5.27 | 20.74 | 43 | [15.07 – 35.74] |
| VC (L) | 65.5 | 16.8 | 25.64 | 12.57 | [32.57 – 98.43] |
| VP (L) | 250 (FIXED) | - | - | - | - |
| CL (L/h) | 33 | 2.86 | 8.66 | 22.29 | [27.39 – 38.6] |
| Within subject variability (WIV) | | | | | |
| Proportional error (%)      26.79 | | | | | |

ME: mean error; SE: Standard error; RES: Residual standard error; BSV: Between subject variability; WSV: Within subject variability; VC: central volume of distribution; VP: Peripheral volume of distribution; Q: Intercompartmental volume of distribution; CL: Total systemic clearance; Ktr: absorption rate; CI: Confidence Interval.
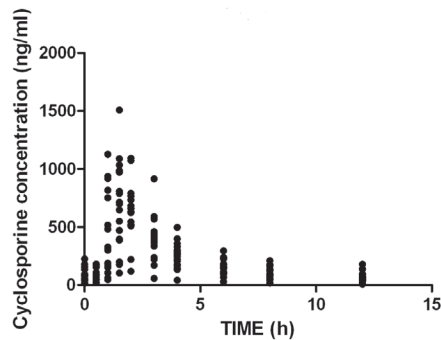


Figure 1: Concentration of Cyclosporine in 17 renal transplant patients participating in the full pharmacokinetics study based on ten blood samples.
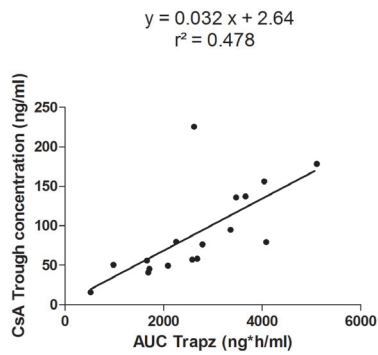
$$y = 0.032\ x + 2.64$$
$$r^2 = 0.478$$

Figure 2: Correlation between AUC calculated based on trapezoidal rule and cyclosporine trough concentration.



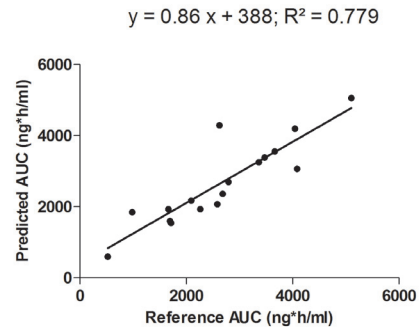$$y = 0.86\ x + 388;\ R^2 = 0.779$$

Figure 4: Correlation of predicted inter dose area under the curve (AUC) of cyclosporine versus reference AUC obtained by the trapezoidal method.
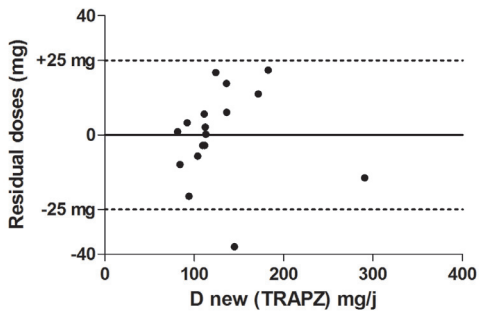


Figure 5: Distribution of residual doses between MAP-BE suggested dose and those obtained by trapezoidal rules.
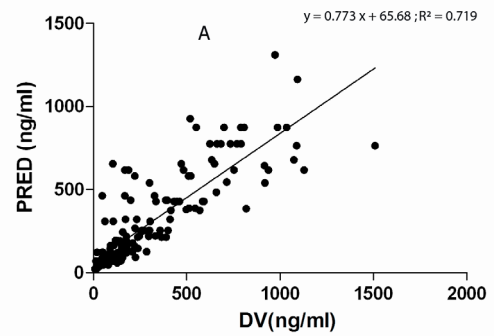


$$y = 0.773\ x + 65.68\ ;R^2 = 0.719$$

Figure 3a: Individual predicted concentrations (IPRED) versus observed concentrations (DV)



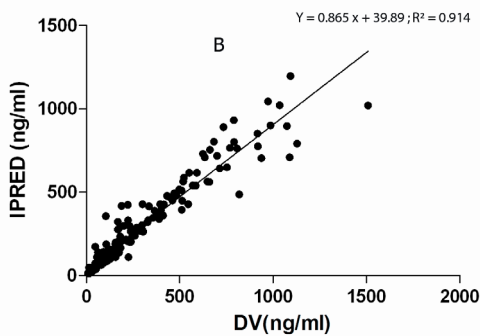$$Y = 0.865\ x + 39.89\ ;R^2 = 0.914$$

Figure 3b: Predicted concentrations (PRED) versus observed concentration (DV)
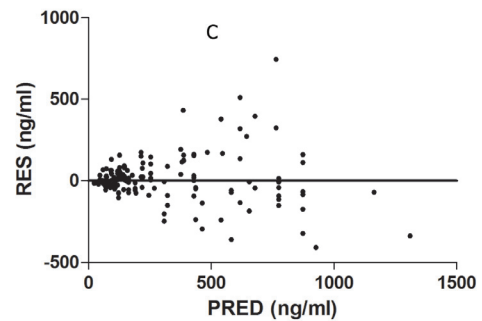


Figure 3c: Individual residuals (RES) versus predicted concentrations (PRED)
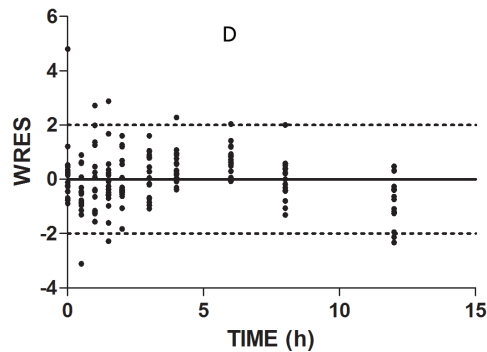
Figure 3d: Individual weighted residuals (WRES) versus sampling time (TIME)

## Evaluation of the Model

Evaluation of the final model using the Bootstrap analysis shows that 71.7% of the 1000 runs were successful and that the mean parameter estimates were not statistically different from those obtained using the original dataset. The mean, SE and 95% CI for each parameter estimated by the bootstrap resampling are shown in the (Table 3,4). Values for bootstrapping and the final model coincided well except SE for CL and VC. The mean and SE of jackknife estimates and 95% CI coincided also with parameter estimate of the final model, except SE for CL and VC. The final model selected was also evaluated using a visual predictive check (VPC) to check its accuracy and robustness. A total of 1000 replicates of the original dataset were simulated using the final model to generate expected concentrations and the 90% prediction intervals. The observed data were overlaid on the prediction intervals and compared visually. Because the cyclosporine dose was different in each patient and the pharmacokinetics for cyclosporine was linear, the VPC was based on dose-normalized concentration.

| | Bootstrap resampling | | | Jackknife estimation | | |
|---|---|---|---|---|---|---|
| Parameter | Mean | SE | 95% CI | Mean | SE | 95% CI |
| Ktr (h$^{-1}$) | 5.37 | 0.12 | [5.13 – 5.6] | 4.69 | 0.086 | [4.51 – 4.86] |
| Vc (L) | 64.83 | 0.22 | [64.39 – 65.26] | 66.43 | 0.47 | [65.48 – 67.38] |
| Vp (L) | 250 | 0.24 | [249.5 – 250.4] | 250 | - | - |
| CL (L/h) | 33.65 | 7.07 | [19.79 – 47.5] | 32.93 | 0.81 | [31.31 – 34.55] |

Table 4: Comparison of 95% confidence intervals estimate by SE of bootstrapping and Jackknife estimate

## Bayesian Estimation

PopPK parameters where used as priors to develop a MAP-BE for the estimation of cyclosporine AUC using a limited sampling strategy. MAP-BE based on the three blood concentrations measured at 0, 60 and 180min post-dose provided a good estimation of cyclosporine AUC. The mean bias between trapezoidal and Bayesian AUCs was 5, 47 + 29% with 82% of the patients having AUC bias < 20%. This MAP-BE is also characterized by a good precision (RMSE = 28.6%). Using a target AUC of 3, 8 mg.h/L and comparing doses calculated by the MAP-BE and those by trapezoidal rules, we found that MAP-BE suggested similar doses to those proposed using all concentrations in 14 out of 17 patients.

## Discussion

We have developed in this study a population pharmacokinetics model for cyclosporine in a Tunisian population of renal transplant patients. It is the first model developed for a generic formulation of cyclosporine and in Tunisian renal transplant patients. In fact, Equoral® is equivalent to Neoral® [12], however bioequivalence studies have some limits. They are done only in healthy young volunteers. Otherwise, cyclosporine absorption differs between healthy volunteers and transplant recipients [13] and varies depending on time after transplantation and on the type of organ graft [14-16] Moreover, patient characteristics such as age [17,18] ethnicity [19,20] or co-morbid disease [19,21,22] also affect cyclosporine absorption. In this case pharmacokinetics models allow a better comprehension of pharmacokinetics comportments of the generic formulation.

Our model was developed using full pk profiles (10 concentrations: from pre-dose to 12 h post-dose) and consisted on a two compartment model with Erlang distribution to describe the absorption phase. Cyclosporine pharmacokinetics models reported previously were essentially based on a one [23] two compartments [24] or three compartment models [25]. Models with transient compartments were also described [26]. Pharmacokinetics of cyclosporine in our population was well described by the Erlang distribution. In fact, the addition of transient compartments to the two compartment model showed an important decrease of the objective function value and a better estimation of pharmacokinetics parameters comparing to the other tested models. In this study all tested covariates are non significant and don't influence the pharmacokinetics of cyclosporine. This may be explained by the little number of patients included in this study. Our results are suitable with those described previously. The CL and VC of this model were 33 l.h$^{-1}$ and 65.5 l respectively. In the literature, cyclosporine CL varies between 28 and 30. l.h$^{-1}$ [23,27,28]. The VC was about 79 [11].

Using PopPK parameters of the final model and on the basis of three blood concentrations measured at 0, 60 and 180 min post-dose, we developed a Bayesian estimator for the estimation of cyclosporine AUC$_{0-12}$. Our Bayesian estimator provided a good estimation of AUC with a mean bias equal to 5, 47 ± 29% and a precision (RMSE) of 28.6%. This Bayesian estimator is able to provide similar dose adjustments to those obtained using all the available time-points. This prediction error should not have important clinical consequences, with respect to the proposed therapeutic range for cyclosporine. In addition our bayesian estimation suggested similar doses in 14 out of 17 patients. Cyclosporine dose adjustment in renal transplant patients was described with Sandimun® and Neoral® formulation. An accuracy of 13.1% was found in the study of Hélène Bourgoin et al. [2] for a Bayesian estimation using three blood concentrations measured at 0, 60 and 120min.

In another hand, dose adjustment using Bayesian estimation seems to be specific of the analytical assay [24]. So it is not recommended to develop MAP-BE for a specific assay using results from a different one.

In summary, we report a popPK model for Equoral® when given to Tunisian kidney recipients. A MAP-BE using only three blood concentrations that estimates accurately Equoral® exposure in these patients was developed and could allow dose adjustments based on the AUC in clinical setting.

## Conclusion

Therapeutic drug monitoring of cyclosporine using twelve concentrations to calculate area under the curve in order to adjust drug doses remains invasive and cannot be achieved frequently in renal transplant patients. We developed in a Tunisian population a pharmacokinetic model for cyclosporine.

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