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Population Pharmacokinetics of Mycophenolic Acid

A Comparison between Enteric-Coated Mycophenolate Sodium and Mycophenolate Mofetil in Renal Transplant Recipients

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Abstract

Objective: The pharmacokinetics of mycophenolic acid (MPA) were compared in renal transplant patients receiving either mycophenolate mofetil (MMF) or enteric-coated mycophenolate sodium (EC-MPS).

Methods: MPA concentration-time profiles were included from EC-MPS- (n = 208) and MMF-treated (n = 184) patients 4–257 months after renal transplantation. Population pharmacokinetic analysis was performed using nonlinear mixed-effects modelling (NONMEM®). A two-compartment model with first-order absorption and elimination was used to describe the data.

Results: No differences were detected in MPA clearance, intercompartmental clearance, or the central or peripheral volume of distribution. Respective values and interindividual variability (IIV) were 16 L/h (39%), 22 L/h (78%), 40 L (100%) and 518 L (490%). EC-MPS was absorbed more slowly than MMF with respective absorption rate constant values of 3.0 h^{-1} and 4.1 h^{-1} ($p < 0.001$) [IIV 187%]. A mixture model was used for the change-point parameter lag-time (t_{lag}) in order to describe IIV in this parameter adequately for EC-MPS. Following the morning dose of EC-MPS, the t_{lag} values were 0.95, 1.88 and 4.83 h for 51%, 32% and 17% of the population (IIV 8%), respectively. The morning t_{lag} following EC-MPS administration was significantly different from both the t_{lag} following MMF administration (0.30 h; $p < 0.001$ [IIV 11%]) and the t_{lag} following the evening dose of EC-MPS (9.04 h; $p < 0.001$ [IIV 40%]). *Post hoc* analysis showed that the t_{lag} was longer and more variable following EC-MPS administration (morning median 2.0 h [0.9–5.5 h], evening median 8.9 h [5.4–12.3 h]) than following MMF administration (median 0.30 h [0.26–0.34 h]; $p < 0.001$). The morning MPA predose concentrations were higher and more variable following EC-MPS administration than following MMF administration, with respective values of 2.6 mg/L (0.4–24.4 mg/L) and 1.6 mg/L (0.2–7.6 mg/L). The correlation between predose concentrations and the area under the plasma concentration-time curve (AUC) was lower in EC-MPS-treated patients ($r^2 = 0.02$) than in MMF-treated patients ($r^2 = 0.48$).

Conclusion: Absorption of MPA was delayed and also slower following EC-MPS administration than following MMF administration. Furthermore, the t_{lag} varied more in EC-MPS-treated patients. MPA predose concentrations were poorly correlated with the MPA AUC in both MMF- and EC-MPS-treated patients.

Background

Mycophenolate mofetil (MMF) is an immunosuppressive agent used in renal transplant recipients to prevent graft rejection. Three clinical trials in renal transplant patients have demonstrated that MMF is more efficacious as an immunosuppressant than azathioprine or placebo.[1-3] Following oral administration, the prodrug MMF is rapidly hydrolysed to the active agent mycophenolic acid (MPA). The majority of MPA is metabolized to the inactive 7-*O*-mycophenolic acid glucuronide (MPAG), which exhibits enterohepatic recirculation (EHC). The minority of MPA is metabolized to the presumably active acyl-glucuronide (AcMPAG). MPA is a selective, reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH). IMPDH has an important role in the *de novo* purine synthesis in T and B lymphocytes.[4] Inhibition of this pathway causes immunosuppression, contributing to the prevention of graft rejection.

Gastrointestinal adverse events are frequently observed in renal transplant recipients treated with MMF. To abrogate these gastrointestinal adverse events and improve the clinical outcome, enteric-coated mycophenolate sodium (EC-MPS) was developed. In two clinical trials,[5,6] EC-MPS 720 mg twice daily and MMF 1000 mg twice daily showed similar efficacy and safety profiles. MPA exposure, reflected by the area under the plasma concentration-time curve (AUC), is similar during administration of EC-MPS 720 mg and MMF 1000 mg, but differences in the pharmacokinetic profile have been reported.[7-9] During EC-MPS therapy, MPA predose plasma concentrations (C_0) are higher, MPA peak concentrations are lower and the time to reach the peak concentration is longer and varies more than with MMF therapy.[7-9]

In MMF-treated renal transplant recipients, it has been demonstrated that biopsy-proven acute rejection is significantly correlated with both the MPA AUC ($p < 0.001$) and MPA C_0 values ($p = 0.01$), whereas no correlation between the efficacy and dose is present.[10] Moreover, the MPA AUC is a better predictor of the risk of rejection than MPA C_0 values.[10] The target range for the MPA AUC in renal transplant recipients cotreated with ciclosporin is 30–60 mg • h/L.[11] This AUC range is more or less associated with C_0 values of 1–3.5 mg/L.[11] Recently, the APOMYGRE (Adaptation de Posologie du MMF en Greffe Rénale) study[12] showed that therapeutic drug monitoring (TDM), using a limited sampling strategy to determine the MPA AUC, can reduce the risk of treatment failure and acute rejection in the first year after renal transplantation. The rates of biopsy-proven rejection were 7.7% in the concentration-controlled group and 24.6% in the group that received fixed doses of MMF ($p = 0.01$).

The aim of this study was to compare the pharmacokinetics of MPA following administration of EC-MPS and MMF. A population pharmacokinetic analysis was performed using concentration-time data obtained from seven clinical studies with EC-MPS and/or MMF. In comparison with the 'classic' two-stage pharmacokinetic analysis, the population pharmacokinetic approach has the advantage that datasets originating from several clinical studies with different sampling schedules can be combined easily. As a result, typical pharmacokinetic parameters and their corresponding interindividual variability (IIV) can be estimated in large, unbalanced and heterogeneous populations.

Patients and Methods

Studies

MPA plasma concentration-time profiles obtained from 259 renal transplant recipients receiving maintenance therapy with either EC-MPS (n = 208 profiles) or MMF (n = 184 profiles) 4–257 months after renal transplantation were combined and analysed simultaneously. The data were obtained from seven different clinical trials[8-10,13-18] and two unpublished studies (table I). All concentration-time data were provided by the respective principal investigators, all of whom are coauthors of this study. The immunosuppressive regimens, number of subjects, number of pharmacokinetic assessments, time after renal transplantation and sampling times after oral administration of the drugs are described in table I. MPA pharmacokinetic profiles were obtained during the daytime. Information with respect to sex, bodyweight, age, serum albumin, serum creatinine and creatinine clearance was not available for all patients. Further details of the studies have been reported elsewhere.[8-10,13-16] Most of the EC-MPS-treated patients were Caucasians in a stable phase after renal transplantation. A comparable group of patients receiving MMF was created by combining data from Caucasian renal transplant patients from a study by Pescovitz et al.[14] and data from patients in the random-

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Table I. Studies included in the dataset

Study	Immunosuppressive drug regimen (no. of PK profiles)	No. of subjects	No. of PK curves	Mean time after transplantation in days (range)	Sampling interval (h)	Sampling times
Hilbrands et al.[a]	EC-MPS + CIC (7)	7	7	2095 (1289–3803)	0–12	12
Neumann et al.[a]	EC-MPS (1) EC-MPS + CIC (6) EC-MPS + TCL (3) EC-MPS + EVL (1)	11	11		0–12	11
Budde et al.[8,9,17,18]	EC-MPS + CIC (43) EC-MPS + CIC + EVL (12) EC-MPS + TCL (42) EC-MPS + TCL + EVL (2) EC-MPS + EVL (9)	47	108	1899 (381–7722)	0–12	10
Cattaneo et al.[15]	EC-MPS + CIC (42)	10	42	525 (180–982)	0–12	12
Tedesco-Silva et al.[13]	EC-MPS + CIC (40) MMF + CIC (40)	40	80	657 (SD 329)	0–12	13
Van Gelder et al.[10,16][b]	MMF + CIC (99)	99	99	140 (127–151)	0–2	5
Pescovitz et al.[14][c]	MMF + CIC (45)	45	45	1183 (235–3795)	0–12	10

a Unpublished data.

b From this study, only data from protocol day 140 was included.

c From this study, only Caucasian renal transplant patients were included in the dataset, since most of the EC-MPS-treated patients were Caucasian.

CIC = ciclosporin; **EC-MPS** = enteric-coated mycophenolate sodium; **EVL** = everolimus; **MMF** = mycophenolate mofetil; **PK =** pharmacokinetic; **TCL** = tacrolimus.

ized concentration controlled trial.[16] Concerning the latter study,[16] only data from protocol day 140 were included in this analysis.

Pharmacokinetic Analysis

The pharmacokinetic data of the patients treated with EC-MPS and/or MMF were pooled. Data from all patients were simultaneously fitted using the nonlinear mixed-effects modelling software program (NONMEM® version VI, level 1.0; GloboMax LLC, Ellicott City, MD, USA). By using NONMEM®, typical pharmacokinetic parameters and their IIV can be estimated for the patient population. In the present study, the first-order method was used, since the first-order conditional estimate method with interaction did not minimize successfully. Since pharmacokinetic parameters for MPA were estimated, all MMF and EC-MPS doses were converted to the equivalent MPA content by multiplying the dose by 0.739 for MMF and by 0.936 for EC-MPS.

In the first step of the population analysis, a compartmental pharmacokinetic model was developed. Typical values for the pharmacokinetic parameters (lag-time [t_{lag}]), absorption rate constant (k_a), volume of distribution of the compartments (V_d), clearance (CL) and intercompartmental clearance (Q) were estimated. Since bioavailability (F) could not be quantified, CL, Q and V_d values of MPA corresponded to the ratios CL/F, Q/F and V_d/F, respectively. IIV for each pharmacokinetic parameter was modelled using an exponential error model (equation 1):

$$CL_i = \theta_{pop} \bullet \exp(\eta_i) \quad \text{(Eq. 1)}$$

where CL_i represents the MPA clearance of the ith individual, θ_{pop} represents the population value for MPA clearance, and η represents the interindividual random effect with a mean of zero and variance of ω^2. The covariance between values for IIV was estimated using a variance-covariance matrix. The concentration data were logarithmically transformed. Residual variability between observed (lnC_{obs}) and predicted (lnC_{pred}) MPA plasma concentrations was described using an additional error model (equation 2):

$$1nC_{obs} = 1nC_{pred} + \varepsilon_i \quad \text{(Eq. 2)}$$

where ε represents the residual random error with a mean of zero and variance of σ^2.

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In NONMEM®, estimation of a change-point parameter, such as the t_{lag}, is difficult, especially when this parameter exhibits large IIV. This estimation problem may be overcome by using a mixture model for the t_{lag}.[19] In this approach, all subjects are directed to a number of subgroups with different typical values for the t_{lag}. Estimation difficulties were further reduced by constraining the t_{lag} with a logit transformation.[20]

In the second part of the modelling procedure, possible differences in pharmacokinetic parameters between MMF and EC-MPS administration were evaluated. Differences were investigated using equation 3:

$$CL_i = \theta_{pop} \bullet \theta^{drug} \quad \text{(Eq. 3)}$$

where drug = 0 for MMF-treated patients and drug = 1 for EC-MPS-treated patients, and θ represents the fractional change in MPA clearance in EC-MPS-treated patients.

The population model was built stepwise. A specific assumption was tested at each step (e.g. a two-compartment model versus a three-compartment model). The main decision criterion was the likelihood ratio test (see Statistical Analysis section). Model adequacy was further evaluated by using various residual plots ('goodness-of-fit' plots) and values of random-effects variances. To analyse the graphical goodness-of-fit, extensive plotting was available through the use of Xpose,[21] a purpose built set of subroutines in S-Plus® version 6.1 software (Insightful Corporation, Seattle, WA, USA).

Bayesian *post hoc* analysis of the developed population model was used to obtain individual estimations of the parameter t_{lag} and the predose concentration following ingestion of EC-MPS and MMF. The t_{lag} values, predose concentrations and the correlation between *post hoc* predose concentrations and MPA exposure were compared between both groups.

Validation

Two procedures were used to validate the final model. As an internal validation method, a bootstrap resampling method was applied.[22] This method has been implemented in the software package Wings for NONMEM® version 612 (Dr N. Holford, March 2007, Auckland, New Zealand). 1000 bootstrap datasets were generated by sampling randomly from the original dataset with replacement. Parameters were estimated for each of the replicate datasets using the final model developed earlier. The validity of the model was evaluated by comparing the median values and 95% percentiles (2.5th–97.5th percentiles) of the bootstrap replicates with the estimates of the original dataset. The final model was further validated by application of a visual predictive check.[23] 100 datasets were simulated from the original dataset using the final model. Per time point, the average simulated concentrations plus 95% confidence intervals were compared graphically with the observed average MPA concentrations.

Statistical Analysis

In NONMEM® modelling, the minimum objective function value (OFV) can be used as a criterion for model selection. If the difference in the OFV between two nested models is larger than the critical value from a chi-squared (χ^2) distribution with degrees of freedom equal to the difference in the number of estimated parameters, the models are significantly different from each other. A decrease in the OFV of >10.83 shows a significant improvement of a nested model with one degree of freedom of $p < 0.001$.

Post hoc values of pharmacokinetic parameters were compared using various statistical tests. Depending on the results of the Kolmogorov-Smirnov test, data were analysed with an unpaired student's t-test and a Mann-Whitney U-test. More than two parameters were compared with an ANOVA or the Kruskal-Wallis test was used. Categorical data were compared using a χ^2 test. Correlation coefficients were determined with a Pearson correlation test. The statistical analyses were performed using SPSS™ version 11.5.0 software for Windows (SPSS Inc., Chicago, IL, USA). Differences between parameters of $p \leq 0.05$ were considered significant.

Results

Data Description

The dataset contained 3764 MPA plasma concentrations obtained from 259 renal transplant recipients. In total, 208 concentration-time profiles were available from patients treated with EC-MPS and 184 from patients treated with MMF. Each patient participated in at least one (median 1, range 1–6) pharmacokinetic assessment of either a 2-hour or a 12-hour AUC at different time points after transplantation. A median of 10 (range 4–15) concentration samples was obtained per AUC. The patient characteristics of both groups are described in table II.

Pharmacokinetic Analysis

Figures 1a and 1b show the observed MPA plasma concentration-time points for EC-MPS- and MMF-treated patients. Some typical concentration-time profiles are shown in figure 2. For both

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Table II. Patient characteristics[a]

Characteristic	EC-MPS	n	MMF	n	p-Value
MPA dose (mg)[b]	674 (337–1348)	208	739 (185–1626)	184	<0.001
Sex (M/F)	117/50	167	89/55	144	0.125
Bodyweight (kg)	76 (40–124)	167	73 (44–108)	144	0.007
Age (y)	45 (21–79)	167	51 (19–74)	144	0.031
Serum creatinine (μmol/L)	156 (71–413)	168	130 (79–280)	143	<0.001
Creatinine clearance (mL/min)	63.0 (27.4–153.4)	166	58.8 (24.9–122.5)	143	0.069
Serum albumin (g/L)	41.3 (27.5–48.1)	167	39.0 (32.0–53.0)	143	0.019
CIC predose (mg/L)	110 (25–700)	109	178 (53–522)	136	<0.001
CIC comedication [n(%)][c]	150 (72)		184 (100)		0.048
TCL comedication [n(%)][c]	47 (23)		0 (0)		<0.001
EVL comedication [n(%)][c]	24 (12)		0 (0)		<0.001

a Data are presented as median (range). Information with respect to sex, bodyweight, age, serum albumin, serum creatinine and creatinine clearance was not available for all patients.

b The amount of the drug was converted to equivalent MPA doses.

c Described as the number of patients cotreated with the drug (percentage of total patients).

CIC = ciclosporin; **EC-MPS** = enteric-coated mycophenolate sodium; **EVL** = everolimus; **F** = female; **M** = male; **MMF** = mycophenolate mofetil; **TCL** = tacrolimus.

formulations, absorption was delayed following ingestion of the drug. Furthermore, in 18 (8.7%) of the profiles of patients taking EC-MPS, MPA predose concentrations were higher than the maximal MPA concentration in the subsequent 12-hour observation period (figure 2b). In all patients receiving MMF, maximum MPA concentrations were higher than predose concentrations.

The concentration-time data of all patients were fitted simultaneously to several pharmacokinetic models. A two-compartment model with first-order elimination adequately described the data. The delayed absorption was characterized by a lag-time and a first-order absorption process (model 1, table III). The latter described absorption better than zero-order absorption, Weibull absorption[24,25] and transit compartments,[26,27] as judged by the OFV and goodness-of-fit plots. Minimization of model 1 was successful in NONMEM®; however, standard errors were not obtained.

Equation 3 was used to evaluate possible differences in pharmacokinetic parameters between EC-MPS- and MMF-treated patients. No significant differences were observed for the volume of

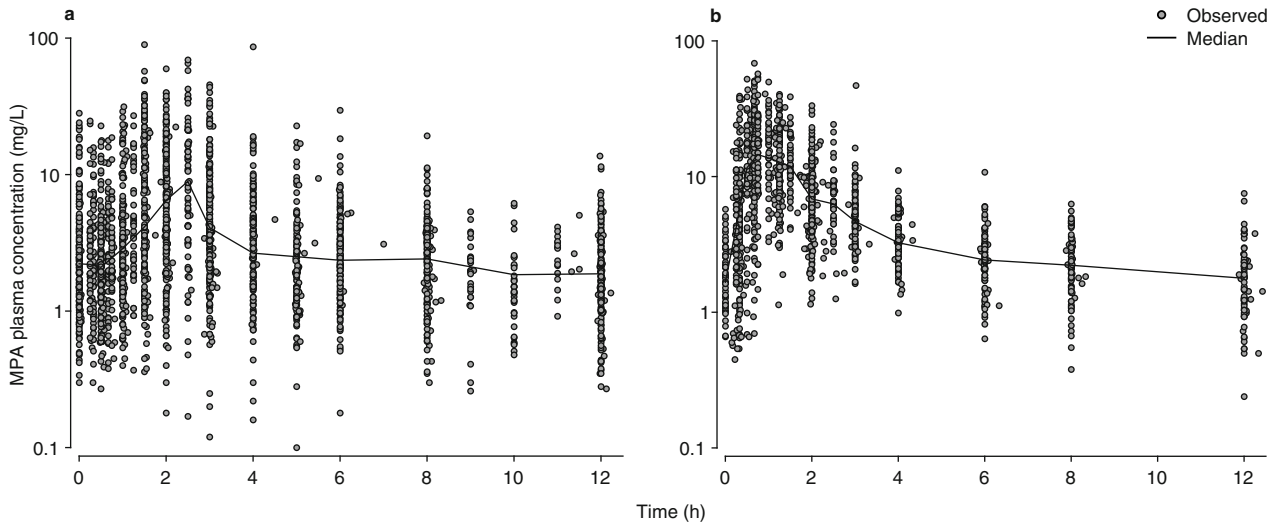

Fig. 1. Observed concentration-time data. Mycophenolic acid (MPA) concentration versus time for (**a**) all patients treated with enteric-coated mycophenolate sodium and (**b**) all patients treated with mycophenolate mofetil.

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distribution of the central compartment (V_1/F), CL/F, the volume of distribution of the peripheral compartment (V_2/F) or Q/F. The t_{lag} was approximately 5-fold longer for EC-MPS than for MMF; the respective values were 0.98 hours and 0.21 hours. Incorporation of the difference in the t_{lag} in model 1 reduced the OFV by 380

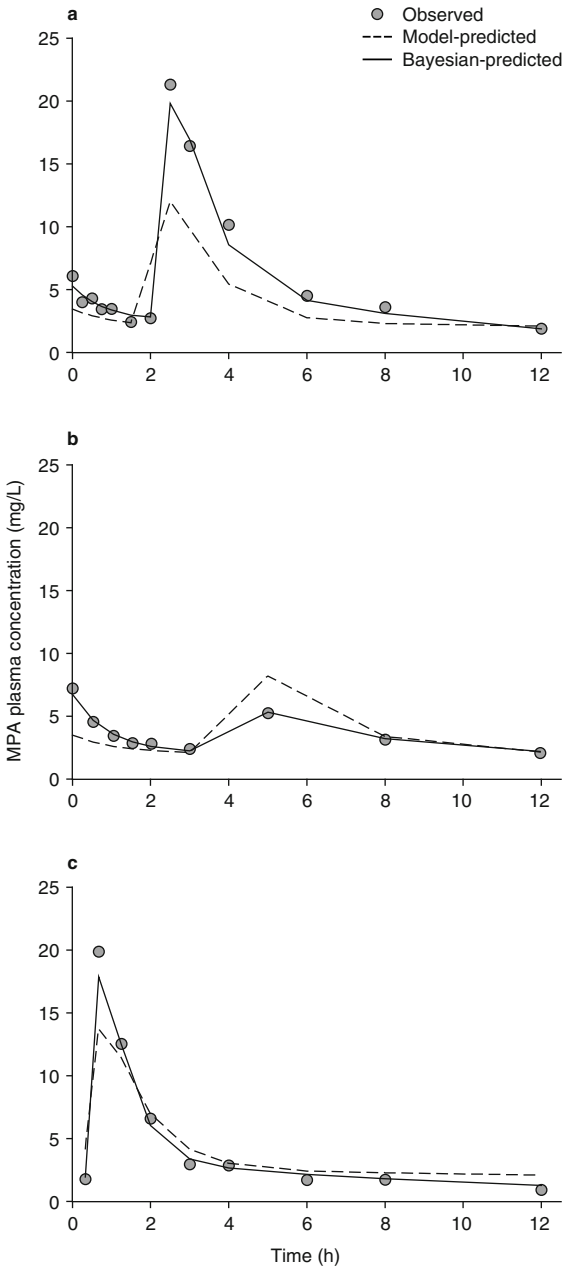

Fig. 2. Observed and predicted characteristic concentration-time profiles. Plots of observed, model-predicted and Bayesian-predicted mycophenolic acid (MPA) concentration versus time from two patients treated with enteric-coated mycophenolate sodium (**a**) and (**b**) and one patient treated with mycophenolate mofetil (**c**). Note that in (**b**), the concentration at time zero was higher than in the following 12-h observation period.

points ($p < 0.001$). Despite the improved fit of the model, goodness-of-fit plots indicated that predose concentrations were underestimated following ingestion of EC-MPS. The inclusion of a separate t_{lag} for the morning and evening doses of EC-MPS significantly improved the model further (model 2, table III, $\Delta OFV = -266$; $p < 0.001$). It should be noted, however, that MPA concentrations were only assessed during the daytime. As a result, the t_{lag} for the evening doses was estimated on the basis of concentration-time points observed before absorption of the morning dose started. No differences were detected in the t_{lag} for the morning and evening doses of MMF. In model 2, the t_{lag} following morning administration of EC-MPS was typically estimated to be 0.97 hours with IIV of 1.1%. Goodness-of-fit plots, however, indicated that these values were underestimated. This underestimation in NONMEM® was due to the difficulty in estimating the change-point parameter t_{lag}, which exhibited considerable IIV. Subsequently, a mixture model was introduced for the t_{lag} of the morning dose of EC-MPS. With an optimum number of three subgroups, a significant decrease in the OFV was obtained when compared with the previous model (model 3, table III, $\Delta OFV = -496$; $p < 0.001$), and also the goodness-of-fit plots showed an improved correlation between predicted and observed concentrations. The introduction of a mixture model on the t_{lag} of the EC-MPS evening dose or MMF did not result in any further improvement of the model. Introduction of a different k_a for MMF and EC-MPS further improved model 3 (model 4, table III, $\Delta OFV = -118$, $p < 0.001$). The k_a was decreased following EC-MPS compared with MMF.

Finally, the model was extended with a bile compartment to describe EHC of MPA.[28] This did not, however, improve the fit of the model to the data. Clearance was not found to be dependent on the use of ciclosporin.

For the final model (model 4, table III), figure 3 depicts the correlations between the observed MPA concentrations, model-predicted MPA concentrations and individual-predicted MPA concentrations, as well as the distribution of the weighted residuals during the dose interval. Data in the model-predicted versus observed (figure 3a) and individual-predicted versus observed (figure 3b) plots are symmetrically distributed around the line of identity, indicating the goodness of the fit. No trends were observed in the weighted residuals versus time plot (figure 3c). The concentration-time curves of the three typical patients were well described by the individual-predicted values (figure 2).

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Table III. Parameter estimates of the pharmacokinetic models

Parameter	Model				Bootstrap	
	1	2	3	4	median	95% percentile (2.5th–97.5th percentile range)
OFV	1328	682	186	68		
t_{lag} EC-MPS and MMF (h)	0.21					
t_{lag} EC-MPS morning 1 (h)		0.97	0.97	0.95	0.96	0.62–0.99
t_{lag} EC-MPS morning 2 (h)			1.88	1.88	1.94	1.39–2.46
t_{lag} EC-MPS morning 3 (h)			4.87	4.83	4.95	3.95–5.98
t_{lag} EC-MPS evening (h)		7.03	8.46	9.04	8.52	2.92–9.29
t_{lag} MMF (h)		0.22	0.30	0.30	0.24	0.18–0.31
k_a EC-MPS and MMF (h^{-1})	1.6	2.4	4.1			
k_a EC-MPS (h^{-1})				3.0	3.9	2.8–5.4
k_a MMF (h^{-1})				4.1	4.1	2.7–5.6
V_1 (L)	62	75	43	40	45	37–58
CL (L/h)	16.2	17.0	16.0	16.0	16.1	14.9–17.2
V_2 (L)	229	430	557	518	394	190–290 775
Q (L/h)	71	32	21	22	22	19–28
POP with t_{lag} EC-MPS morning 1			0.50	0.51	0.51	0.29–0.67
POP with t_{lag} EC-MPS morning 2			0.32	0.32	0.32	0.16–0.53
POP with t_{lag} EC-MPS morning 3			0.18	0.17	0.17	0.23–0.12
Residual error	0.51	0.45	0.41	0.39	0.39	0.36–0.43
Interindividual variability (%)						
t_{lag} EC-MPS and MMF	0.1					
t_{lag} EC-MPS morning	–	1.1	2.9	8.0	1.0	0–14
t_{lag} EC-MPS evening	–	155	57	40	59	35–6000
t_{lag} MMF	–	39	33	11	12	1.0–34
k_a	15 000	310	175	187	200	158–360
V_1	15 100	210	96	100	114	81–172
CL	40	37	38	39	38	33–43
V_2	3 500	410	500	490	390	171–293 500
Q	1 010	105	70	78	71	56–96

CL = clearance; **EC-MPS** = enteric-coated mycophenolate sodium; $\mathbf{k_a}$ = absorption rate constant; **MMF =** mycophenolate mofetil; **OFV** = minimum objective function value; **POP** = part of the population; **Q** = intercompartmental clearance; $\mathbf{t_{lag}}$ = lag-time; $\mathbf{V_1}$ = volume of distribution of the central compartment; $\mathbf{V_2}$ = volume of distribution of the peripheral compartment.

Validation

The original dataset was used to generate 1000 bootstrap datasets, which were fitted with the final model. The estimated pharmacokinetic parameters from the bootstrap analysis compared favourably with the estimations of the final model, indicating the validity of the final model (table III). The visual predictive check (figure 4) revealed an acceptable agreement between the 95% confidence interval band of 100 simulated datasets and the average observed concentration. However, there appeared to be an underprediction of the maximum concentration for EC-MPS and a small overprediction of the MPA concentration at 6 hours for both drugs.

Post Hoc Analysis

Individual Bayesian estimations of the t_{lag} and predose concentrations were compared for the various subgroups. Following EC-MPS ingestion, the t_{lag} was longer than following MMF ingestion (figure 5). The absorption of MPA following the EC-MPS evening dose was remarkably delayed. As a result, the t_{lag} between the EC-MPS morning dose, the EC-MPS evening dose and the MMF dose

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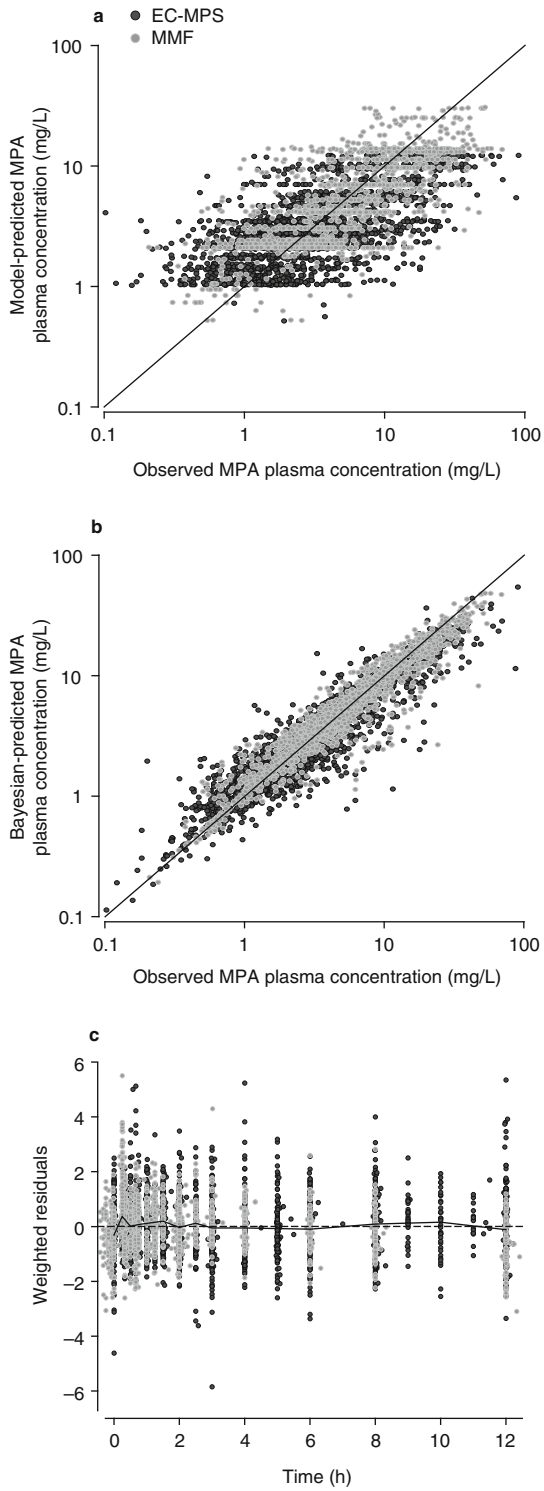

Fig. 3. Goodness-of-fit plots for the final model (model 4). Model-predicted mycophenolic acid (MPA) concentration versus observed MPA concentration (**a**), individual-predicted MPA concentration versus observed concentration (**b**) and weighted residuals versus time (**c**). The solid line in (**a**) and (**b**) is the line of identity. The solid line in (**c**) is the average of the weighted residuals. **EC-MPS** = enteric-coated mycophenolate sodium; **MMF** = mycophenolate mofetil.

was significantly different ($p < 0.001$): the median values and range were 2.0 hours (0.9–5.5 hours), 8.9 hours (5.4–12.3 hours) and 0.30 hours (0.26–0.34 hours), respectively.

Subsequently, the *post hoc* MPA predose concentrations of EC-MPS- and MMF-treated patients were compared (figure 6). The median MPA morning predose concentrations (C_0) (and range) were 2.6 mg/L (0.4–24.4 mg/L) following EC-MPS ingestion and 1.5 mg/L (0.1–4.8 mg/L) following MMF ingestion. The evening predose concentrations (C_{12}) were 1.6 mg/L (0.1–4.8 mg/L) for EC-MPS-treated patients and 2.1 mg/L (0.2–6.2) for MMF-treated patients. C_0 values of EC-MPS-treated patients were almost 2-fold higher than EC-MPS C_{12} values and MMF C_0 values ($p < 0.05$).

Figure 7 shows the correlation between MPA predose concentrations and the MPA AUC. The correlation coefficient was higher in MMF treated-patients ($r^2 = 0.48$; $p < 0.001$) than in EC-MPS-treated patients ($r^2 = 0.02$; $p < 0.001$).

Discussion

This is the first study in which a population pharmacokinetic model was developed for MPA in patients receiving either MMF or EC-MPS. Application of nonlinear mixed-effects modelling allowed combination of heterogeneous datasets and assessment of pharmacokinetic parameters in a large population of 259 renal transplant patients. In the present study, clinically relevant differences in absorption pharmacokinetics were observed between the two formulations. Differences in the pharmacokinetic profile of MPA between both drugs have been described earlier, but only with a limited number of patients ($n \leq 40$).[7-9,15]

The final model and pharmacokinetic parameters were comparable with previously published models for MPA in patients using MMF.[29-31] In other population pharmacokinetic studies in renal transplant patients taking MMF, absorption of MPA was characterized by a double absorption-phase model[32] or zero-order absorption.[33] In the present study, implementation of these absorption characteristics models did not improve the fit of the model to the data, as indicated by the minimum objective function and the goodness-of-fit plots. Weibull absorption or transit compartment absorption did not improve the model either.[24-27]

The absorption of MPA was more delayed and variable in EC-MPS-treated patients than in MMF-treated patients. Furthermore, the absorption of MPA was slower following EC-MPS ingestion. These differences resulted in higher MPA predose concentrations in EC-MPS-treated patients. In earlier studies,[7-9,15] higher MPA predose concentrations and lower and delayed maximum concentrations were reported for EC-MPS. The present analysis demon-

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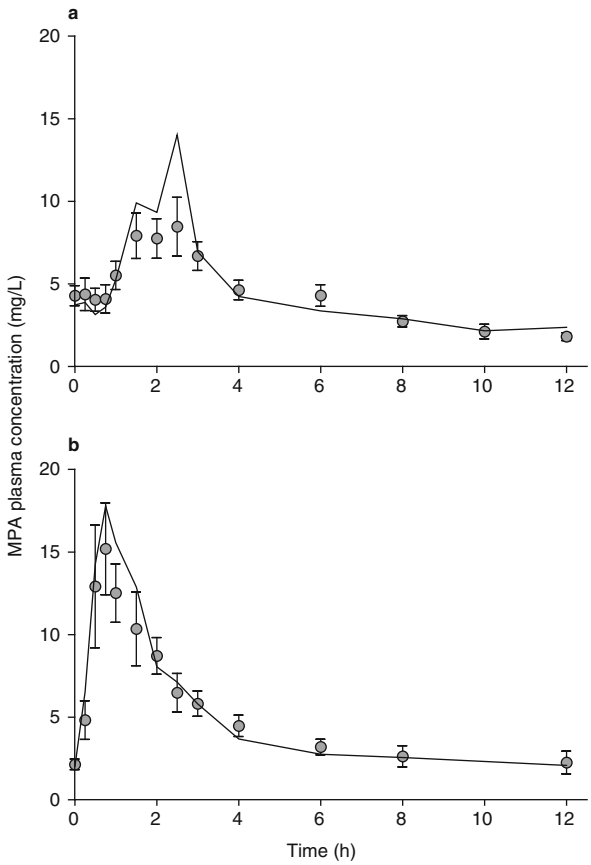

Fig. 4. Visual predictive check. Comparison of 100 simulated datasets (mean ± 95% confidence interval) with the average observed concentrations (solid line) for enteric-coated mycophenolate sodium (**a**) and mycophenolate mofetil (**b**). The 100 datasets were simulated on the basis of the final model.

strated that this is explained by a longer t_{lag} and slower absorption following ingestion of EC-MPS. Clearly, MPA absorption is delayed in patients using EC-MPS due to the enteric coating of the drug. Moreover, the formulation of the drug produces greater IIV in the t_{lag} for EC-MPS than for MMF (figure 5).

Interestingly, the t_{lag} was estimated to be longer for the evening dose than for the morning dose (figure 5). As a result, in a considerable number of patients, the predose concentrations were comparable with the maximal concentration observed following the morning dose (figure 2b). The longer t_{lag} for the evening dose is likely to be the result of the circadian effect of gastric emptying. Gastric emptying has been reported to be delayed by 53.6% in the evening.[34] Two studies[35,36] in Japanese renal transplant recipients treated with MMF showed delayed MPA absorption at night compared with the daytime.

The rate of absorption of MPA was lower in EC-MPS-treated patients than in MMF-treated patients (3.0 vs 4.1 h^{-1}). This difference was independent of the observed differences in the t_{lag}. Nevertheless, the absorption of MPA was fast in both formulations, with absorption half-lives of 0.23 hours for EC-MPS and 0.17 hours for MMF. As a result, the observed differences in the rate of absorption will not be clinically relevant.

An alternative explanation for the high predose concentration could be the presence of EHC following the evening dose of EC-MPS. An attempt was made to include EHC in the model, but the dataset did not contain information allowing accurate description of the recirculation process. In case of cotreatment with ciclosporin, EHC may be decreased by ciclosporin-reduced inhibition of the multidrug resistance-associated protein 2 (MRP2) enzyme. MRP2 has been reported to be responsible for the excretion of MPAG in bile.[37] It has been indicated that elevated MPAG concentrations increase clearance of MPA through interaction at the protein-binding site.[38,39] The possible effect of ciclosporin cotreatment on MPA clearance was tested in the population model. However, no significant influence of ciclosporin on MPA clearance was detected.

In this study, EC-MPS- and MMF-treated patients exhibited different demographic and pathophysiological characteristics. In a previous study, the relationship between patient characteristics and pharmacokinetic parameters was extensively studied.[30] In this study, exposure to MPA was reported to be significantly influenced by renal function, albumin and haemoglobin levels and the ciclosporin predose concentration. In the present study, albumin levels were different in both groups. However, this small

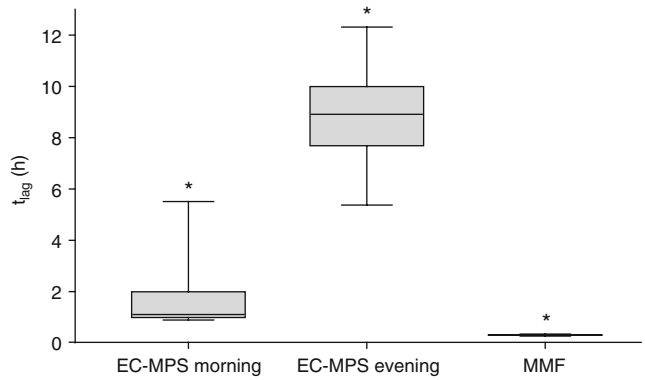

Fig. 5. Delay in mycophenolic acid absorption. Box plot of Bayesian-predicted lag-time (t_{lag}) following ingestion of the morning and evening doses of enteric-coated mycophenolate sodium (EC-MPS) and ingestion of mycophenolate mofetil (MMF; there was no difference between the morning and evening doses). The box represents the median and the 25th and 75th percentiles of the data. The whiskers represent the range. * indicates a significant difference from the other groups ($p < 0.001$).

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difference (41.3 vs 39.0 g/L) was not considered to be of clinical relevance. Cotreatment with ciclosporin was tested as a covariate of the final model but showed no significant influence.

No deviations were present in the plot of weighted residuals versus time (figure 3c). However, in the visual predictive check, a small overestimation was observed at 6 hours, which was probably caused by the presence of EHC in some patients. It should be noted that in the present study, samples were only collected following the morning dose. A better insight into possible diurnal variation of absorption or the possible contribution of EHC should be obtained by taking samples after the evening dose as well.

A mixture model was needed to describe the variability in the t_{lag}. NONMEM® software handles the t_{lag} as a change-point parameter, which causes an abrupt increase in the absorption rate at a certain time point. This nonphysical approach makes it difficult for NONMEM® to estimate the exact change-point and especially the variability of the parameter. A mixture model makes it possible to estimate the amount of variability by dividing the population into subgroups. A transit absorption model (with serial compartments) may also be used to avoid the estimation problem of the t_{lag}.[26,27] However, in the present study, implementation of this model did not produce realistic estimations. Through implementation of the mixture model for the t_{lag} following the morning dose of EC-MPS in the model, variability in this parameter could adequately be described. Furthermore, it allowed the estimation of individual t_{lag} values and predose concentrations by Bayesian *post hoc* analysis. Morning predose concentrations were 2.6 mg/L for EC-MPS and 1.6 mg/L for MMF (figure 6). The higher MPA predose concentrations in patients taking EC-MPS can be explained by the delayed absorption, especially following the evening dose, and its corresponding IIV. As a result, MPA morning predose concentrations ranged from 0.2 to 7.6 mg/L for MMF and from 0.4 to 24.4 mg/L for EC-MPS. Budde et al.[40] previously reported similar results; MPA predose concentrations were 31.1% higher with EC-MPS (2.40 mg/L) than with MMF (1.83 mg/L), with increased interindividual (123% vs 76%) and intraindividual variability (64% vs 42%).

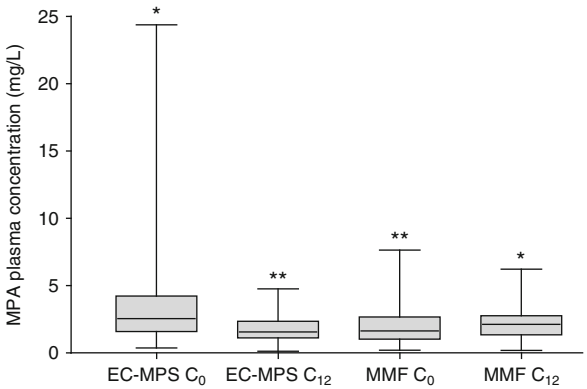

Fig. 6. Predose levels of mycophenolic acid (MPA). Box plot of Bayesian-predicted MPA predose concentrations in the morning (C_0) and evening (C_{12}) for patients using enteric-coated mycophenolate sodium (EC-MPS) and mycophenolate mofetil (MMF). The box represents the median and the 25th and 75th percentiles of the data. The whiskers represent the range. * indicates a significant difference from the predose concentration of all other groups ($p < 0.05$). ** indicates a significant difference from the EC-MPS C_0 and the MMF C_{12} ($p < 0.05$).

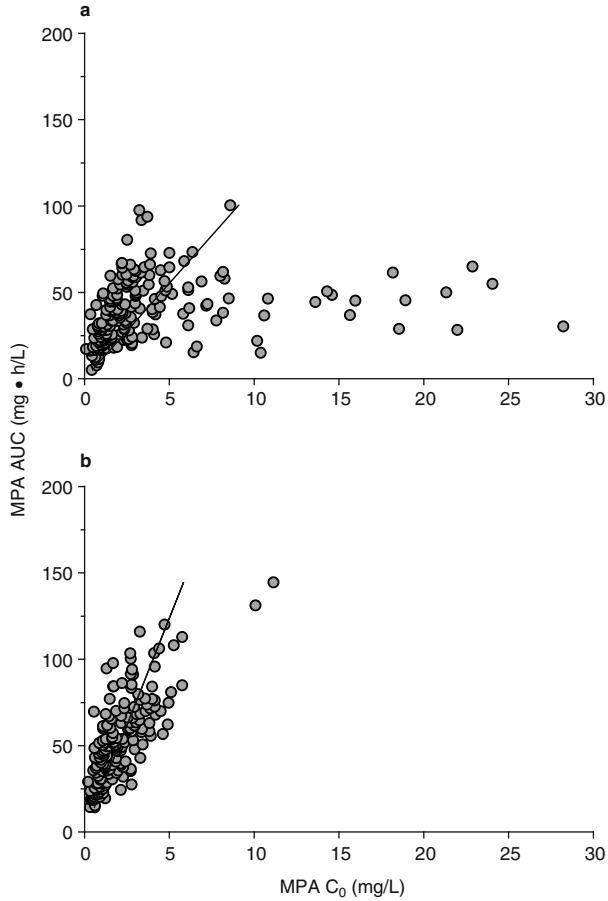

Fig. 7. Correlation of the area under the plasma concentration-time curve (AUC) and mycophenolic acid (MPA) predose concentration (C_0). Correlation between the MPA AUC and the MPA C_0 following administration of enteric-coated mycophenolate sodium [$r^2 = 0.02$; $p<0.001$] (**a**) and mycophenolate mofetil [$r^2 = 0.48$; $p < 0.001$] (**b**). The solid line represents the trendline.

The increased IIV in the t_{lag}, rate of absorption and predose concentrations has important implications for the application of TDM in patients using EC-MPS. Greater variability explains the poor relationship between MPA predose concentrations and the AUC in EC-MPS-treated patients (r^2 0.02 vs 0.48). Budde et al.[40] also compared this correlation between EC-MPS and MMF and reported comparable results (r^2 0.16 vs 0.45). Because AUC

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measurements are more difficult to perform in clinical practice, limited sampling strategies or *a posteriori* Bayesian algorithms are alternatives to accomplish reliable estimations of the MPA AUC in MMF-treated renal transplant recipients.[41,42] The relevance of TDM with such Bayesian algorithms was recently demonstrated by Le Meur and colleagues.[12,43] Because of the unpredictability of the absorption time, development of a practically applicable limited sampling strategy for EC-MPS will be impracticable. A complete AUC from time zero to 12 hours (AUC_{12}) is likely to be necessary to obtain reliable estimates of MPA exposure in patients treated with EC-MPS. This will limit the feasibility of TDM for this drug.

Conclusion

A population pharmacokinetic model has been developed in which the pharmacokinetics of MPA following oral administration of both EC-MPS and MMF were compared. Following ingestion of EC-MPS, absorption of MPA into the central circulation was slower and more delayed in comparison with MMF. Moreover, the IIV of the t_{lag} was greater in EC-MPS-treated patients. As a consequence, MPA predose concentrations reflect MPA exposure even worse in patients using EC-MPS than in patients using MMF. It is expected that clinically feasible limited sampling strategies will not reliably reflect MPA exposure in patients taking EC-MPS, because of the unpredictable absorption profile of EC-MPS.

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