Pharmacokinetics of mycophenolic acid and its phenyl glucuronide metabolite in kidney transplant recipients with renal impairment

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Abstract

Introduction: The aim of the study was to analyse the influence of renal impairment on the pharmacokinetic parameters (PK) of mycophenolic acid (MPA) and its glucuronide metabolite (MPAG) in renal transplant recipients.
Material and methods: The study included 43 adult patients during the maintenance period (> 6 months) following renal transplantation, treated with mycophenolate mofetil (MMF), calcineurin inhibitors (CNI) (tacrolimus or cyclosporine) and steroids. The study compared patients with normal renal function (n = 17; creatinine clearance (C_{cr}) > 60 ml/min) and with renal impairment (n = 26; C_{cr} < 60 ml/min). Areas under the 4-h curve ($AUC_{0\text{-}4\ h}$) of MPA and MPAG were determined using a validated HPLC method.
Results: The renal impairment group showed significantly increased $AUC_{0\text{-}4\ h}$ and pre-dose (C_0) for MPAG compared to patients with normal renal function and increased MPA C_0. However, there was no significant difference in MPA $AUC_{0\text{-}4\ h}$ between patients with renal impairment and patients with normal renal function. In multivariate analysis some MPA and MPAG PK parameters were correlated with sex, CNI co-administered and body weight.
Conclusions: Although MPAG is an inactive metabolite, its accumulation in patients with renal impairment can be unfavourable. The results of our study indicate that solely MPA C_0 determination in patients receiving MMF may be insufficient in clinical practice because of great inter-patient variability of this PK parameter caused mainly by enterohepatic recirculation.

Key words: kidney transplantation, immunosuppressive agents, mycophenolate mofetil metabolites, pharmacokinetics, renal impairment.

Introduction

Mycophenolate mofetil (MMF, CellCept®) is the most widely used antiproliferative immunosuppressive drug in patients after solid organ transplantation, often co-administered with calcineurin inhibitors (CNI) and corticosteroids [1].

Pharmacologically inactive MMF after oral administration is rapidly and entirely hydrolysed into an active metabolite – mycophenolic acid (MPA). The MPA is a non-nucleoside, uncompetitive and reversible inosine monophosphate dehydrogenase inhibitor, which participates in guanosine triphosphates *de novo* synthesis. As a consequence, MPA inhibits the

proliferation of T and B lymphocytes, preventing the acute rejection of a transplanted organ as well as decreasing the frequency of late rejection after one year and consecutive years [2, 3]. The MPA undergoes enterohepatic recirculation. It is converted into an inactive phenyl glucuronide (MPAG), which is excreted into bile and hydrolysed into MPA in the presence of β-glucuronidase, produced by intestinal bacteria, and subsequently reabsorbed in the intestines. It was found that, on average, the enterohepatic recirculation takes part in about 40% (10-60%) of the entire MPA exposure [4].

The MPA as well as MPAG pharmacokinetics (PK) show great inter-patient variability depending on race, sex, concomitant clinical condition (e.g. kidney or liver impairment, diseases with coexisting hypoalbuminaemia), interactions with drugs influencing the PK of MPA and MPAG, time elapsed after renal transplantation and pharmacogenetic factors [4-6].

The MPAG is eliminated mainly by the kidney and the increase of its concentration may indicate the deterioration of renal function. Compared to patients with normal renal function, MPAG concentration in patients with impaired renal function is several times greater. Uncontrolled MPAG concentration increase causes MPA displacement from protein compounds and the increase of free MPA, which might be the cause of higher pharmacological activity of the drug and the intensification of its adverse effects. The influence of renal failure on total MPA concentration is still unclear. There are no unequivocal recommendations for MMF dosing in patients with renal failure [4, 7, 8].

The aim of the study was to analyse the influence of renal impairment on the PK of MPA and its metabolite MPAG in renal transplant recipients.

Material and methods

Forty-three adult patients during the maintenance period (> 6 months) following renal transplantation receiving MMF in combination with cyclosporine (CsA) (n = 21) or tacrolimus (Tac) (n = 22) and corticosteroids were considered. The MMF dose varied from 0.50 g/day to 2.00 g/day and was administered most often twice a day. The study included patients with normal renal function (n = 16; creatinine clearance (C_{cr}) > 60 ml/min) and with renal impairment (n = 27, C_{cr} < 60 ml/min). Clinical characteristics of the patients are presented in Table I. Blood samples were collected into tubes containing EDTA at the following time points: before the morning dose of MMF (C_0), and subsequently 40 min, 1, 2, 3, 4 h after dosing.

Plasma MPA and MPAG concentrations were determined using a high-performance liquid chromatography (HPLC) method described previously [9, 10]. Briefly, the separation was performed using a Supelcosil™ LC-18-DB column. The mobile phase consisted of acetonitrile and orthophosphoric acid (50 mmol/l) in a 50 : 50 ratio and indomethacin was used as an internal standard. The MPAG plasma concentration was estimated after MPAG enzymatic hydrolysis into MPA in β-glucuronidase presence (activity 89.4 U/ml). The MPAG concentrations were

Table I. Characteristics of study patients

Number of patients	All (n = 43)	C_{cr} > 60 ml/min (n = 17)	C_{cr} < 60 ml/min (n = 26)
Male/female	23/20	11/6	12/14
CsA/Tac	21/22	8/9	13/13
Corticosteroid use	36	12	24
Proteinuria (yes/no)	9/34	1/16	8/18
Median (range)			
Age [years]	44 (23-69)	44 (24-57)	44 (23-69)
Time after transplantation [years]	4.1 (0.6-10.9)	3.8 (0.6-10.8)	4.4 (1.2-10.9)
Body weight [kg]	74 (44-109)	75 (47-109)	73.5 (44-105)
Body mass index [kg/m^2]	25.2 (16.1-36.8)	25.8 (21.2-36.5)	23.7 (16.1-36.8)
Body surface area [m^2]	1.86 (1.37-2.35)	1.89 (1.37-2.35)	1.85 (1.39-2.22)
MMF dose [g/day]	1.50 (0.50-2.00)	1.00 (1.00-2.00)	1.50 (0.50-2.00)
CsA dose [mg/day]	175 (75-275)	162.5 (100-250)	175 (75-275)
Tac dose [mg/day]	4 (1-12)	4 (1-12)	4 (2-9)
Serum creatinine [mg/dl]	1.7 (0.8-4.8)	1.3 (0.8-1.7)	2.1 (1.0-4.8)*
C_{cr} [ml/min]**	53.7 (20.4-114.7)	75.2 (60.5-114.7)	44.9 (20.4-59.7)*

*C_{cr} – creatinine clearance, CsA – cyclosporine, Tac – tacrolimus, MMF – mycophenolate mofetil, *p < 0.05, patients with C_{cr} > 60 ml/min vs. < 60 ml/min, Mann-Whitney test, **estimated by the Cockcroft-Gault equation*

calculated as a result of subtraction of MPA molar concentration before the hydrolysis from MPA concentration after the enzymatic hydrolysis (C_{MPAG} = $C_{MPA\ after\ enzymatic\ hydrolysis} - C_{MPA\ before\ hydrolysis}$). The MPAG was generously supplied by Roche Pharmaceuticals (Palo Alto, CA).

The analysis method had a linear range of 0.1-25.0 µg/ml and 10-250 µg/ml for MPA and MPAG, respectively. Accuracy of MPA and MPAG batches ranged from 97.4% to 106.4% and from 96.5% to 116.6%, respectively, and the precision, expressed as the percentage of coefficient of variation (% CV), ranged from 0.8% to 6.9% and from 0.9% to 17.4%, respectively.

The following PK parameters for MPA and MPAG were calculated: pre-dose concentration (C_0), maximum concentration (C_{max}) and area under the plasma concentration – time curve from 0 to 4 h ($AUC_{0\text{-}4\ h}$) using the linear trapezoidal rule. Inter-patient variability was assessed as % CV. C_{cr} was estimated using the Cockcroft-Gault formula.

All statistical tests were performed using Statistica software version 8.0 and p value < 0.05 was considered significant. Chi-square test was used for the evaluation of qualitative data. Normality was determined by Shapiro-Wilk W test. Data were evaluated by the Mann-Whitney test and Spearman correlation analysis. Multivariate analysis was performed to evaluate the influence of various clinical determinants on MPA and MPAG PK parameters. For multivariate analysis both PK parameters corrected and uncorrected for MMF dose were examined. In the remaining analyses only dose-corrected values were considered.

The study was performed following the recommendations of the Declaration of Helsinki and approved by the Bioethical Commission at the Poznan University of Medical Sciences. Informed consent was obtained from all patients prior to initiating the study.

Results

The two groups of patients (with C_{cr} above or below 60 ml/min) were comparable for sex, age, time elapsed after renal transplantation, body weight, MMF dose and for number of patients receiving CsA or Tac. For groups with normal and impaired renal function, medians of serum creatinine were 1.3 mg/dl and 2.1 mg/dl, respectively, and median C_{cr} 75.2 ml/min and 44.9 ml/min, respectively.

The MPA C_0 values were significantly higher in patients with impaired renal function than in patients with normal renal function. However, $AUC_{0\text{-}4\ h}$ and C_{max} values were not significantly different between the two groups (Figure 1, Table II). Moreover, the values of PK parameters for MPAG ($AUC_{0\text{-}4\ h}$, C_0 and C_{max}) were also significantly higher in patients with impaired renal function (Table II). Comparable differences for MPA and MPAG PK parameters were observed between groups in particular immunosuppressive regimens; however, the differences for MPA C_0 values were barely significant (Table III).

In univariate analysis, MPAG PK parameters ($AUC_{0\text{-}4\ h}$, C_0, C_{max}) were negatively correlated with C_{cr} and positively correlated with serum creatinine (Figure 2). Within MPA PK parameters, only C_0 was negatively correlated with C_{cr} and positively correlated with serum creatinine. Similar correlations were found in particular immunosuppressive regimens, although the serum creatinine correlation with MPA C_0 in patients receiving MMF in combination with CsA was statistically insignificant (Table IV).

In multivariate analysis the results are consistent with univariate analysis. Additionally, some MPA and MPAG PK parameters were correlated with sex, CNI co-administered and body weight. No correlations with proteinuria were observed (Tables V and VI).

For MPA and MPAG PK parameters, high CV values were observed, which in patients with impaired

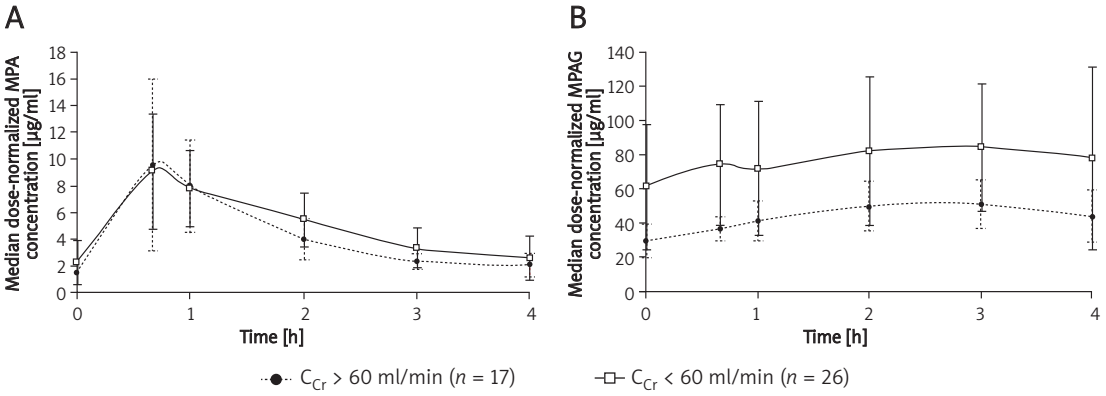

Figure 1. Dose-corrected (**A**) mycophenolic acid (MPA) and (**B**) mycophenolic acid glucuronide (MPAG) concentration-time profiles classified by renal function (creatinine clearance (C_{cr}) > 60 ml/min vs. < 60 ml/ min). The results are presented as median ± standard deviation. Concentrations are corrected to a daily dose of 1 g mycophenolate mofetil

Table II. Dose-corrected PK parameters* of MPA and MPAG classified by renal function

Parameter	All (n = 43)	CV (%)	C_{cr} > 60 ml/min (n = 17)	CV (%)	C_{cr} < 60 ml/min (n = 26)	CV (%)	Value of p**
MPA							
$AUC_{0\text{-}4\ h}$ [µg × h/ml]	19.40 (8.71-35.46)	31.0	19.01 (14.45-30.48)	23.4	21.25 (8.71-35.46)	34.7	0.285
C_0 [µg/ml]	1.93 (0.44-5.26)	60.4	1.48 (0.44-2.39)	43.3	2.24 (0.50-5.26)	55.6	0.010
C_{max} [µg/ml]	10.35 (3.74-24.13)	40.9	10.35 (5.50-24.13)	42.0	10.07 (3.74-18.92)	39.9	0.650
MPAG							
$AUC_{0\text{-}4\ h}$ [µg × h/ml]	235.68 (112.67-857.26)	57.0	172.47 (112.67-306.15)	29.3	299.94 (170.11-857.26)	47.8	< 0.001
C_0 [µg/ml]	36.44 (8.26-185.90)	72.9	29.65 (8.26-53.63)	41.8	61.01 (29.63-185.90)	60.8	< 0.001
C_{max} [µg/ml]	68.21 (33.95-240.30)	58.2	50.94 (33.95-87.49)	27.6	103.92 (44.81-240.30)	47.6	< 0.001

*PK – pharmacokinetic, MPA – mycophenolic acid, MPAG – 7-O-mycophenolic acid glucuronide, CV – coefficient of variation, C_{cr} – creatinine clearance, AUC – area under the concentration-time curve, C_0 – pre-dose concentration, C_{max} – maximum concentration, *the results are presented as median (range), **comparison between patients with C_{cr} > 60 ml/min and < 60 ml/min, Mann-Whitney test*

Table III. Dose-corrected PK parameters* of MPA and MPAG in patients treated with Tac or CsA classified by renal function

	Tac (n = 22)		Value of p*	CsA (n = 21)		Value of p**
	C_{cr} > 60 ml/min (n = 9)	C_{cr} < 60 ml/min (n = 13)		C_{cr} > 60 ml/min (n = 8)	C_{cr} < 60 ml/min (n = 13)	
MPA						
$AUC_{0\text{-}4\ h}$ [µg × h/ml]	19.96 (14.83-30.48)	21.91 (11.83-35.46)	0.537	16.51 (14.45-23.71)	20.58 (8.71-32.47)	0.311
C_0 [µg/ml]	1.98 (0.73-2.30)	2.46 (0.76-5.26)	0.037	1.11 (0.44-2.39)	1.90 (0.50-4.37)	0.060
C_{max} [µg/ml]	13.96 (5.50-24.13)	9.20 (5.63-18.92)	0.643	8.90 (6.20-18.08)	10.49 (3.74-17.17)	0.717
MPAG						
$AUC_{0\text{-}4\ h}$ [µg × h/ml]	189.06 (112.67-229.25)	298.05 (170.11-588.54)	0.014	168.36 (124.12-306.15)	359.29 (195.42-857.26)	0.002
C_0 [µg/ml]	31.06 (10.70-42.47)	39.07 (29.63-133.84)	0.014	25.66 (8.26-53.63)	66.80 (33.99-185.90)	0.003
C_{max} [µg/ml]	50.94 (33.95-68.21)	100.43 (44.81-226.41)	0.021	52.13 (39.77-87.49)	115.50 (61.67-240.30)	0.002

*PK – pharmacokinetic, MPA – mycophenolic acid, MPAG – 7-O-mycophenolic acid glucuronide, Tac – tacrolimus, CsA – cyclosporine, C_{cr} – creatinine clearance, AUC – area under the concentration-time curve, C_0 – pre-dose concentration, C_{max} – maximum concentration, *the results are presented as median (range), **comparison between patients with C_{cr} > 60 ml/min and < 60 ml/min, Mann-Whitney test*

renal function exceeded 30% for all PK parameters evaluated. The CV values were lower for MPA $AUC_{0\text{-}4\ h}$ compared to MPA C_0 (Table II).

Discussion

In our study we analysed the influence of renal function on MPA and MPAG PK in patients during the maintenance period following renal transplantation. The concentrations of both MMF metabolites (MPA and MPAG) varied widely, particularly in patients with impaired renal function, despite MMF dose correction. Similar variability was also presented by other authors [11-13].

Total drug exposure is best demonstrated by $AUC_{0\text{-}12\ h}$. In clinical practice this parameter is difficult to assess, especially in patients treated in clinics during the maintenance period following renal transplantation. In our study, blood samples were collected within 4 h after drug administration due to the short duration of the patient's stay in hospital during a routine appointment in a transplant

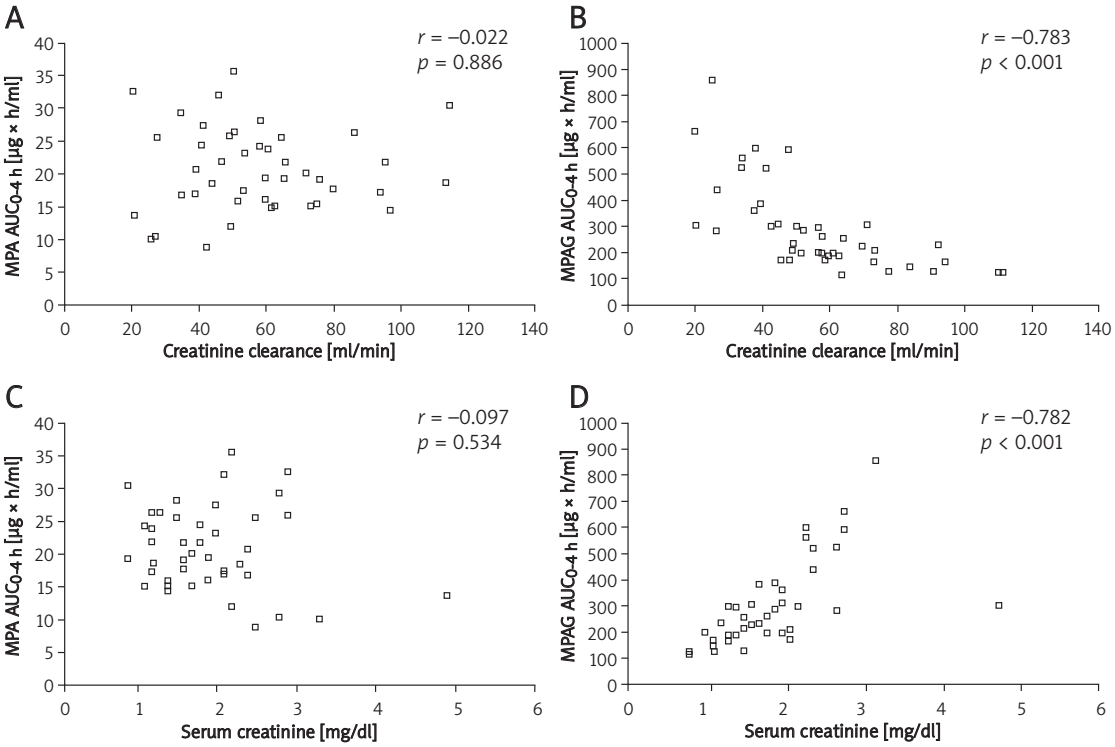

Figure 2. Correlation between creatinine clearance (**A-B**) or serum creatinine (**C-D**) and mycophenolic acid (MPA) or mycophenolic acid glucuronide (MPAG) area under the curve (AUC) in renal transplant recipients

Table IV. Spearman's rank correlation between creatinine clearance or serum creatinine and PK parameters of MPA and MPAG in patients treated with Tac or CsA

	All (n = 43)		Tac (n = 22)		CsA (n = 21)	
	r	p	r	p	r	p
Creatinine clearance [ml/min]						
MPA						
$AUC_{0\text{-}4\ h}$ [µg × h/ml]	–0.023	0.886	0.068	0.763	–0.178	0.440
C_0 [µg/ml]	–0.406	0.007	–0.494	0.019	–0.460	0.036
C_{max} [µg/ml]	0.202	0.194	0.289	0.193	0.043	0.854
MPAG						
$AUC_{0\text{-}4\ h}$ [µg × h/ml]	–0.783	< 0.001	–0.668	< 0.001	–0.860	< 0.001
C_0 [µg/ml]	–0.793	< 0.001	–0.702	< 0.001	–0.849	< 0.001
C_{max} [µg/ml]	–0.724	< 0.001	–0.589	0.004	–0.848	< 0.001
Serum creatinine [mg/dl]						
MPA						
$AUC_{0\text{-}4\ h}$ [µg × h/ml]	–0.098	0.534	–0.078	0.730	–0.127	0.584
C_0 [µg/ml]	0.333	0.029	0.494	0.020	0.208	0.365
C_{max} [µg/ml]	–0.258	0.095	–0.312	0.158	–0.152	0.510
MPAG						
$AUC_{0\text{-}4\ h}$ [µg × h/ml]	0.782	< 0.001	0.756	< 0.001	0.810	< 0.001
C_0 [µg/ml]	0.739	< 0.001	0.691	< 0.001	0.762	< 0.001
C_{max} [µg/ml]	0.713	< 0.001	0.625	0.002	0.816	< 0.001

PK – pharmacokinetic, MPA – mycophenolic acid, MPAG – 7-O-mycophenolic acid glucuronide, Tac – tacrolimus, CsA – cyclosporine, AUC – area under the concentration-time curve, C_0 – pre-dose concentration, C_{max} – maximum concentration

Table V. Multivariate analysis of clinical parameters influencing MPA PK parameters

Independent variables	Relation	Partial value of *p*	Model value of *p*	Model *R* coefficient
MPA C_0 [mg/l]				
Sex [men/women]	NS	0.138	0.003	0.544
CNI [CsA/Tac]	NS	0.064		
MMF dose [g]	Positive	0.022		
C_{cr} [ml/min]	Negative	0.008		
MPA C_0 [mg/l]				
MMF dose [g]	NS	0.075	0.033	0.435
C_{cr} [ml/min]	NS	0.055		
Proteinuria [yes/no]	NS	0.562		
MPA $AUC_{0\text{-}4\ h}$ [mg × h/l]				
Sex [men/women]	Positive	0.017	< 0.001	0.593
MMF dose [g]	Positive	< 0.001		
C_{cr} [ml/min]	NS	0.694		
MPA $AUC_{0\text{-}4\ h}$ [mg × h/l]				
MMF dose [g]	Positive	< 0.001	0.001	0.569
C_{cr} [ml/min]	NS	0.420		
Proteinuria [yes/no]	NS	0.682		
MPA C_{max} [mg/l]				
Body weight [kg]	NS	0.055	0.007	0.438
MMF dose [g]	Positive	0.002		
C_{cr} [ml/min]	Positive	0.039		
MPA C_{max} [mg/l]				
MMF dose [g]	Positive	0.001	0.003	0.532
C_{cr} [ml/min]	Positive	0.046		
Proteinuria [yes/no]	NS	0.372		
MPA C_0 /dose [mg/l/g]				
Sex [men/women]	NS	0.173	< 0.001	0.565
CNI [CsA/Tac]	Negative	0.007		
C_{cr} [ml/min]	Negative	0.004		
MPA C_0 /dose [mg/l/g]				
C_{cr} [ml/min]	Negative	0.042	0.098	0.323
Proteinuria [yes/no]	NS	0.792		
MPA $AUC_{0\text{-}4\ h}$/dose [mg × h/l/g]				
Sex [men/women]	Positive	0.017	0.015	0.449
CNI [CsA/Tac]	NS	0.061		
C_{cr} [ml/min]	NS	0.613		
MPA $AUC_{0\text{-}4\ h}$/dose [mg × h/l/g]				
C_{cr} [ml/min]	NS	0.565	0.582	0.159
Proteinuria [yes/no]	NS	0.466		
MPA C_{max}/dose [mg/l]				
Body weight [kg]	Negative	0.012	0.036	0.332
C_{cr} [ml/min]	NS	0.055		

Table V. Cont.

Independent variables	Relation	Partial value of *p*	Model value of *p*	Model *R* coefficient
MPA C_{max}/dose [mg/l]				
C_{cr} [ml/min]	NS	0.061	0.066	0.349
Proteinuria [yes/no]	NS	0.307		

MPA – mycophenolic acid, PK – pharmacokinetic, C_0 – pre-dose concentration, NS – not significant, CNI – calcineurin inhibitor, CsA – cyclosporine, Tac – tacrolimus, MMF – mycophenolate mofetil, C_{cr} – creatinine clearance, AUC – area under the concentration-time curve, C_{max} – maximum concentration

Table VI. Multivariate analysis of clinical parameters influencing MPAG PK parameters

Independent variables	Relation	Partial value of *p*	Model value of *p*	Model *R* coefficient
MPAG C_0 [mg/l]				
Sex [men/women]	Positive	< 0.001	< 0.001	0.842
Body weight [kg]	Positive	< 0.001		
MMF dose [g]	Positive	< 0.001		
C_{cr} [ml/min]	Negative	< 0.001		
MPAG C_0 [mg/l]				
MMF dose [g]	Positive	< 0.001	< 0.001	0.704
C_{cr} [ml/min]	Negative	< 0.001		
Proteinuria [yes/no]	NS	0.191		
MPAG $AUC_{0\text{-}4\ h}$ [mg × h/l]				
Sex [men/women]	Positive	< 0.001	< 0.001	0.847
Body weight [kg]	Positive	< 0.001		
MMF dose [g]	Positive	< 0.001		
C_{cr} [ml/min]	Negative	< 0.001		
MPAG $AUC_{0\text{-}4\ h}$ [mg × h/l]				
MMF dose [g]	Positive	< 0.001	< 0.001	0.681
C_{cr} [ml/min]	Negative	< 0.001		
Proteinuria [yes/no]	NS	0.526		
MPAG C_{max} [mg/l]				
Sex [men/women]	Positive	< 0.001	< 0.001	0.832
Body weight [kg]	Positive	< 0.001		
MMF dose [g]	Positive	< 0.001		
C_{cr} [ml/min]	Negative	< 0.001		
MPAG C_{max} [mg/l]				
MMF dose [g]	Positive	< 0.001	< 0.001	0.651
C_{cr} [ml/min]	Negative	0.001		
Proteinuria [yes/no]	NS	0.689		
MPAG C_0/dose [mg/l/g]				
Sex [men/women]	Positive	< 0.001	< 0.001	0.873
Body weight [kg]	Positive	< 0.001		
CNI [CsA/Tac]	Positive	0.047		
C_{cr} [ml/min]	Negative	< 0.001		
MPAG C_0/dose [mg/l/g]				
C_{cr} [ml/min]	Negative	< 0.001	< 0.001	0.661
Proteinuria [yes/no]	NS	0.130		

Table VI. Cont.

Independent variables	Relation	Partial value of *p*	Model value of *p*	Model *R* coefficient
MPAG $AUC_{0\text{-}4\ h}$/dose [mg × h/l/g]				
Sex [men/women]	Positive	< 0.001	< 0.001	0.886
Body weight [kg]	Positive	< 0.001		
CNI [CsA/Tac]	Positive	0.015		
C_{cr} [ml/min]	Negative	< 0.001		
MPAG $AUC_{0\text{-}4\ h}$/dose [mg × h/l/g]				
C_{cr} [ml/min]	Negative	< 0.001	< 0.001	0.583
Proteinuria [yes/no]	NS	0.501		
MPAG C_{max} [mg/l]				
Sex [men/women]	Positive	< 0.001	< 0.001	0.782
Body weight [kg]	Positive	< 0.001		
C_{cr} [ml/min]	Negative	< 0.001		
MPAG C_{max} [mg/l]				
C_{cr} [ml/min]	Negative	< 0.001	0.001	0.524
Proteinuria [yes/no]	NS	0.861		

MPAG – 7-O-mycophenolic acid glucuronide, PK – pharmacokinetic, C_0 – pre-dose concentration, CNI – calcineurin inhibitor, CsA – cyclosporine, Tac – tacrolimus, MMF – mycophenolate mofetil, C_{cr} – creatinine clearance, NS – not significant, AUC – area under the concentration-time curve, C_{max} – maximum concentration

clinic. The MPA C_0 is the most often used parameter in clinical practice. Its value may be considerably influenced by MPAG enterohepatic recirculation, resulting in the second MPA plasma concentration peak (C_{max2}) approximately 6-12 h after drug administration. In our study, higher MPA C_0 as well as MPAG C_0, C_{max} and $AUC_{0\text{-}4\ h}$ values were observed in patients with impaired renal function regardless of CNI used, whereas there were no differences in the values of the other MPA PK parameters (C_{max} and $AUC_{0\text{-}4\ h}$). Elevated MPA C_0 values may indicate intensified enterohepatic recirculation due to MPAG concentration increase in patients with impaired renal function. The correlations between renal function and MPAG concentrations as well as MPA C_0 suggest that the cause of the differences observed between two groups is the dependence of MPAG concentration and indirectly MPA C_0 on renal function. The results concerning MPAG are consistent with the literature. However, the influence of renal function on MPA PK parameters is still unclear.

Similar results concerning MPA and MPAG PK parameters were obtained by Gonzalez-Roncero *et al.* [14]. The authors demonstrated not only the influence of renal function on MPA C_0 and MPAG AUC but also its lack on MPA AUC. The studies by Zanker *et al.* [15], Morgera *et al.* [16] and Weber *et al.* [17] also observed higher MPAG AUC in renal transplant recipients with lower C_{cr} than in patients with normal glomerular filtration. However, values of MPA AUC did not differ significantly. On the other hand, the results for MPA obtained by Mohammadpur *et al.* [18] were different. According to this study, significantly higher MPA $AUC_{0\text{-}12\ h}$ values along with unchanged C_0 and significantly higher MPA C_{max2} values were observed in patients with impaired renal function. The authors also found a negative correlation for C_{cr} and MPA AUC. The use of abbreviated MPA profiles in our study may be the reason for different AUC results compared with the Mohammadpur *et al.* study. The abbreviated profiles do not include MPA C_{max2} associated with enterohepatic recirculation. In contrast to these studies, van Hest *et al.* [19] and Weber *et al.* [20] observed a total MPA concentration decrease in patients with impaired renal function. It was suggested that the concentration decrease was due to the accumulation of MPAG, which displaced MPA from its protein compounds, increasing free MPA concentration and its clearance. The controversies concerning the influence of renal failure on MPA concentration values may be explained by Naesens *et al.* [21]. The authors observed increased MPA and MPAG concentration values in patients with moderately reduced renal function (C_{cr} ranging from 30 ml/min to 60 ml/min), whereas decreased total MPA concentration values were observed in patients with severe graft dysfunction (C_{cr} < 30 ml/min), similarly as in the study by van Hest *et al.* [19]. This may explain the lack of differences in MPA $AUC_{0\text{-}4\ h}$ and C_{max} values between groups with C_{cr}

above or below 60 ml/min in our study, because the group with impaired renal function included patients with moderate as well as with severe graft dysfunction. Nevertheless, our study showed higher MPA C_0 values in patients with C_{cr} < 60 ml/min, which may indicate intensified enterohepatic recirculation in patients with impaired renal function as found in the study by Mohammadpur *et al.* [18].

Proteinuria may also be considered as a factor influencing MPA and MPAG PK parameters. Naesens *et al.* [21] demonstrated correlations between MPA PK parameters and proteinuria. However, in our study in the multivariate analysis no relations between MPA and MPAG PK parameters were observed. It may be due to the small number of patients (n = 9) with proteins determined in urine.

In conclusion, renal failure, irrespective of immunosuppressive regimen, influences the MPAG PK parameters and MPA C_0 by increasing the values in patients with impaired renal function. The results of our study indicate that solely MPA C_0 determination in patients receiving MMF may be insufficient in clinical practice because of great inter-patient variability of this PK parameter caused mainly by enterohepatic recirculation. It may lead to wrong decisions concerning the pharmacotherapy, particularly in patients with impaired renal function. It seems to us that the monitoring of MPA and MPAG AUC may allow MMF dosage regimens to be optimized, and as a result improve the early prevention of adverse effects in these patients.

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References

1. Morris RG. Immunosuppressant drug monitoring: is the laboratory meeting clinical expectations? Ann Pharmacother 2005; 39: 119-27.
2. Mamelok R. From mechanisms to long-term benefits. Transplantation 2005; 79 (3 Suppl): S43-4.
3. Arns W. Noninfectious gastrointestinal (GI) complications of mycophenolic acid therapy: a consequence of local GI toxicity? Transplant Proc 2007; 39: 88-93.
4. Staatz CE, Tett SE. Clinical pharmacokinetics and pharmacodynamics of mycophenolate in solid organ transplant recipients. Clin Pharmacokinet 2007; 46: 13-58.
5. de Winter BC, Mathot RA, van Hest RM, van Gelder T. Therapeutic drug monitoring of mycophenolic acid: does it improve patient outcome? Expert Opin Drug Metab Toxicol 2007; 3: 251-61.
6. Morissette P, Albert C, Busque S, St-Louis G, Vinet B. In vivo higher glucuronidation of mycophenolic acid in male than in female recipients of a cadaveric kidney allograft and under immunosuppressive therapy with mycophenolate mofetil. Ther Drug Monit 2001; 23: 520-5.
7. Ting LS, Partovi N, Levy RD, Riggs KW, Ensom MH. Pharmacokinetics of mycophenolic acid and its glucuronidated metabolites in stable lung transplant recipients. Ann Pharmacother 2006; 40: 1509-16.
8. Pawiński T, Durlik M, Szlaska I, Urbanowicz A, Majchrzak J, Gralak B. Comparison of mycophenolic acid pharmacokinetic parameters in kidney transplant patients within the first 3 months post-transplant. J Clin Pharm Ther 2006; 31: 27-34.
9. Seebacher G, Weigel G, Wolner E, et al. A simple HPLC method for monitoring mycophenolic acid and its glucuronidated metabolite in transplant recipients. Clin Chem Lab Med 1999; 37: 409-15.
10. Graj J, Chrzanowska M. Validation of HPLC method for therapeutic drug monitoring of mycophenolic acid in renal transplant recipients. Probl Ter Monit 2006; 1: 3-10.
11. Liang MZ, Lu YP, Nan F, Li YP. Pharmacokinetics of mycophenolic acid and its glucuronide after a single and multiple oral dose of mycophenolate mofetil in Chinese renal transplantation recipients. Transplant Proc 2006; 38: 2044-7.
12. Kuypers DR, Vanrenterghem Y, Squifflet JP, et al. Twelve-month evaluation of the clinical pharmacokinetics of total and free mycophenolic acid and its glucuronide metabolites in renal allograft recipients on low dose tacrolimus in combination with mycophenolate mofetil. Ther Drug Monit 2003; 25: 609-22.
13. Ting LS, Partovi N, Levy RD, Riggs KW, Ensom MH. Pharmacokinetics of mycophenolic acid and its phenolic-glucuronide and ACYI glucuronide metabolites in stable thoracic transplant recipients. Ther Drug Monit 2008; 30: 282-91.
14. González-Roncero FM, Gentil MA, Brunet M, et al. Pharmacokinetics of mycophenolate mofetil in kidney transplant patients with renal insufficiency. Transplant Proc 2005; 37: 3749-51.
15. Zanker B, Schleibner S, Schneeberger H, Krauss M, Land W. Mycophenolate mofetil in patients with acute renal failure: evidence of metabolite (MPAG) accumulation and removal by dialysis. Transpl Int 1996; 9: S308-10.
16. Morgera S, Budde K, Lampe D, et al. Mycophenolate mofetil pharmacokinetics in renal transplant recipients on peritoneal dialysis. Transpl Int 1998; 11: 53-7.
17. Weber LT, Lamersdorf T, Shipkova M, et al. Area under the plasma concentration-time curve for total, but not for free, mycophenolic acid increases in the stable phase after renal transplantation: a longitudinal study in pediatric patients. German Study Group on Mycophenolate Mofetil Therapy in Pediatric Renal Transplant Recipients. Ther Drug Monit 1999; 21: 498-506.
18. Mohammadpur AH, Nazemian F, Abtahi B, Naghibi M. Influence of renal graft function on mycophenolic acid pharmacokinetics during the early period after kidney transplant. Exp Clin Transplant 2008; 6: 276-81.
19. van Hest RM, van Gelder T, Vulto AG, Shaw LM, Mathot RA. Pharmacokinetic modelling of the plasma protein binding of mycophenolic acid in renal transplant recipients. Clin Pharmacokinet 2009; 48: 463-76.
20. Weber LT, Shipkova M, Armstrong VW. The pharmacokinetic-pharmacodynamic relationship for total and free mycophenolic acid in pediatric renal transplant recipients: a report of the german study group on mycophenolate mofetil therapy. J Am Soc Nephrol 2002; 13: 759-68.
21. Naesens M, de Loor H, Vanrenterghem Y, Kuypers DR. The impact of renal allograft function on exposure and elimination of mycophenolic acid (MPA) and its metabolite MPA 7-O-glucuronide. Transplantation 2007; 84: 362-73.