Pharmacokinetics of Mycophenolic Acid During the Early Period After Renal Transplant

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Objectives: **Mycophenolic acid, the active metabolite of mycophenolate mofetil, is administered with cyclosporine and oral steroids to prevent acute rejection after renal transplant. The aim of this study was to investigate correlations among time after transplant, subjects' demographics, and mycophenolate mofetil dosage according to body weight with mycophenolic acid pharmacokinetics during the early posttransplant period.**

Patients and Methods: **Mycophenolic acid plasma levels of 19 patients were determined by a validated high-performance liquid chromatographic method at the steady state soon after transplant when graft function was good (glomerular filtration rate ≥ 70 mL/min). All patients received a fixed dosage of mycophenolate mofetil (1 g b.i.d.) in combination with cyclosporine and steroids. The area under the time-concentration curve (AUC) and mycophenolic acid plasma clearance were measured for each patient.**

Results: **The AUC from zero to 12 hours and trough levels increased as the time after transplant increased ($P < .05$), but mycophenolic acid plasma clearance decreased over time ($P = .02$). There was a correlation between total body weight and the AUC ($P = .01$, $r^2 = –0.627$) as well as between total body weight and mycophenolic acid clearance ($P = .04$, $r^2 = 0.555$). No statistically significant differences were found regarding mycophenolic acid plasma level, AUC, and mycophenolic acid plasma clearance with regard to sex or age of the subjects ($P > .05$). The mycophenolate mofetil dosage according to body weight correlated positively with the AUC ($P = .01$, $r^2 = 0.628$), but there was a negative correlation between total body weight and mycophenolic acid plasma clearance ($P = .02$, $r^2 = –0.604$).**

Conclusions: **Our results demonstrate that total body weight, time after transplant, and mycophenolate mofetil dosage according to body weight affect mycophenolic acid pharmacokinetics. We suggest that mycophenolic acid pharmacokinetics monitoring is necessary to individualize mycophenolate mofetil dosing during the early posttransplant period.**

Key words: *Drug kinetics, Mycophenolate mofetil, Total body weight*

Mycophenolic acid, the active metabolite of mycophenolate mofetil, exerts its immunosuppressive action by blocking lymphocyte proliferation via inhibition of inosine monophosphate dehydrogenase (1). It has been shown that mycophenolate mofetil, when administered in combination with cyclosporine and a steroid, statistically significantly reduces the risk of acute rejection during the early posttransplant period more than does azathioprine or placebo (2). Mycophenolic acid is metabolized to the inactive metabolite mycophenolate glucuronide by glucuronyl transferase in the kidney and liver. A second peak concentration of mycophenolic acid is often observed during enterohepatic recirculation as mycophenolate glucuronide converts to mycophenolic acid via glucuronidase of the gastrointestinal flora (3). Alterations in enterohepatic recirculation have a role in the interindividual and intraindividual variability of mycophenolic acid plasma levels (4). There is a relationship between the mycophenolic acid area under the time-concentration curve (AUC) and risk of acute rejection in both adult and pediatric patients

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during the early posttransplant period (3, 5), but the value of the therapeutic drug monitoring of mycophenolic acid in preventing that rejection has not been established. Therapeutic drug monitoring is recommended during the early period after transplant when the patient's mycophenolic acid level is a good indicator of acute rejection (6). Mycophenolate mofetil has a narrow therapeutic index (7), and there is a poor correlation between the mycophenolate mofetil dosage and the concentration response (6), the pharmacokinetics of which varies greatly among adult and pediatric kidney recipients (8). One longitudinal study of patients receiving fixed doses of mycophenolate mofetil revealed a greater than 10-fold range in the mycophenolic acid AUC during the first 2 weeks after transplant (9).

There is a high degree of intraindividual variability in the AUC (range, 0-12 hours) in the early posttransplant period. A reduction in that variability 3 months after transplant has been demonstrated (3), and a clear relationship between mycophenolic acid pharmacokinetics and clinical outcome has been shown (10). In renal transplant patients, changes have been observed in mycophenolic acid pharmacokinetics over time (especially during the first month after transplant) (11). Thus, mycophenolate mofetil is a good choice for therapeutic drug monitoring during the early posttransplant period. Mycophenolate mofetil also may help minimize the adverse effects of other drugs and may reduce the risk of acute rejection during the early posttransplant period.

The individual demographic characteristics that may influence mycophenolic acid pharmacokinetics have not been identified. Most therapeutic regimens require that mycophenolate mofetil be administered in fixed dosages (1 g b.i.d.), and dosing is not based on the patient's body weight.

The aim of this study was to investigate the correlation of several factors (ie, time after transplant, the demographic characteristics of the subjects, and mycophenolate mofetil dosage according to body weight) with mycophenolic acid pharmacokinetics in renal transplant patients with a glomerular filtration rate of ≥ 70 mL/min to define the value of individualized mycophenolate mofetil dosing during the early posttransplant period.

Patients and Methods

Nineteen renal transplant recipients (10 women, 9 men; age range, 18-52 years) treated at the Transplant Center of Imam-Reza Hospital in Mashhad, Iran, participated in this study. Patients were considered for admission to the study if both their liver and renal graft functioning were within normal limits and their mycophenolic acid blood levels had reached the steady state. Patients who tested seropositive for cytomegalovirus and had received ganciclovir or polyclonal antibodies were excluded from participation. The trial was performed in accordance with the requirements of the 1975 Declaration of Helsinki and was approved by the ethics committee at Mashad University of Medical Sciences. Written informed consent was obtained from each patient before the study was initiated.

The immunosuppressive protocol, which began the day of surgery, was a fixed dosage of mycophenolate mofetil (1 g b.i.d.) and the standard dosage of cyclosporine (10 mg/kg/d). Cyclosporine dosing was adjusted to achieve whole blood cyclosporine trough levels of 200 to 250 ng/mL for the first 2 postsurgical months, and methylprednisolone (1000 mg) was administered intravenously during and after surgery for 3 consecutive days. Prednisolone (1 mg/kg/d) was administered orally on day 4, and that dosage was gradually tapered.

Blood sampling and drug assays

Twelve venous blood samples were taken at 0 (predose), 20, 40, 60, and 90 minutes as well as at 2, 3, 4, 6, 8, 10, and 12 hours after each dose for each profile. Plasma samples were immediately removed after centrifugation (10 min at 10 000 *g*) and were stored at –70°C until they were analyzed. Plasma mycophenolic acid levels were determined by high-performance liquid chromatography as described by Wai-Ping and colleagues (12).

Pharmacokinetics and statistical analyses

The mycophenolic acid AUC (range, 0-12 hours) was calculated with the linear trapezoidal rule. The maximum concentrations ($C_{max}1$, $C_{max}2$) and maximum times ($t_{max}1$, $t_{max}2$) were the observed values. Apparent mycophenolic acid plasma clearance was calculated by dividing the mycophenolate mofetil dose by the AUC. Continuous data were tested for normal distribution by the Kolmogorov-Smirnov test. An independent samples *t* test was used for data in a normal distribution, and the Mann-Whitney *U* test was used for data in a nonnormal distribution. All data are presented as means ± SD, or as a median and range according to variable distribution. Correlation coefficients were calculated with Pearson's r correlation, and linear regression analyses were also performed. All statistical analyses were performed with SPSS

software (Statistical Package for the Social Sciences, version 11.5, SSPS Inc, Chicago, IL, USA). A *P* value less than .05 was considered statistically significant.

Results

The patients' characteristics are summarized in Table 1. In patients given mycophenolate mofetil (1 g b.i.d.), the AUC (range, 0-12 hours) was 11.52 to 66.95 mg.h/L, which showed individual variability during the early posttransplant period. The first peak concentration ($C_{max}1$) was achieved rapidly with $t_{max}1$ at a range of 0.3 to 3. There was a second peak concentration ($C_{max}2$) in the AUC of 13 patients within 6 to 10 hours ($t_{max}2$) after administration of mycophenolate mofetil. The mean value ± SD of $C_{max}2$, which was 1.98 ± 1.89, was attributed to enterohepatic recirculation. In our study, enterohepatic recirculation contributed to 22% of the AUC (range, 0-12 hours) and may have had a role in interindividual pharmacokinetics variability. A summary of the pharmacokinetics of mycophenolic acid is provided in Table 2.

Neither height nor body mass index correlated with the mycophenolic acid AUC ($P > .05$). There were no statistically significant differences with regard to mean AUC values in patients aged 35 years or older and those younger than 35 years ($P = .5$). The mean mycophenolic acid AUC value was higher in women than it was in men; however, this result was not statistically significant (39.1 ± 17.82 vs 31.26 ± 18.47, $P = .5$). The mean mycophenolic acid plasma clearance level did not statistically significantly differ according to the patient's sex ($P > .05$); however, a statistically significant difference between the sexes was found when mean trough levels were compared ($P = .02$) (Figure 1). There was a correlation between the total body weight and AUC ($P = .01$, $r^2 = –0.627$) as well as between total body weight and mycophenolic acid plasma clearance ($P = .004$, $r^2 = 0.555$). The AUC and the trough level statistically significantly increased with time (mycophenolic acid trough level, $r = 0.575$ and $P = .01$; mycophenolic acid AUC, $r = 0.592$ and $P = .008$), but the apparent mycophenolic acid plasma clearance decreased with time after transplant ($r = –0.508$, $P = .03$). The patients' renal function did not affect the AUC. Serum creatinine did not correlate with AUC as well as glomerular filtration rate did ($P > .05$). No correlation was found for either mycophenolic acid trough level or AUC and white blood cell count (mycophenolic acid trough level, $r = 0.018$; $P = .957$; mycophenolic acid AUC, $r = –0.491$; $P = .15$) or the hematocrit value (mycophenolic acid trough level, $r = 0.223$; $P = .509$; mycophenolic acid AUC, $r = 0.115$; $P = .751$).

To investigate the relationship between drug-related adverse effects and mycophenolic acid pharmacokinetics, patients were divided into 2 groups: those with diarrhea and those without diarrhea. There were no statistically significant between-group differences with regard to mean trough level, AUC, and $C_{max}1$ ($P > .05$).

Table 1. Patient demographics

No. of patients	19
Age (y, mean ± SD)	29.11 ± 9.7
Sex (women/men)	10/9
Height (cm, mean ± SD)	162.8 ± 8.72
TBW (kg, mean ± SD)	55.02 ± 10.21
LBW (kg, mean ± SD)	42.51 ± 6.64
BMI (kg/m², mean ± SD)	21.02 ± 3.66
Serum creatinine level (mM , mean ± SD)	1.25 ± 0.33
GFR (mL/min, median, range)	67.02 (77.31 - 132.87)
ALT (U/L, mean ± SD)	39.4 ± 29.6
AST (U/L, mean ± SD)	19.4 ± 7.9
Time after transplant (d, mean ± SD)	17.47 ± 6.07
Donor status	Deceased donor = 8, Living donor = 11
Mycophenolate mofetil (mg/kg, mean ± SD)	37.59 ± 7.35
Prednisolone dose (mg/d, median, range)	30 (20-45)
Cyclosporine dose (mg/d, median, range)	275 (200-350)

Abbreviations: ALT, alanine amino transferase; AST, aspartate amino transferase; BMI, body mass index; GFR, glomerular filtration rate; LBW, lean body weight; TBW, total body weight

Table 2. The pharmacokinetics of mycophenolic acid

AUC (0-12 hours) (mg.h/L, mean ± SD)	35.39 ± 14.94
$C_{max}1$ (mg/L, median, range)	16.03 (6.81 - 61.97)
$t_{max}1$ (h, median, range)	1.5 (0.3-3)
Trough level (zero hour) (mg/L, median, range)	0.73 (0.1-4.6)
Clearance (L/h, median, range)	30.99 (13.91-81.6)

Abbreviations: AUC, Area under the curve (range, 0-12 hours); $C_{max}1$, (first peak concentration); $t_{max}1$, time to reach $C_{max}1$.

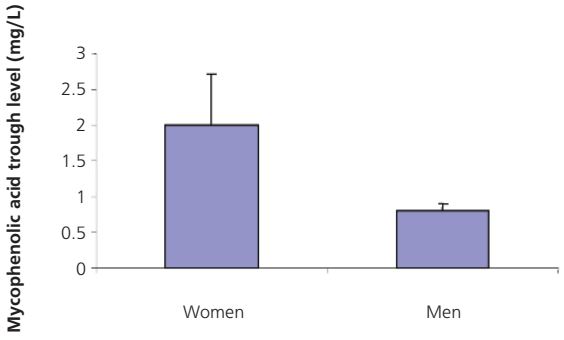

Figure 1. Correlation between the mean mycophenolic acid trough level and sex.

Mycophenolate mofetil dosage (in mg/kg) correlated with glomerular filtration rate ($r = –0.663$, $P = .014$) and ideal body weight ($r = –0.778$, $P = .002$). The mycophenolate mofetil dosage (in mg/kg) correlated positively with the AUC ($P = .01$, $r^2 = 0.628$); however, there was a negative correlation between mycophenolate mofetil dosage (in mg/kg) and mycophenolic acid plasma clearance ($P = .02$, $r^2 = –0.604$) (Figures 2 and 3).

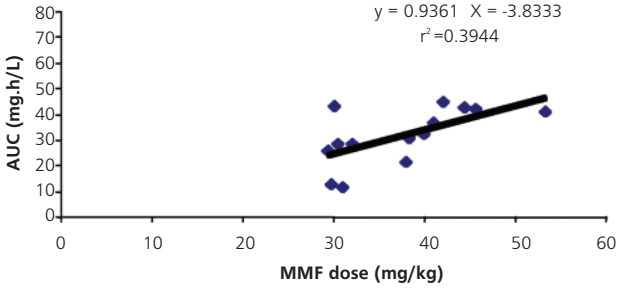

Figure 2. Correlation of mycophenolate mofetil (MMF) dosage by body weight (in mg/kg) with area under the time-concentration curve (AUC).

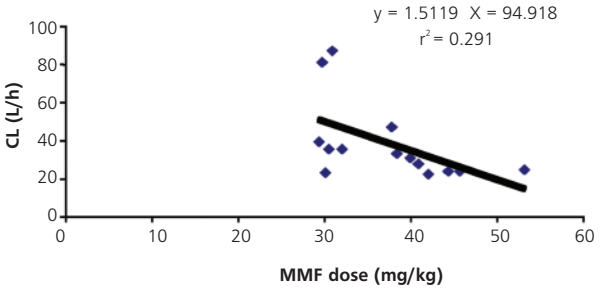

Figure 3. Correlation between mycophenolate mofetil (MMF) dosage by body weight (in mg/kg) with clearance (CL).

Discussion

Therapeutic drug monitoring of mycophenolate mofetil could help ensure adequate therapeutic exposure to mycophenolic acid and may prevent adverse effects from mycophenolate mofetil or acute rejection during the early posttransplant period. The mycophenolic acid AUC in an approximate range of 30 to 60 mg.h/L seems to be a reasonable target for decreasing the risk of acute rejection during the early and maintenance periods following transplant (7). The incidence of acute rejection has been shown to increase when the mycophenolic acid AUC value decreases to less than 30 mg.h/L during the first month after renal surgery (13). In our study, approximately 36% of the patients who received fixed dosages of mycophenolate mofetil had a mycophenolic acid AUC value below the accepted target level. One reason for this may be concurrent cyclosporine treatment, which interferes with mycophenolic acid pharmacokinetics by inhibiting enterohepatic recirculation. At 1-year follow-up, none of the patients had experienced acute rejection. Mycophenolate mofetil was characterized by a large interindividual variability and a greater than 10-fold variation in the AUC (range, 0-12 hours) after patients had received fixed dosages during the first weeks after surgery (9). We found an interindividual variability in pharmacokinetics that was manifested as an approximate increase up to 6 times in the mycophenolic acid AUC (range, 0-12 hours). The pharmacokinetics profile was characterized by rapid absorption, with the first peak concentration developing within 0.3 to 3 hours after dosing, after which rapid distribution and metabolism occurred. In 13 patients, a second peak concentration occurring between 6 and 10 hours after dosing that contributed to enterohepatic recirculation. The pattern of the concentration-time profile was similar to that in other studies (7, 14). Race, time after transplant, co-adminstered immunosuppressive drugs, and presence of some conditions such as diabetes mellitus or impaired renal or hepatic function might have caused differences between the study groups.

As in other studies (4, 15), we found that neither mycophenolic acid AUC nor mycophenolic acid plasma clearance was affected by the subjects' age. In contrast to the results of the study by Le Guellec and colleagues (11), our study revealed no correlation between height and AUC. Our study investigated the association of sex and mycophenolic acid pharmacokinetics. We found that the mycophenolic acid AUC and clearance were not statistically significantly different between the sexes, probably because of complications in endocrine function during the early posttransplant period. However, the mean mycophenolic acid trough level was statistically significantly different between the sexes. Our results differed from those of other studies that showed that the mycophenolic acid AUC was higher in women than it was in men. That difference may be due to the common metabolic pathway of mycophenolate mofetil and estrogens and the similar binding site to uridyl glucuronyl transferase-1A that is involved in the glucuronidation of mycophenolic acid (15).

Several studies have assessed the correlation between mycophenolic acid pharmacokinetics, total body weight, and mycophenolate mofetil dosage according to body weight. Renal transplant patients lost body weight within the first month after transplant because of the catabolic effects of surgery, loss of excess fluid, delayed graft function, and/or decreased dietary intake during the early posttransplant period (16). We found that during the

early posttransplant period, total body weight might have been a factor that influenced mycophenolic acid pharmacokinetics, because the total body weight correlated with mycophenolic acid plasma clearance and with the AUC. In contrast to our study, the results of research by Johnson and colleagues (4) showed that there was no correlation between total body weight and the mycophenolic acid AUC (range, 0-12 hours) during the first month after transplant. Another study (17) demonstrated a weak negative correlation between weight and mycophenolic acid AUC. That lack of correlation might have been due to enterohepatic recirculation (17).

We attempted to determine an acceptable relationship between mycophenolic acid pharmacokinetics according to body weight. We found correlations between mycophenolic acid plasma clearance, AUC, and mycophenolate mofetil dosage according to body weight. To our knowledge, this is the first study to show correlations between glomerular filtration rate and lean body weight and mycophenolate mofetil dosage according to body weight. Kuriata-Kordek and colleagues (15) suggested that mycophenolate mofetil dosage by body weight might independently influence mycophenolic acid pharmacokinetics; thus, weight could be an important factor regarding mycophenolic acid pharmacokinetics when individualizing dosing of mycophenolate mofetil. However, these results need further investigation.

We also studied the effect of time after transplant on mycophenolic acid pharmacokinetics. As have other investigators, we observed that the mycophenolic acid trough level and the AUC increased and the mycophenolic acid plasma clearance decreased with time (7, 18). In a study by Pawinski and colleagues, the mean total mycophenolic acid AUC was 30% to 50% lower in the first weeks after transplant than it was 2 to 6 months after transplant (7). Factors such as alternations in mycophenolic acid protein binding have been shown to cause a 35% decrease in the mycophenolic acid free fraction and a reduction in mycophenolic acid metabolism over time (18, 19). High dosages of glucocorticoids during the early posttransplant period may contribute to that effect (20). Wollenberg and colleagues (21) have reported that the mycophenolic acid trough level does not differ significantly over time but that the mycophenolic acid $C_{max}1$ increases over time because of alternations in drug absorption. Even though the subjects received a fixed dosage of mycophenolate mofetil, we found interpatient differences in the clearance, trough level, AUC, and $C_{max}1$ that correlated with the time after transplant.

An approximate 22% increase in the total mycophenolic acid AUC has been observed in patients with good early renal graft function when compared with the AUC in patients with impaired renal function (7, 22). Therefore, renal function (reflected in serum creatinine level) could be an important predictor of the mycophenolic acid AUC and must be monitored during the first month after transplant (4). In our study, no correlation was observed between serum creatinine level and mycophenolic acid AUC. Wollenberg and colleagues (21) reported no correlation between serum creatinine level and mycophenolic acid AUC. However, Pawinski and colleagues (7) found a negative correlation between serum creatinine level and mycophenolic acid AUC. They suggested that this inverse relationship likely occurred because of changes in the protein binding of mycophenolic acid during the first month after transplant. Johnson and colleagues (4) reported that the serum creatinine level as a covariate affects the mycophenolic acid AUC (range, 0-12 hours). Our study was performed in patients whose renal graft function was within normal limits (glomerular filtration rate > 70 mL/min) and whose serum creatinine level was similar (range, 0.8-1.9 mM), and these factors might have affected the results of our statistical analyses.

Some investigators have suggested that diarrhea may affect mycophenolic acid exposure by causing changes in mycophenolate mofetil absorption (6). Our data did not show a correlation between diarrhea and pharmacokinetics such as $C_{max}1$, trough level, or AUC. This result supports the findings of van Gelder and colleagues (23), who explained that such a correlation may be related to the mycophenolate mofetil dosage.

In conclusion, after having considered changes in pharmacokinetics and body weight during the first posttransplant month, we suggest that mycophenolic acid exposure based on the mycophenolate mofetil dosage alone produces mycophenolic acid concentrations that are lower or higher than the desired range, and that weight is an important factor in individualizing mycophenolate mofetil therapy. Additional pharmacokinetics studies are necessary to confirm these results.

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