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ARTICLE

Mycophenolic Acid Pharmacokinetics Early After Kidney Transplant

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Objectives: **To determine the mycophenolic acid pharmacokinetic profile early after transplant in Iranian kidney graft recipients.**

Materials and Methods: **A cross-sectional study was performed during 6 months in 31 patients who recently had kidney transplant and received fixed doses of mycophenolate mofetil (2 g/d). The plasma levels of mycophenolic acid were determined by high performance liquid chromatography.**

Results: **The mean first mycophenolic acid peak level was 10 ± 5 mg/L. The mean mycophenolic acid area under the curve was 26 ± 19 mgh/L and apparent clearance was 57 ± 55 L/h. The mycophenolic acid area under the curve values of only 8 patients (26%) were within the therapeutic range (30-60 mgh/L). The first, second, and third mycophenolic acid peak levels correlated significantly with mycophenolic acid area under the curve (*P* < .05). Mycophenolic acid concentration at 10 hours had the highest correlation with mycophenolic acid area under the curve (r=0.962; *P* < .05). No statistically significant differences were evident in the mean mycophenolic acid area under the curve between men and women.**

Conclusions: **There was a high degree of variation between different patients in mycophenolic acid pharmacokinetics early after kidney transplant.**

Key words: Allograft, Renal, Rejection, Immunosuppression, Mycophenolate mofetil

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Table 1. Demographic Characteristics of the Study Patients With Kidney Transplant*

Table 2. Pharmacokinetics Parameters of Mycophenolic Acid in the Study Population*

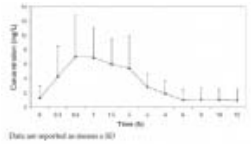

Figure 1. Mycophenolic Acid Concentration Against Time for the Study Population (n=31)

Introduction

Mycophenolate mofetil (MMF) was introduced in clinical practice in 1995.[1] In 3 large clinical trials, MMF reduced acute rejection by 30% to 50% compared with azathioprine or placebo in the first 6 months after renal transplant.[2-4] In contrast with azathioprine, MMF has a selective effect on the proliferation of B and T lymphocytes by inhibiting inosine monophosphate dehydrogenase.[5] Therefore, azathioprine use has been discontinued in many regimens. In recent protocols, MMF is used as part of maintenance immunosuppressive therapy worldwide.[6]

After oral administration, MMF is rapidly and extensively absorbed and hydrolyzed by serum esterase to its active metabolite, mycophenolic acid (MPA).[7] The pattern of plasma MPA alteration in healthy individuals demonstrates a first peak level (C_{max1}) at approximately 1 hour after MMF administration. Mycophenolic acid is metabolized to pharmacologically inactive phenolic glucuronide metabolite by uridine diphosphate glucuronosyltransferase (UDP-GT) in the kidney and liver. A secondary plasma MPA peak level (C_{max2}) is often observed 6 to 12 hours after oral administration, suggesting enterohepatic circulation via phenolic glucuronide metabolite conversion to MPA by the glucuronidase of gastrointestinal flora.[8, 9]

There is an association between the MPA concentration-time curve, quantified by the area under the curve (AUC), and risk of acute rejection in both adult and pediatric patients early after transplant.[9, 10] Furthermore, early after transplant, high variations between patients in AUC has been documented.[11, 12] Therefore, therapeutic drug monitoring of MMF is recommended early after transplant.[13] The main purpose of this study was to determine the MPA pharmacokinetic profile early after transplant in Iranian kidney graft recipients.

Methods and Materials

Study protocol

This cross-sectional study was performed during 6 months at a kidney transplant ward of an affiliated hospital. The study protocol was approved by the Institutional Review Board and Ethics Committee of the hospital, and written informed consent was obtained from each patient before blood sampling. Patients of a consecutive series were included 9 to 10 days after kidney transplant. They all had normal renal graft functioning (serum creatinine < 123.76 µmol/L). All patients received MMF (2 g/d orally) as a part of the immunosuppression protocol. Patients who were seropositive for *cytomegalovirus* and/or received ganciclovir or polyclonal antibodies were excluded from the study. Patients with liver enzymes > 3 times above the upper limit of normal also were excluded. Demographic data (age, sex, and weight), time after transplant, first serum creatinine level after transplant, and serum creatinine at the time of blood sampling (9-10 days after kidney transplant) were recorded.

Blood sampling and drug assays

A 4.5 mL peripheral venous blood sample was withdrawn from the patients into a tube containing ethylenediaminetetraacetic acid before the patients received MMF (time, 0 min) and at 20, 40, 60, and 90 minutes and 2, 3, 4, 6, 8, 10, and 12 hours after receiving half of 2-gram daily dosage of oral MMF. Each blood sample was centrifuged at 5000 rpm for 15 minutes and the plasma fraction was

isolated and stored at -70°C until analyzed.

Plasma concentration of MPA was analyzed by a validated high performance liquid chromatography method. A stock solution of MPA (concentration, 1 g/L) in methanol (high performance liquid chromatography grade) was prepared and further diluted with methanol to obtain a diluted solution (400 mg/L). This solution was used to prepare different concentrations of MPA standard solutions (range, 0.1 to 80 mg/L). Naproxen solution (concentration, 40 mg/L; volume, 50 µL) as internal standard and acetonitrile (500 µL) were added to MPA standard solutions (450 µL). The solutions were mixed for 1 minute and centrifuged at 10 000 rpm for 10 minutes. Clear supernatant (50 µL) was then injected 3 times into the high performance liquid chromatography column. Chromatographic analysis of MPA was achieved with a reversed phase column (length, 250 mm; inner diameter, 4.6 mm; particle size, 10 µm) (C-18 Hamilton PRP-1, Hamilton Company, Reno, NV, USA) connected to a suitable guard column (length, 25 mm; inner diameter, 2.3 mm, particle size, 12-20 µm) (Hamilton Company). The mobile phase consisted of acetonitrile and 0.02 M potassium dihydrogen phosphate buffer (volume:volume, 51:49; with 85% phosphoric acid added to adjust the pH to 3) and was pumped at a flow rate of 1 mL/minute. Detection was made by an ultraviolet detector (wavelength, 215 nm). Mycophenolic acid and internal standard peaks were extrapolated (retention time: MPA peak, 7.30 min; internal standard peak, 11.35 min). The calibration curve was obtained (range, 0.1-80 mg/L). The equation of the best fit regression line was y = 0.0657x + 0.0101 (r^2=0.9986). The mean recovery of MPA from serum was 94.8%. The within- and between-day coefficient of variations for MPA concentration ranged from 0.6% to 8.2% and 1.9% to 6.1%. The MPA concentration was determined by the ratio of the MPA peak area to the area of the internal standard. The peak concentration (C_{max}) and time of peak concentration (t_{max}) were determined directly from the plasma concentration-time curve. The MPA AUC was calculated using the linear trapezoidal rule. The apparent MPA clearance (CL/f) was calculated by dividing the MMF dosage by the AUC.

Statistical analyses

Categorical data are expressed as a percentage. Continuous variables are reported as means ± standard deviation (SD). The relation between age, weight, and MMF daily dosage (mg/kg/d) and MPA AUC and CL/f were examined with Pearson product moment correlation test. The Pearson product moment correlation test also was used to assess the correlation between MPA AUC and the first, second, and third MPA peak levels (C_{max1}, C_{max2}, C_{max3}) and each determined MPA concentration. Independent *t* test was used to compare mean MPA AUC between men and women, patients younger and older than 40 years, and patients < 60 kg and > 60 kg. Statistical analyses were performed with statistical software (Statistical Package for the Social Sciences, version 11.5, SPSS Inc., Armonk, NY). Statistical significance was defined by $P < .05$.

Results

During the 6 months of the study, 31 kidney transplant recipients (23 men and 8 women) were included (Table 1). All kidney transplants were the first transplants received by the patients, and all transplanted kidneys were from living donors. The immunosuppression regimen consisted of MMF (Table 1) in combination with an oral glucocorticoid (prednisolone 2 mg/kg/d the day before surgery, 1 mg/kg/d on the first day after surgery and then 5-10 mg/d over 4 weeks) and a calcineurin inhibitor (cyclosporine at an initial dosage of 5 mg/kg/d and then was adjusted to achieve target 2 h post-dosing [C2] levels between 800-1000 µg/L during the first 6 months after surgery).

The mean MPA plasma concentration-time profiles and the pharmacokinetics parameters of MPA of the 31 patients showed that the mean C_{max1} was detected at a time range of 18 to 120 minutes (range of t_{max1}) (Table 2 and Figure 1). The second peak had mean C_{max2} at 1.5 to 10 hours (range of t_{max2}) after MMF administration in 26 patients (84%) (Table 2). The pattern of MPA concentration alteration showed a third peak (C_{max3}) in 8 patients (26%) at 6 to 10 hours (range of t_{max3}) after MMF administration (Table 2). According to calculation by the linear trapezoidal rule, the mean MPA AUC had a wide range, with much variation between patients (Table 2). The MPA AUC values were below 30 to 60 mgh/L in 22 patients (71%) and were within 30 to 60 mgh/L in 8 patients (26%). A wide range of MPA CL/f also was observed (Table 2).

The Pearson correlation analysis showed that there was no statistically significant relation between MPA AUC and age (r=-0.087; not significant), weight (r=0.095; not significant), or MMF daily dosage (r=-0.081; not significant). Age, weight, or MMF daily dose also did not correlate with CL/f. However, there was a statistically significant correlation between MPA AUC and C_{max1} (r=0.559; $P = .001$), C_{max2} (r=0.451; $P < .03$), and C_{max3} (r=0.836; $P = .01$). Furthermore, MPA AUC correlated significantly with all determined MPA concentrations ($P < .05$). The MPA concentrations at 20 minutes had the lowest (r=0.419), and at 10 hours the highest (r=0.962), correlations with MPA AUC. Independent t test showed that the mean MPA AUC and CL/f values were similar in women and men (MPA AUC: women, 31 ± 17 mgh/L; men, 25 ± 19 mgh/L; not significant) (MPA CL/f: women, 42 ± 21 L/h; men, 62 ± 52 L/h; not significant). There were no statistically significant differences in MPA AUC and CL/f values between patients younger or older than 40 years or patients with body weight < 60 kg or > 60 kg.

Discussion

Therapeutic drug monitoring of MMF early after transplant may demonstrate adequate therapeutic immunosuppressive effects and may prevent acute rejection episodes or adverse reactions.[14, 15] The pattern of the concentration-time profile of MMF in the present study was consistent with other studies.[8, 16] The C_{max1} was evident within 18 to 120 minutes after dosing. Rapid absorption was followed by rapid distribution and metabolism. The C_{max2} observed in 26 patients (84%) between 1.5 and 10 hours after dosing may be attributed to the enterohepatic recirculation.[17] The t_{max2}

reported from 2 similar surveys in Iran (range, 6-10 h)[18, 19] were within the range observed in the present study. Congruent with the present study, a previous study showed a statistically significant correlation between MPA AUC and C_{max2} in kidney transplant patients early after transplant ($r=0.58$; $P < .05$).[20]

Large variation in MPA plasma level between patients was noted in the present study. Kidney transplant recipients receiving the same doses of MMF may have > 10-fold variation in MPA AUC during the initial weeks after transplant.[21] Pharmacogenetics (UDP-GT gene polymorphism), coadministered immunosuppressants (calcineurin inhibitors), comorbidities (diabetes mellitus and liver disease), and graft function after transplant may contribute to AUC variation between individuals.

The results of several studies in kidney transplant recipients have suggested that MPA AUC in the approximate range of 30 to 60 mgh/L could be a target for decreasing the risk of acute rejection during the early and maintenance periods after transplant.[14, 17] The AUC of only 8 patients (26%) in the present study were within the therapeutic range. In contrast with the current findings, our previous study on 21 kidney transplant recipients at 3 months after transplant showed that the MPA AUC of 17 patients (81%) ranged from 30 to 60 mgh/L (unpublished data). In another study, 12 of 19 kidney transplant recipients (64%) early after transplant (time after transplant, 17 ± 6 d) had MPA AUC values within the therapeutic range.[18] These differences could be explained partially by the varied times after transplant. The mean MPA AUC in the present study was much lower than that reported previously (42 mgh/L) in a study of MPA pharmacokinetic parameters after a 2 g/d MMF dose in 46 kidney transplant recipients, from 6 to 9 months after transplant.[15] Several studies in kidney transplant recipients have demonstrated that the mean total MPA AUC is 30% to 50% lower in the first few weeks after transplant than at 2 to 6 months after transplant.[17, 22] Considering renal function early after transplant (normal versus impaired), not more than 22% increase in the AUC of total MPA is detected.[23] The lower MPA AUC in the early than later periods after transplant could be, in part, a result of a pharmacokinetics drug interaction between MMF and cyclosporine. High doses of cyclosporine inhibit the enterohepatic recirculation of MPA.[24, 25] In addition, protein binding changes with time after transplant, with the free fraction decreasing and total MPA concentrations increasing over time. This may decrease the MPA clearance and increase the MPA AUC.[26] Other plausible factors contributing to this phenomenon are poor gastrointestinal MMF absorption in the preoperative phase[27] and increased MPA metabolism by high glucocorticoid doses that may induce UDP-GT expression.[28]

In the present study, there was no significant difference of MPA AUC or CL/f between men and women. A previous study showed similar mean MPA AUC values in women and men (women, 39 ± 18 mgh/L; men, 31 ± 18 mgh/L; not significant) early after renal transplant.[18] In another study, higher MPA levels were reported in women than men.[25] A higher MPA concentration may be expected in women because MMF and estrogens have a common metabolic pathway and similar binding site to UDP-GT.[8, 25]

Other characteristics of the present cohort, including age, weight, and MMF daily dose, did not affect MPA pharmacokinetic parameters (AUC and CL/f). The present results are consistent with a previous study that reported that MPA and MPA glucuronide AUC were not predicted by patient weight, age, or serum alkaline phosphatase during the first month after kidney transplant.[12] Another study showed that body weight was a poor predictor of MPA AUC in renal transplant recipients.[29] In contrast with these results, a statistically significant correlation previously was shown between total body weight and MPA AUC ($r=-0.627$; $P = .01$) and CL/f ($r=0.555$; $P = .004$); the MMF daily dosage (mg/kg/d) correlated significantly with MPA AUC ($r=0.628$; $P = .01$) and CL/f ($r=-0.604$; $P = .02$).[18] Another study suggested that MMF dosage in relation to body weight independently may affect MPA pharmacokinetics.[25] There is controversy about the relation between body weight and MPA pharmacokinetics parameters, and further studies in large cohorts are warranted to clarify the precise role of body weight in the pharmacokinetics of MPA.

Despite the fact that MPA AUC from 0 to 12 hours is the best predictor of acute graft rejection, the determination of MPA AUC for graft recipients is not feasible in clinical practice because it is costly, laborious, and requires multiple blood samples. Therefore, an abbreviated MPA AUC value based on a single or limited sampling of blood could be an appropriate, convenient, and practical alternative. The MPA concentration at 10 hours after MMF administration had the highest correlation with MPA AUC in the present study. A previous study showed a regression model with MPA concentrations at 10 hours (C10), with an equation (AUC = [14.46 × C10] + 15.547) that best predicted MPA AUC from 0 to 12 hours.[20] Unlike these results, another study demonstrated that MPA concentration at 2 hours had the highest correlation with MPA AUC ($r=0.622$) in Thai kidney transplant recipients.[30] Various factors could explain these differences, including race, immunosuppression protocol, time from transplant, or MMF dosage. All patients in the present study received cyclosporine as a calcineurin inhibitor, but the Thai subjects were on cyclosporine or tacrolimus.[30] Furthermore, the present study was performed early (9 or 10 days) after kidney transplant, but the minimum time from transplant in the Thai study was 4 months.[30]

Adverse gastrointestinal effects are common in patients taking MMF, but changing from MMF to enteric-coated mycophenolate sodium in patients with severe gastrointestinal adverse effects maybe an alternative to lessen these symptoms. In this way, graft rejection caused by MMF dose reduction could be prevented. Using enteric-coated mycophenolate sodium may have the same therapeutic effect as MMF, with better tolerance and potential to use higher doses.[31] With enteric-coated mycophenolate sodium, similar to MMF, limited sampling times may be related to AUC, and multiple blood sampling may not be required. [32]

The present study has several limitations. The survey was performed in a single center, and the results may be susceptible to a center effect and may not be reproducible in other settings. All blood sampling was performed only 9 or 10 days after kidney transplant, and evaluating the possible effect of time after transplant on MPA pharmacokinetic parameters was not feasible. All patients had normal graft function, and the effect of renal graft dysfunction on MPA pharmacokinetics in our cohort is unknown. Furthermore, common MMF adverse reactions such as diarrhea, leukopenia, and anemia were not recorded, and we did not investigate the relation between MMF adverse reactions and pharmacokinetic parameters.

In summary, the present data showed much variation in MPA pharmacokinetics between different patients early after kidney transplant. The MPA concentration at 10 hours had the highest correlation with MPA AUC, and the MPA AUC values of most patients were below the therapeutic range. Therefore, therapeutic drug monitoring of MMF early after kidney transplant may be necessary to individualize the dosing and minimize the risk of acute graft rejection.

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