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Pharmacokinetic study of mycophenolic acid in Iranian kidney transplant patients.

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ABSTRACT

Background: The purpose of this study was to characterize the pharmacokinetic parameters of mycophenolic acid (MPA) in Iranian kidney transplant patients.
Methods: Plasma MPA concentration of mycophenolate mofetile (MMF) 1 gram two times a day was measured in 21 Iranian kidney transplant recipients receiving treatment. Patients who entered the study had been transplanted for more than 3 months and their drug level was supposed to be at steady state. MMF concentration was measured with High- Performance Liquid Chromatography (HPLC).
Results: The plasma MPA concentration-time curve was characterized by an early sharp peak at about 1 hour postdose. The mean Area Under Curve (AUC), Cmax and Tmax were 47.0±18.3 µg.h/ml, 18.6±8.5 µg/ml and 1.0±0.5 hours respectively.
Conclusion: The plasma MPA concentration-time curve pattern of Iranian patients was similar and consistent with previously reported profiles in other populations taking the same dose.

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Introduction

Mycophenolate mofetile (MMF) is a potent immunosuppressive drug that has replaced Azathioprine in 90% of all transplants regimens in the United States (1). MMF reduces the incidence of acute rejection episodes (2), improves the long-term graft survival (3), and allows the reduction and/or withdrawal of calcineurin inhibitors in chronic transplant nephropathy both in adults and children (4-7). MMF, which is a prodrug formulated to enhance active mycophenolic acid (MPA) bioavailability (8), is rapidly absorbed from the gastrointestinal tract after administration and hydrolyzed to form the active metabolite, mycophenolic acid (9). MPA exerts its immunosuppressive effects by inhibition of inosine monophosphate dehydrogenase (IMPDH), the enzyme involved in the de novo synthesis of purine nucleotides (10). In clinical practice, a fixed daily dose is usually used without monitoring blood levels. Doses are adjusted according to gastrointestinal side effects and blood counts (11).

Following oral administration, the plasma profile of MPA in healthy subjects shows a rapid rise to achieve a peak value of plasma MPA concentration at about 1 hour postdosing. A secondary plasma MPA peak is seen at 6 to 12 hours after oral MMF administration, suggesting enterohepatic circulation (12). Relationships between MPA concentration and effects have been investigated in heart and renal transplant patients, based on single-timepoint samples such as maximal plasma concentration

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(Cmax), pre-dose concentrations, or on Area Under the concentration-time Curve (AUC) (13-18). In renal transplant patients, the incidence of rejection was influenced by MPA, AUC and, although less strongly, by concentration right before the next dose ($C_{predose}$) (19). Concentration-controlled trials in renal transplant patients have confirmed that risk of biopsy-proven acute rejection was higher in the group allocated to low MPA concentrations, although in patients reporting adverse effects high concentration of MPA has been reported (19, 20).

There is now a consensus for Therapeutic Drug Monitoring (TDM) of MPA in the initial post-transplantation phase. This has been recommended primarily to detect patients with low concentrations to prevent under-immunosuppression. The role of TDM in the control of adverse effects has to be evaluated further (21-24). Pharmacokinetic studies of MPA in renal transplant patients show that there is a large variability in the AUC, time to peak plasma concentration (Tmax), and Cmax (24-26). The objective of this study was to characterize the pharmacokinetics of MPA in Iranian kidney transplant patients who received cyclosporine, prednisolone and MMF routinely. A secondary objective was to correlate demographic and other drug consumption which would affect MPA pharmacokinetics.

Patients and methods

This study was an open-labeled evaluation of MPA pharmacokinetics in Iranian kidney transplant patients. Inclusion criteria were: patients older than 18 years of age who had kidney transplantation for more than 3 months and serum creatinin <1.4mg/dl. All patients were using prednisolone, cyclosporine and MMF with dose of 1 gram two times routinely.

Patients with systemic bacterial, fungal, or viral infection, those who were currently receiving treatment for acute rejection, pregnancy or lactation, and patients with liver function tests 3 or more times of upper limit normal were excluded.

This study was approved by the institutional review board, and patient consent was obtained. Multiple blood samples from patients were collected in Vacutainer tubes containing EDTA: before dosing, 0.33, 0.66, 1, 2, 3, 4, 6, 7, 8, 9, 10 and 12 hours after dosing. After immediate centrifugation, plasma of these samples was obtained and frozen at –80 ˚C until analysis.

Measurement of MPA concentration

Plasma concentration of MPA was analyzed by a validated HPLC method. A stock solution of MPA in methanol was prepared at a concentration of 1mg/ml. The stock solution was further diluted (methanol/water, 50/50) to obtain a solution of 200 µg/ml. Plasma standard solutions were prepared from the 200 µg/ml solution at concentrations ranging from 0.1 µg/ml to 40 µg/ml. 100 µl of plasma or plasma MPA standards were added to 10 µl of 40 µg/ml naproxen solution as internal standard and 100 µl of acetonitril. The mixture was vortex mixed for 1 min and centrifuged at 10,000 g for 10 min; 50 µl of clear supernatant was then injected on to the HPLC column.

Chromatographic analysis of MPA was achieved with a C-18 Hamilton PRP-1 reversed phase column (250 mm × 4.6 mm i.d., particle size 10 µm) (Hamilton company, Reno, Nevada) connected to a suitable Hamilton guard column (25×2.3 mm, particle size 12-20 m) (Hamilton company, Reno, Nevada). Chromatography was carried out at ambient temperature with a flow rate of 1.0 ml/min, and monitored at a UV wavelength of 215 nm. The isocratic mobile phase was acetonitril /0.02 M potassium dihydrogenphosphate buffer (pH adjusted to 3 with phosphoric acid 85%) (51/49).

The total run time was 14 min. Within-run variability and between-run variability ranged from 2.1% to 7.8% and from 1.2% to 19.3%, respectively. The concentration of MPA was determined by the ratio of its peak area in relation to that of the internal standard.

Pharmacokinetic data analysis

MPA AUC was determined using the linear trapezoidal rule. Cmax and Tmax were determined directly from the plasma concentration-time curve. Apparent clearance was calculated with standard pharmacokinetic formula.

Statistic analysis between MPA pharmacokinetic parameters and patients characteristics was performed using Pearson´s correlation coefficient using the SPSS program. MPA AUC and concentrations at different times were evaluated for correlation with demographic factors such as age, sex, weight, time after transplantation, physiologic parameters (such as serum creatinine), and pharmacologic parameters (such as cyclosporine daily dose, prednisolone daily dose and MMF dose as mg/kg). Results are expressed as the mean ± SD or mean (range). A P-value of less than 0.05 was considered to be statistically significant.

Results

A total of 21 kidney transplant recipients (14 men and 7 women) were entered into the study. Characteristics of these patients are listed in Table I. All patients in this study received living donor grafts. There were two cases of re-transplantation. Mean age of the patients was 49 years (27-70) and mean weight was 69.9 Kg (49-95.5). The mean serum creatinine of the 21 patients at sampling day was 1.12 mg/dl (0.81-1.4). The mean cyclosporine dose administered to the patient on the study day was 136.9 mg/day (75-250) correspond to a mean of 1.97

Table 1. Patient's Demographics.

Demographics	
Number of patients	21
Sex	
Male	14
female	7
Age (years, mean ±SD)	49.0 ± 9.9
Weight(kg, mean ±SD)	69.9 ± 11.7
Retransplantation	2
Biochemical parameters (mean ± SD)	
Serum creatinine (mg/dl)	1.12 ± 0.19
Aspartate aminotransferase (IU/L)	21.7 ± 9.7
Alanine aminotransferase (IU/L)	24.6 ± 16.8
Total bilirubin (mg/dl)	0.91± 0.3
Dose of immunosuppressants (mean ± SD)	
Dose of mycophenolate mofetile (MMF)/weight (mg/kg/day)	29.4 ± 5.0
Dose of cyclosporine (mg/day)	136.9 ± 38.4
Dose of cyclosporine (mg/kg/day)	1.97 ± 0.49
Dose of prednisolone (mg/day)	5.1± 2.0

mg/kg (1.25-3.06). One patient complained of minor GI adverse effects. The mean prednisolone dose administered was 5.12 mg/day (2.5-10) or 0.074 mg/kg (0.03-0.13).

MPA pharmacokinetics

Mean plasma concentration and standard deviation of MPA in 21 kidney transplant patients is depicted in Figure I. Table 2 shows pharmacokinetic parameters of MPA in these patients. The pharmacokinetic profiles of MPA are characterized by an early and sharp increase of MPA concentration, with the first peak concentration being reached at 1.0 hour (0.67-2 hours) after dosing. These profiles were consistent with rapid absorption and rapid conversion of MMF to MPA, followed by rapid distribution and metabolism of generated MPA. Secondary increase in plasma MPA levels occurred in all patients at 8.1 (4-12) hours after dosing, consistent with previously described enterohepatic circulation of MPA glucuronide (MPAG) (12, 13, 27).

Tertiary increase in plasma MPA levels occurred in 10 patients, but this increase was small and occurred at 10.2 (8-12) hours after dosing. Because these increases interfered with the accurate calculation of the terminal half-life of MPA, the values for half-life were not determined in this study.

There was a substantial inter-individual variation of MPA AUC, Cmax, and Tmax values among the patients. The mean MPA AUC in Iranian kidney transplantation recipients was 47.0±18.3 µg.h/ml (25.5-107.8). The peak concentration of MPA was reached at 1.0±0.5 hours after dosing, and the mean maximal MPA concentration was 18.6±8.5 µg/ml. The mean oral MPA clearance (CL/F) was 23.5 ± 6.9 l/hr (9.2-39.2).

Correlation of pharmacokinetic parameter and patient characteristics

To determine the factors affecting AUC or serum concentration of MPA, a correlation analysis between AUC or serum concentration of MPA at different times and patient's demographic characteristic was performed (table III). The patient's age and weight had no relation with AUC of MPA ($p = 0.178$, $r = 0.305$ and $p = 0.085$, $r = -0.385$ respectively). Although MPA AUC did not show a statistically significant difference according to the patient's gender (one sample t test, $p = 0.127$), mean AUC of MPA in female was higher than that of males (53.26 and 43.96 µg.h/ml respectively), even though they were given the same doses of MMF. Time since transplantation had a positive relationship with MPA AUC ($p = 0.034$, $r = 0.465$). MMF total daily dose, MMF normalized dose, cyclosporine and prednisolone daily or weight normalized dose also did not show a linear relation to AUC of MPA or MMF serum concentration. Serum creatinine at sampling

Table 2. Pharmacokinetic parameteres of MPA in Iranian kidney recipients.

	Number of patients	Minimum	Maximum	Mean ± SD
AUC (µg.h/ml)	21	25.51	107.85	47.06 ± 18.36
$Tmax_1$ (h)	21	0.67	2.0	1.06 ± 0.49
$Cmax_1$ (µg/ml)		5.57	34.47	18.67 ± 8.59
$Tmax_2$ (h)	21	4.0	12.0	8.14 ± 2.1
$Cmax_2$ (µg/ml)	21	0.62	8.39	2.65 ± 1.81
$Tmax_3$ (h)	10	8.0	12.0	10.20 ± 1.62
$Cmax_3$ (µg/ml)	10	1.38	4.97	2.42 ± 1.31
Cl (L/h)	21	9.27	39.21	23.58 ± 6.96

AUC: Area Under Curve, Cl: Renal Clearance.

Table 3. Correlation between Area Under Curve (AUC) and demographic, biochemical and pharmacologic factors.

	Weight	Age	Time after transplantation	MMF Dose as mg/kg	Total daily dose of cyclosporine	Cyclosporine Dose as mg/kg
r	-0.385	0.305	0.465	0.383	-0.362	-0.207
p-value	0.085	0.178	0.034	0.087	0.107	0.368
	Total daily dose of prednisolone	Prednisolone Dose as mg/kg	Serum Creatinine	Hematocrit	WBC	Hemoglobin
r	-0.075	0.110	-0.191	-0.143	0.016	-0.112
p-value	0.748	0.635	0.408	0.536	0.946	0.630

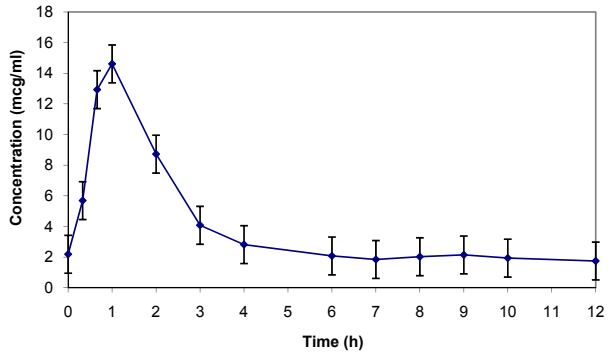

Figure 1. Mean mycophenolic acid (MPA) plasma concentration-time profiles of 21 Iranian kidney transplant patients.

day had no association with AUC and MPA concentration at any time. We did not find any relationship between MPA, AUC and MPA concentration at different times and hematocrit or white blood cell count or hemoglobin.

Discussion

As many studies on MPA pharmacokinetics in kidney and heart transplant patients have been performed, MPA pharmacokinetics has come to be better known. However, MPA pharmacokinetics in Iranian transplant patients has never been characterized before.

A growing number of studies suggest significant inter-individual variability of MPA pharmacokinetic among transplant recipients (11, 12, 17, 18, 28-33). Our study accordingly showed a large inter-individual variability in Iranian kidney transplant recipients, such that AUC of patients was widely spread between 25.51 and 107.85 µg.h/ml. Different factors may contribute to this variability including wide variability in the first-pass gut and/or liver metabolism and clearance of MPA as a result of polymorphisms in the promoter of UDP-glucuronosyl transferase 1A9 gene, enterohepatic cycling (18, 29, 34) and concomitant drugs (such as cyclosporine and glucocorticoids) (28, 35-39). Lack of correlation between dosage and MPA plasma concentration could be a consequence of this high variability.

Rapid increase in plasma concentration within 0.6-2 hours of dosing and a second peak observed at 4 to 12 hours is consistent with the results reported by Cho et al. (12), Bullingham (13), and Brunet (27).

The second peak of MPA in plasma observed in patients between 4 and 12 h after dosing, is most likely due to enterohepatic circulation of MPA from its metabolite (MPAG) (10, 28, 35, 38, 27).

The mean AUC of MPA in this study was calculated to be 47.0 µg.h/ml. Comparing this value to the data of Shaw et al., (40) revealed that AUC of MPA in Iranian patients are higher than those of African-American patients (36.2±10.9 µg.h/ml), who took the same dose of MMF (P=0.013), while it is not significantly different from AUC obtained by Brunet et al. (27) (49.8±24.8) (P=0.503) and AUC of Caucasian patients reported by Shaw et al. (40) (46.8 ± 17.6 µg.h/ml) (P=0.948). This variability may be due to population differences, effect of interacting concomitant drugs (kind and dose) and or time since transplantation. For example, in the study by Shaw et al., all patients were transplanted less than three month before sampling time or in the study of Brunet et al., a mean of 38.5 months passed since transplantation. However, in accordance with the results of Shaw et al. (28) and Engelbertink et al. (41), AUC of MPA has a positive correlation with time since transplantation that may be due to lower dosage of cyclosporine and glucocorticoids in patients with earlier transplantation.

The patient's age and weight were not related to the AUC value of MPA. Women had greater AUC value than men, but this difference was not statistically significant. This finding is in accordance with the results of Cho et al. (12) and Kuriala-Kordek et al. (36) and is probably due to the common metabolic pathway of MMF and estrogens as well as the same binding sites at UGT1A.

Some studies (28, 35-39, 42) have revealed that AUC of MPA or its concentration at certain times has a negative correlation with the blood level of cyclosporine or prednisolone. Blood levels of cyclosporine or prednisolone were not measured in our study and therefore investigation of a correlation between cyclosporine or prednisolone level and AUC of MPA or MPA concentration at different

times was not possible.

In conclusion, this study revealed that pharmacokinetic parameters of MPA in Iranian transplant patients are similar to other populations. Also, due to large inter-individual variability measuring serum levels can help in prevention of unnecessary exposure to MPA or undesirable low levels.

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