ORIGINAL ARTICLE

Pharmacokinetics of Mycophenolic Acid in Liver Transplant Patients After Intravenous and Oral Administration of Mycophenolate Mofetil

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The bioavailability of mycophenolic acid (MPA) after oral administration of mycophenolate mofetil (MMF) has been reported to be more than 90% in healthy volunteers, and in kidney and thoracic organ transplant patients. Such information is limited in liver transplant (LTx) patients. The present study compares the pharmacokinetics of MPA after intravenous (IV) and oral administrations of MMF in LTx recipients. Pharmacokinetic parameters were calculated using WinNonlin software. A total of 12 deceased donor LTx patients initially received IV MMF and were switched to oral MMF after 2-7 days (mean, 3.3 ± 1.7) when oral feeds were started. Multiple blood samples were drawn immediately prior to and after IV or oral MMF and the plasma concentration of MPA was measured. The mean peak plasma concentrations and the area under the plasma concentration vs. time curve (AUC) were significantly higher after IV MMF compared to oral MMF (peak plasma concentrations of 10.7 ± 2.1 μg/mL for IV vs. 4.5 ± 2.8 μg/mL for oral; $P = 0.0001$; and AUC of 28.9 ± 7.1 μg · hr/mL for IV vs. 12.8 ± 4.2 μg · hr/mL for oral; $P = 0.0001$). The oral bioavailability of MPA was 48.5 ± 18.7%. The systemic clearance, half-life, and steady state volume of distribution of MPA were 26.9 ± 6 L/hour, 5.5 hours, and 85 liters, respectively. The terminal disposition half-life was not significantly different between the 2 routes of administration. In conclusion, during the early postoperative period, LTx recipients have MPA exposure with oral MMF of less than half that of IV MMF. Use of IV MMF immediately post-LTx may provide an immunological advantage. ***Liver Transpl 13:791-796, 2007.*** © **2007 AASLD.**

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Mycophenolate mofetil (MMF) is a nonnephrotoxic immunosuppressive agent that is used in conjunction with calcineurin inhibitors such as cyclosporine and tacrolimus to prevent rejection after solid-organ transplantation. MMF is rapidly converted to mycophenolic acid (MPA; the active moiety), by esterase in the gut and liver. At the present time, the esterase deficiency, impaired function of esterase, or rate limiting aspects of this agent are unknown. MPA is a noncompetitive inhibitor of inosine monophosphate dehydrogenase and prevents the de novo synthesis of purine nucleotides in proliferating T and B lymphocytes.[1-3]

The benefits of MMF in reducing acute rejection episodes were first reported in kidney transplant (KTx) patients.[4-6] In liver transplant (LTx) patients, the use of MMF with calcineurin inhibitors has met with limited success, as more than 50% of the patients discontinued MMF for a variety of reasons.[7-10] Recently, we have reported a substantial reduction in acute rejection episodes when MMF was administered intravenously (IV) with tacrolimus in live donor liver transplantation.[11]

All of the early clinical trials in KTx and LTx recipients were performed using the oral formulation of MMF. More than 90% of MMF is reported to be absorbed after

Abbreviations: MMF, mycophenolate mofetil; MPA, mycophenolic acid; KTx, kidney transplant(ation); LTx, liver transplant(ation); IV, intravenous(ly); AUC, area under the plasma concentration vs. time curve.

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oral administration in healthy volunteers, KTx patients, and heart transplant patients.[12-14] However, limited studies have been carried out to evaluate the pharmacokinetics of MPA in LTx patients. A time-dependent increase in trough MPA plasma concentrations has been reported after oral MMF administration in LTx recipients.[15] Similarly, a progressive increase in the area under the plasma concentration vs. time curve (AUC) of MPA following a fixed dosing regimen has also been reported in LTx patients.[16] These progressive changes have been attributed in part to an increase in plasma protein binding of MPA with time after LTx. The contribution of incomplete bioavailability of MPA to the lower AUC during the early posttransplantation period has not been previously evaluated. In this study we evaluated the pharmacokinetics of MPA in LTx patients after IV and oral administration of MMF during the immediate postoperative period in an effort to understand the bioavailability of MPA from MMF.[17]

TABLE 1. Characteristics of Patients

Gender (male:female)	11:1
Mean age (yr)	
Recipients (SD)	51.5 ± 13.1
Donor (SD)	51.3 ± 13.5
Mean weight (kg)	86.9 ± 22.6
Mean height (cm)	174.7 ± 5.3
Body mass index (kg/m^2)	29.11 ± 6.9
Mean body surface area (m^2)	2.06 ± 0.27
Diagnosis	
Hepatitis C	5
Ethanol	3
Cryptogenic	1
Autoimmune	1
Sclerosing cholangitis	1
Biliary atresia	1

Abbreviation: SD, standard deviation.

MATERIALS AND METHODS

Study Design and Patients

Between January 2005 and November 2005, 12 consenting adult deceased donor LTx recipients were prospectively enrolled in an institutional review board–approved protocol to study the pharmacokinetics of MPA after MMF administration. Children (age <18 yr), and pregnant and lactating women were excluded.

Treatments

All patients were initiated on IV MMF at a dose of 1 gm twice daily (constant 2-hour infusion) for 2 to 7 days (mean, 3.3 ± 1.7; median, 2.5 days), and then converted to oral MMF 1 gm twice daily when oral feeds were commenced.

In addition, study patients received oral tacrolimus, starting at a dose of 0.05 mg/kg twice daily. The dose of tacrolimus was adjusted as per the clinical conditions, and the target trough levels were normally maintained around 8-10 ng/mL. The patients also received 500 mg of methylprednisolone prior to reperfusion of the liver and then 100 mg twice a day of methylprednisolone that was tapered to 20 mg twice a day over the next 5 days.

Blood Collection and Sample Preparation

Serial blood samples were drawn at 0 (predose), and at 1, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, and 12 hours after starting IV MMF on the second or third postoperative day. Similarly, 2-3 days after conversion to oral MMF, serial blood samples were drawn at 0 (predose) and at 1, 2, 3, 4, 5, 6, 8, 10, and 12 hours after oral administration of MMF. Blood samples were drawn in BD Vacutainer tubes (Wilburn, Kernesville, NC) spray-coated with potassium ethylene diamine tetraacetic acid, kept on ice until centrifugation. Plasma was transferred into a clear tube and frozen at −20°C until analysis. The plasma concentration of MPA was measured using a high-performance liquid chromatographic method that has been validated in our laboratory based on the method described by Shipkova et al.[18] During the study period, none of the patients were on oral antacid, cholestyramine, or any other drug known to interfere with the absorption of MMF.

Calculations and Statistical Analysis

Various pharmacokinetic parameters were calculated using noncompartmental analysis with WinNonlin software (version 4.1; Pharsight Corporation, Mountainview, CA). The parameters calculated included terminal disposition rate constant (λz), terminal disposition half-life, AUC, apparent systemic clearance, apparent steady state volume of distribution, and mean residence time after IV administration. The peak plasma concentrations, time to reach peak concentration, last plasma concentration at 12 hours, terminal disposition half-life, AUC, bioavailability, and mean residence time were calculated after oral administration of MMF. Each of these parameters is presented as mean and standard deviation. Statistical comparison of different parameters was made using *t*-test (SPSS software, Windows-based version 14.0, Chicago, IL). A *P* value of <0.05 was considered statistically significant.

RESULTS

The characteristics of the patients, including the primary diagnosis and the age and gender distribution, are shown in Table 1. The laboratory values for the patients in the study are shown in Table 2. All the patients participated in the IV pharmacokinetic study; however, blood samples were not obtained from 1 patient after oral administration of MMF. A total of 12 IV profiles and 11 oral pharmacokinetics profiles were available for analysis. The mean plasma concentrations of MPA over time in all the patients after IV MMF and oral MMF are shown in Figure 1. The pharmacokinetic parameters of MPA after IV and oral administration of MMF are shown in Table 3. There was a wide variation in various pharmacokinetic parameters of

TABLE 2. Mean Laboratory Values on Study Day

MMF	WBC	Hct	Plat	BUN	Creat	Alb	T Bili	AST*	ALT*	ALK*	GGT*
IV	12.2	29.2	68.8	42.5	1.9	2.3	3.5	916.8	698.2	84.8	74.3
Oral	8.3	29.4	87.9	33.9	1.4	2.5	2.3	60.1	184.1	117.4	270.3

Abbreviations: WBC, white blood cell count (10^3/mL); Hct, hematocrit (%); Plat, platelet count (10^3/mL); BUN, blood urea nitrogen (mg/dL); Creat, creatinine (mg/dL) Alb, albumin (gm/L); T Bili, Total bilirubin (mg/dL); AST, aspartate aminotransferase (U/L); ALT, alanine aminotransferase (U/L); ALK, alkaline phosphate (U/L); GGT, gamma glutamyl transpeptidase (U/L).
*$P < 0.05$ between IV and oral study days.

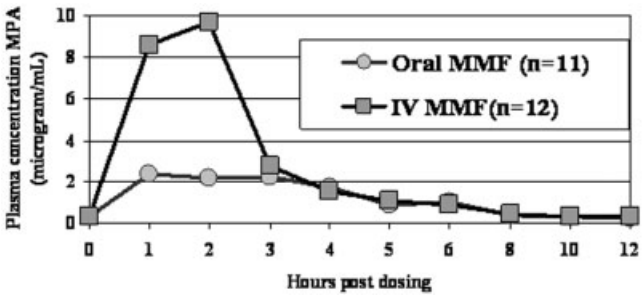

Figure 1. Mean plasma concentrations of MPA over time after initiation of dosing.

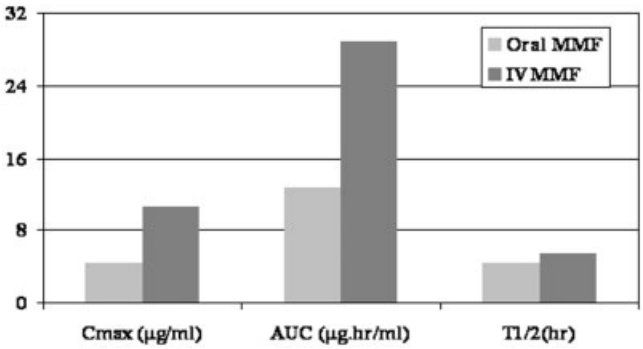

Figure 2. MPA pharmacokinetic parameters after IV and oral administration of MMF. Maximum concentration (Cmax), Area under plasma concentration vs. time curve (AUC) and half-life ($T_{1/2}$).

MPA in LTx patients after IV and oral MMF administration.

Generally, the plasma concentrations were higher at most of the time points examined during IV therapy compared with oral therapy. The mean peak plasma concentration of MPA was 10.7 ± 2.1 μg/mL after IV administration compared to 4.5 ± 2.8 μg/mL (P = 0.0001) after oral administration. The mean AUC was more than 2-fold higher after IV administration compared with the oral administration of equivalent doses of MMF (28.9 ± 7.1 μg/mL/hour for IV vs. 12.8 ± 4.2 μg/mL/hour for oral; P = 0.0001). The mean 12-hour trough concentrations were 1.4 times higher with IV compared with oral treatment (0.33 ± 0.17 vs. 0.23 ± 0.16 μg/mL; P = 0.09). The overall mean bioavailability of MPA after oral administration was 48.5 ± 18.7%. The terminal disposition rate constant and the terminal disposition half-life, were similar after IV and oral administration. The other pharmacokinetics parameters are given in Table 3.

Discussion

The benefit of MMF as part of a primary therapy or rescue therapy has been well documented in solid organ transplant patients.[4,5,19-25] The advantages of using MMF with a calcineurin inhibitor are also well established in KTx.[19,20,26-28] In LTx recipients, however, the benefits of MMF are not as substantial, which may be partly related to the poor bioavailability during the early postoperative period. Efficacy also may influenced by the higher rate of withdrawal of MMF, in part related to the toxicity profile of the oral formulation.[8-10,29]

The present study shows that the bioavailability of oral MMF is less than 50% in LTx recipients, which is much lower than that reported in healthy volunteers and heart transplant patients. IV MMF in LTx patients provides 2.4 times higher peak plasma concentration and 2.2 times higher drug exposure (AUC) and 1.4 times higher trough concentrations of MPA compared to oral MMF. The use of IV MMF immediately post-LTx may provide an immunological advantage.[11]

Prior to this report there has been only 1 short report on the pharmacokinetics of MPA after IV administration of MMF in LTx patients. The AUC of MPA after administration of 1.75 gm MMF at 24 hours after LTx was reported to be 42.85 ± 21.7 μg · hr/mL in 6 patients.[30] When the AUC data were normalized to the dose administered, the value is similar to what is observed in the present report. The terminal disposition half-life observed in the present study is shorter than what has been reported in normal subjects.[31]

We have reported a time-dependent increase in trough plasma concentrations of MPA after LTx in patients on a fixed dosing regimen of MMF. This increase was associated with an increase in the plasma albumin concentration over time after LTx.[15] We also have reported an increase in total AUC of MPA over time after LTx based on sequential pharmacokinetic studies after oral MMF. This AUC increase was attributed to an increase in the plasma protein binding of MPA.[16] Recently, Brunet et al.[32] have demonstrated low MPA AUC in the first month post-LTx, in agreement with our previous observation. The contribution of changes in the

TABLE 3. Pharmacokinetic Parameters of MPA After IV and Oral MMF

	IV MMF								
Case #	Cmax (μg/mL)	Tmax (hours)	C12 (μg/mL)	Lambda_z (hours − 1)	HL_Lambda_z (hours)	AUCINF_obs (μg. mL/ hour)	Cl_obs (L/hour)	Vss_obs (L)	MRTINF_obs (hours)
1	11.5	2	0.5	0.09	7.3	37.1	19.9	93.6	4.7
2	12.7	2	0.2	0.14	7.1	25.7	28.8	95.2	3.3
3	9.8	2	0.3	0.18	7.0	29.2	25.3	95.5	3.8
4	10.4	2	0.1	0.10	6.4	23.5	31.5	65.2	2.1
5	8.1	1	0.3	0.10	5.0	24.1	30.7	104.7	3.4
6	10.0	1	0.4	0.10	2.5	32.3	22.9	62.8	2.7
7	11.3	1	0.4	0.11	9.6	35.9	20.6	109.3	5.3
8	7.2	2	0.3	0.14	2.8	18.8	39.4	93.6	2.4
9	14.7	2	0.8	0.28	2.2	44.1	16.8	49.2	2.9
10	12.1	2	0.1	0.07	5.0	25.2	29.3	59.0	2.0
11	11.8	2	0.2	0.25	4.0	25.4	29.1	62.6	2.2
12	9.3	1	0.3	0.31	7.2	25.8	28.7	128.4	4.5
Mean	10.73	1.67	0.33	0.15	5.52	28.92	26.89	84.93	3.27
SD	2.05	0.49	0.17	0.08	2.31	7.13	6.16	24.45	1.10
Median	10.84	2.00	0.33	0.12	5.72	25.75	28.70	93.59	3.12

	Oral MMF								
Case #	Cmax (μg/mL)	Tmax (hours)	C12 (μg/mL)	Lambda_z (hours − 1)	HL_Lambda_z (hours)	$AUC_{0\text{-}12}$ (μg.mL/ hour)	CLss_F (L/hour)	Bioavailabiity (%)	MRTINF_obs (hours)
1	1.8	2	0.3	0.17	4.0	10.0	73.9	27.0	6.6
2	1.3	4	0.2	0.20	3.4	7.7	95.7	30.0	5.3
3	2.7	4	0.4	0.12	5.7	14.0	52.7	48.0	7.7
4	4.3	1	0.1	0.12	5.6	8.4	88.3	36.0	3.9
5	5.3	6	0.3	0.12	5.9	14.0	52.8	58.0	8.2
6	1.3	2	0.1	0.28	2.5	6.8	109.3	21.0	5.2
7	10.7	1	0.1	0.12	6.0	16.7	44.2	47.0	2.6
8	6.3	3	0.1	0.21	3.3	12.9	57.1	69.0	3.5
10	4.8	3	0.6	0.16	4.3	19.4	38.0	77.0	7.2
11	6.9	2	0.2	0.15	4.5	17.6	42.1	69.0	3.9
12	3.6	2	0.2	0.15	4.7	13.3	55.4	52.0	4.6
Mean	4.46	2.73	0.23	0.17	4.54	12.8	64.49	48.55	5.35
SD	2.84	1.49	0.16	0.06	1.19	4.2	23.81	18.64	1.86
Median	4.34	2.00	0.18	0.15	4.52	13.35	55.38	48.00	5.23
P value	0.0001	0.012	0.09	0.06	0.18	0.0001			0.003

Abbreviations: Cmax, maximum concentration; Tmax, time to reach maximum concentration; C12, concentration at 12 hours; Lambda_z, disposition rate constant; HL_Lambda_z, half-life; AUCINF_obs, area under the curve concentration; Cl_obs, clearance; Vss_obs, volume of distribution; MRTINF_obs, mean residence time; CLss_F, apparent oral clearance at steady state.

bioavailability of MPA to the observed increase in AUC was not assessed in these earlier studies.

Large interpatient variation in the pharmacokinetics of MPA after oral administration has been reported in different patient populations.[22,33-41] Brunet et al.[32] have also demonstrated variability of the pharmacokinetics and pharmacodynamics of MPA among LTx patients. Differences in liver function, renal function, other coadministered drugs, and plasma protein binding appear to contribute to this variability. Variability in the pharmacokinetics of MPA after oral administration of MPA within the same individual also has been reported in different patient populations.[42] Kuypers et al.[43] reported serial increases in $AUC_{(0\text{-}12)}$ over the first 3 months post-KTx. Shaw et al.[44] have reported increases in MPA AUC with increased albumin binding over time in KTx patients. Atcheson et al.[45] and Merkel et al.[46] independently have made similar observations in KTx. Majority of the patients with liver failure have low albumen concentration, which could affect binding of MMA. Furthermore, lower albumin levels after prolong intraabdominal operation, which involves temporary clamping of the portal vein, can cause edema of the bowel, which could also interfere with the absorption of the drug in the post-LTx period.

MMF has been shown to be rapidly converted to MPA in

vivo.[31] This deesterification process does not appear to be altered in the presence of severe renal or liver impairment. The bioavailability of MPA after oral administration of MMF has been reported to be high in normal subjects, heart transplant patients, and heart-lung transplant patients. Bullingham et al.[13,31] demonstrated 96% bioavailability of oral MMF in healthy individuals. Armstrong et al.[12] documented a mean bioavailability of 95% after oral MMF in heart transplant patients. Ensom et al.[14] showed no difference in AUC of MPA in heart and lung transplant patients when studied at 15, 23, and 125 days posttransplantation. Pescovitz et al.[47] reported significantly higher AUCs with IV MMF compared with oral dosing, but with similar trough plasma concentrations of MPA. In the present report, we have shown the apparent bioavailability of the oral formulation of MMF to be about 49% between days 4 and 9 post-LTx. It is possible that the bioavailability may be even lower in the first few days post-LTx.

MPA AUC correlates with rejection and toxicity.[48] In KTx, trough concentrations of MPA <2 $\mu g/mL$[41] were associated with increased rates of rejection, while AUCs >40 $\mu g \cdot hr/mL$ were associated with better renal function.[39,41] Higher rates of side effects in KTx have been reported to correlate with higher trough level and higher AUC.[41,49] In a dose-finding study of MMF, less than 2 gm/day of oral MMF in KTx was found to have no clinical benefits.[2] If the oral bioavailability of MPA is reduced in LTx recipients, 1 gm twice daily would not provide the same drug exposure as in KTx and thus may not reach the level required for clinical effect. Bioavailability may be important in LTx patients, in whom inadequate absorption of the oral formulation may impair the efficacy of the drug. Overall, MPA drug exposure may be increased by increasing the oral dose of MMF in the immediate postoperative period. However, higher doses may not be tolerated after major upper abdominal surgery. In this setting, the IV formulation offers complete bioavailability, with higher peak plasma concentration values, as well as better tolerability. Use of IV administration of MMF has been associated with higher rates of rejection-free survival after LTx at our center.[11]

In conclusion, the oral bioavailability of MPA from MMF is less than 50% in the immediate LTx postoperative period, in contrast with studies in normal subjects and those in renal, and heart and lung transplant patients. IV MMF provides significantly higher plasma concentrations, with higher peak concentrations and greater overall drug exposure (higher AUC). Along with reduced gastrointestinal toxicity, these factors are essential to achieve a higher rate of rejection-free survival with tacrolimus and steroid in live donor and deceased donor LTx. Prospective clinical studies are needed to assess whether IV MMF also may allow the use of lower doses of calcineurin inhibitors, delayed introduction of calcineurin inhibitors, and use of lower induction doses of steroids. These results will provide the basis for better utilization of the immunosuppressive potential of MMF in organ transplant patients.

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