Pharmacokinetics of Mycophenolic Acid after Mycophenolate Mofetil Administration in Liver Transplant Patients Treated with Tacrolimus

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The pharmacokinetics of mycophenolic acid (MPA) was studied after oral administration of mycophenolate mofetil (MMF) in 8 liver transplant patients. The mean (± SD) maximum MPA plasma concentration of 10.6 (± 7.5) mg/ml was achieved within 0.5 to 5 hours. The mean (± SD) steady-state area under the plasma concentration versus time curve (AUC_{0-12}) was 40 (± 30.9) mg/ml/h. The mean (± SD) half-life was 5.8 (± 3.8) hours. There was poor correlation between trough blood concentrations of tacrolimus (r = –0.004) or serum creatinine (r = 0.689) with MPA AUC, while the serum bilirubin concentrations correlated (r = 0.743) well with MPA AUC, suggesting impairment in MPA conjugation in patients with liver dysfunction. The mean (± SD) ratio of the AUC of mycophenolic acid glucuronide (MPAG) to MPA was 64 (± 84), which correlated significantly with serum creatinine (r = 0.72) but not with serum bilirubin concentrations (r = 0.309), indicating accumulation of MPAG in patients with renal dysfunction. In 7 primary liver transplant patients on the same dose of MMF, the trough plasma concentrations of MPA during the first week of therapy ranged from < 0.3 to 1.5 µg/ml. The MPA concentrations increased by several folds during the next few weeks, which correlates well with increases in serum albumin concentrations. Changes in albumin appear to partially contribute to the variations in the pharmacokinetics of MPA in liver transplant patients.

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Mycophenolate mofetil (MMF; morpholinoethyl ester of mycophenolic acid [MPA]) is the prodrug of MPA. Mycophenolic acid is a potent, noncompetitive inhibitor of inosine monophosphate dehydrogenase and prevents de novo synthesis of guanosine nucleotides and blocks T and B cell proliferation.[1-3] After oral administration, mycophenolate mofetil is rapidly converted to MPA in the body and is excreted as the glucuronide conjugate (MPAG) in the urine and bile.

Three separate double-blind randomized trials involving MMF have been carried out in primary kidney transplant patients in Europe, United States, Canada, and Australia. In these studies, the efficacy of MMF in combination with cyclosporine and steroid was compared with the efficacy of cyclosporine, steroid, and azathioprine or that of cyclosporine, steroid, and placebo. Significantly reduced rejection episodes were noted with MMF therapy in all three trials.[4-6]

Several clinical trials have documented tacrolimus to be an effective immunosuppressive drug following liver transplantation (LTx).[7-11] The safety and efficacy of MMF in combination with tacrolimus have recently been studied in renal transplant patients. In the present study, we (1) evaluated the pharmacokinetics of MPA in primary LTx patients within the first 30 days after transplantation and initiation of MMF therapy and (2) examined the trough concentrations of MPA during the first few weeks after transplantation in separate groups of primary liver transplant patients treated with tacrolimus and MMF.

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PATIENTS AND METHODS

Patients

The protocol was part of the study approved by the Biomedical Institutional Review Board to evaluate the addition of MMF to tacrolimus therapy in primary LTx patients. Prior written informed consent was obtained from all the participants. All the patients enrolled in the study received tacrolimus and steroid with 1 g of MMF given twice a day. While the initial dose of tacrolimus was 0.15 mg/kg/day given in two divided doses, tacrolimus dose was adjusted based on whole-blood concentrations (5-25 ng/ml) of tacrolimus. Tacrolimus and MMF were administered at the same time in the morning and in the evening in all the patients.

Study Design

The pharmacokinetics of MPA was evaluated in a group of 8 liver transplant patients during one dosing interval after the morning dose within a month after transplantation and the initiation of MMF therapy. Multiple blood samples were collected in green-top Vacutainers at 0, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, and 12 hours. Plasma was obtained by centrifugation at room temperature and was analyzed for MPA and MPAG. In a separate group of 7 patients, fasting blood samples were collected in the morning prior to MMF administration during the first few weeks after transplantation. Trough concentrations of MPA (6 to 13 observations in each patient) were measured and related to various biochemical parameters.

Analysis

The plasma concentrations of MPA and MPAG were measured by high-pressure liquid chromatography (HPLC). Standard curves were constructed with pure MPA (Sigma) dissolved in methanol or MPAG dissolved in acetonitrile and added to MPA-free or MPAG-free plasma. For MPA analysis, the plasma samples (250 µl) were mixed with the internal standard solution (diazepam in methanol) and 1 ml of 0.1 N HCL and loaded onto a solid-phase extraction column (Waters C-18 seppak cartridge); the column was washed with water, and MPA was finally eluted with 2 ml methanol. The eluent was evaporated and reconstituted in the mobile phase (41% acetonitrile, 59% water) and injected onto a C-18 Picotag column (300 mm long × 3.9 mm) maintained at 50°C. The eluents were monitored at 254 nM. The retention time for MPA was 6 minutes, and the internal standard was 11 minutes. The standard curve was linear from 0.3 to 25 µg/ml. The recovery of MPA from the plasma was > 75%. The intraday variations (n = 7) of the assay at 1.9 and 6.2 µg/ml were 8.6% and 6.2%, respectively. The interday variations (n = 7) at 1 and 4.8 µg/ml were 7.9% and 4.8%, respectively.

To measure the unbound fraction of MPA in plasma, two plasma samples obtained during each kinetic study were spiked with 20 µg/ml of MPA and subjected to ultrafiltration at room temperature. The plasma concentration of total and unbound MPA was measured by HPLC. The unbound fraction was calculated as the ratio of unbound concentration to total concentration.

For MPAG analysis, a protein precipitation procedure was used (Les Shaw, personal communication, 1998) along with minor modification of published column conditions.[12] To plasma samples (20 ul), phenolphthalein glucuronide in methanol/water was added as an internal standard, and proteins were precipitated with acetonitrile. The mixture was vortexed and centrifuged. The supernatant was injected on a 25 cm Hypersil BDS 5U C-18 column (Altech); a mobile phase of 0.05% phosphoric acid and acetonitrile (75:25) at a flow rate of 1 ml/min was used. The eluents were monitored at 254 nM. The retention time for MPAG was 10.2 minutes, and the internal standard was 11.5 minutes. The standard curve was linear from 2.5 to 200 ug/ml. The coefficient of variation (CV) was 3.7% at 25 ug/ml.

The whole-blood tacrolimus concentrations were measured using the microparticulate enzyme immunoassay (MEIA IMX—Abbott) technique.[13] Linear regression analysis was used to calculate the correlation between several parameters.

Noncompartmental pharmacokinetic analysis was performed on the collected data according to standard methods.[14]

RESULTS

Pharmacokinetics of MPA

Group I. The demographics of patients in group I are shown in Table I. The plasma concentration versus time profile of MPA following an oral dose of 1 g of MMF in 3 liver transplant recipients is shown in Figure 1. The various pharmacokinetics parameters estimated in each patient are listed in Table II. The observed peak plasma concentration (C_{max}) of MPA varied from 3.9 to 21.5 µg/ml (mean ± *SD*, 10.6 ± 7.5; median = 7.1). The peak plasma concentrations of MPA were achieved be-

tween 0.5 and 5 hours (t_{max}) (mean ± *SD*, 1.8 ± 1.6; median = 1.5). The area under the plasma MPA concentration versus time curve (AUC_{0-12}) ranged from 7.3 to 102.3 mg/ml/h (mean ± *SD*, 40 ± 30.9; median = 32.3). A small secondary increase in plasma concentration-time profile possibly due to enterohepatic circulation of MPA was observed in some patients. The half-life of MPA varied from 3.2 to 13.4 hours (mean ± *SD*, 5.8 ± 3.8; median = 4.5). In this group of subjects, there were significant correlations between trough plasma concentration of MPA and MPA AUC ($r = 0.752$; $p = 0.031$) and also between bilirubin concentration and MPA AUC ($r = 0.743$; $p = 0.035$). Poor correlation was observed between serum creatinine and AUC of MPA ($r = 0.689$; $p = 0.06$) or between the trough blood tacrolimus concentrations and AUC of MPA ($r = -0.004$; $p = 0.99$). The percent unbound MPA ranged from 2.0 to 6.3, with a mean (± *SD*) of 3.9 (± 1.6).

Figure 2 shows the plasma concentration versus time profile of MPAG in 3 patients. The minimum plasma concentration of MPAG ranged from 12.9 ug/ml to 116 ug/ml; the maximum plasma concentration of MPAG ranged from 36.9 ug/ml to 188 ug/ml. Maximum plasma concentrations of MPAG were typically seen between 1 and 4 hours after MMF administration. In 2 patients, a secondary peak in MPAG was observed around 8 hours. Table III describes the AUC for MPA and MPAG and the AUC ratio for MPAG and MPA. There was a significant correlation ($r = 0.72$; $p = 0.046$) between serum creatinine concentrations and the MPAG/MPA AUC ratio. The highest AUC ratio of 249 was observed in a patient with the highest serum creatinine concentration. On the other hand, there was poor correlation between serum bilirubin concentrations and the AUC ratios ($r = 0.309$; $p = 0.456$).

Table IV describes the biliary and urinary excretion of MPA and MPAG. Nearly 82% of the total dose of MMF administered appeared in the bile and urine as MPA or MPAG. On the average, less than 1% and 4% of the dose administered was excreted as MPA, and 26% and 49% of the dose was excreted as MPAG in the bile and the urine, respectively. In general, more MPAG was excreted in the urine than in the bile, but for 2 patients with serum creatinine of greater than 3 mg/dl, more MPAG was recovered in the bile than in the urine.

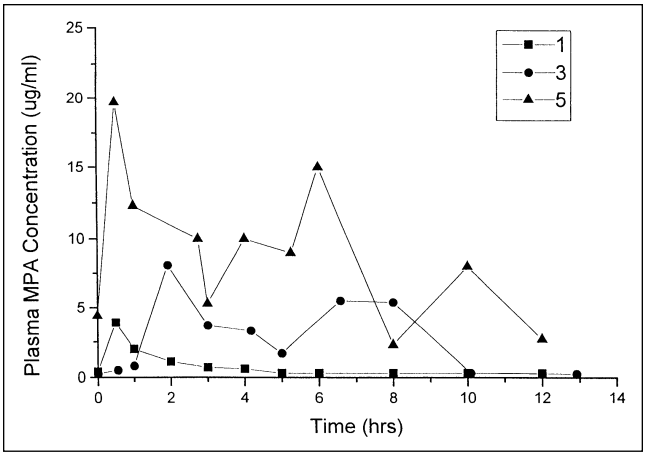

Figure 1. Mycophenolic acid (MPA) plasma concentration versus time curve in 3 patients (1 with the highest bilirubin [patient 5], 1 with the highest serum creatinine [patient 1], and 1 with normal bilirubin and serum creatinine [patient 3]) receiving a dose of 1 g of mycophenolate mofetil (MMF) bid po.

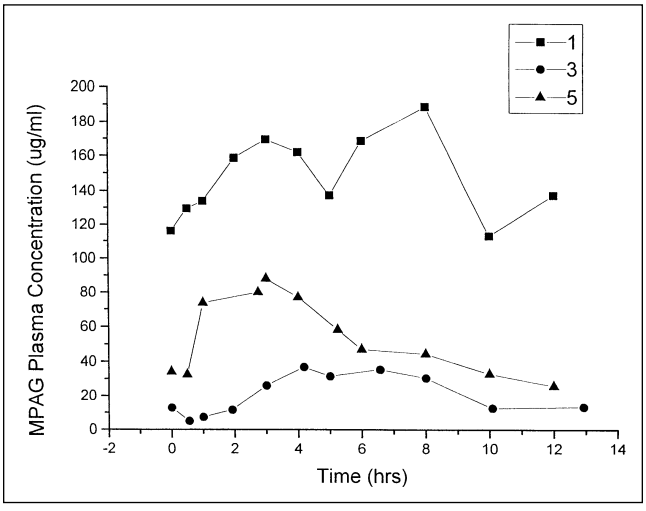

Figure 2. Mycophenolic acid glucuronide (MPAG) plasma concentrations in 3 liver transplant patients (1 with the highest bilirubin [patient 5], 1 with the highest serum creatinine [patient 1], and 1 with normal bilirubin and serum creatinine [patient 3]) receiving 1 g of mycophenolate mofetil (MMF) bid po.

Trough Concentrations of MPA

Group II. The demographics of the patients in group II are shown in Table V. Tacrolimus dose, the 12-hour trough blood concentrations of tacrolimus, MMF dose, and the plasma MPA concentrations, along with the biochemical profiles indicative of renal and liver function of patients in group I, are shown in Table VI. The 12-hour trough plasma concentrations of MPA among the different patients studied varied from less than 0.3 to 5.5 μg/ml during the first 50 days posttransplantation. The trough plasma MPA concentrations in individual patients varied 4- to 18-fold over this time period. There was an increase in trough MPA concentration with time in all the patients, and this was

Table I Patient Demographics: Group I

Number	Age (years)/ Gender	Diagnosis	Body Weight (Kg)	Days from Transplantation	Total Bilirubin (mg/dl)	BUN (mg/dl)	Creatinine (mg/dl)	Albumin (μg/dl)
1DS	42/M	HCV	80	30	1.4	83	4.3	2.8
2CS	53/M	HCV	81.1	28	1.3	46	2.1	2.4
3CW	65/M	PNC-E	55.5	12	1.6	10	0.7	2.0
4DN	31/F	FHF	52.1	11	1.8	10	0.9	3.0
5DA	21/M	PNC-C	65.6	18	2.4	17	0.8	3.2
6ND	60/F	PBC	131.3	6	1.3	68	4.2	3.1
7DZ	67/F	PNC-C	68	8	2.3	8	0.7	
8WC	53/M	PNC-E	66.1	11	0.4	87	3.3	

PBC, primary biliary cirrhosis; HCV, hepatitis C virus; PNC-E, ethanol-induced postnecrotic cirrhosis; FHF, fulminant hepatic failure; PNC-C, cryptogenic cirrhosis.

Table II Pharmacokinetic Parameters of MPA Group I Patients

Patients	MMF Dose (Gm)	Days on MPA Therapy	TAC Dose (mg)	TAC Trough Level (ng/ml)	MPA Trough Concentration (ug/ml)	MPA Peak Concentration (ug/ml)	t_{max} (h)	AUC (ug/ml/h)	Half-Life (h)	MPA % Unbound
1DS	1 bid	30	4 bid	4.2	0.4	3.9	0.5	7.3	3.2	6.3
2CS	1 bid	28	2 bid	9.5	0.3	4.2	2.0	12.7	3.9	5.2
3CW	1 bid	12	8 bid	38.3	< 0.3	8.1	1.9	37.4	NA	4.4
4DN	1 bid	11	5 bid	10.8	0.6	21.5	1.0	46.6	NA	2.9
5DA	1 bid	18	12 bid	9.9	4.4	19.7	0.5	102.3	5.4	2.2
6ND	1 bid	6	4 bid	14.7	0.6	6.0	3.0	24.5	5.0	2.0
7DZ	1 bid	8	9 bid	5.6	0.3	17.1	0.5	62.6	13.4	2.8
8WC	1 bid	11	3 bid	7.3	1.7	4.3	5.0	27.1	3.7	5.2
Mean					1.1	10.6	1.8	40.0	5.8	3.9
SD					1.4	7.5	1.6	30.9	3.8	1.6
Median					0.5	7.1	1.5	32.3	4.5	3.7

MPA, mycophenolic acid; MMF, mycophenolate mofetil; TAC, tacrolimus; NA, not available due to secondary peak interference; bid, twice a day.

Table III Summary Data on MPA and MPAG

Initials	C_{min} MPAG µg/ml	C_{max} MPAG µg/ml	MPA-AUC (µg/ml/h)	MPAG-AUG (µg/ml/h)	MPAG-AUC/ MPA-AUC	Serum Creatinine (mg/dl)	Serum Bilirubin (mg/dl)
1DS	116	169	7.3	1816	249	4.3	1.4
2CS	108	148	12.7	1443	114	2.1	1.3
3CW	12.9	36.9	37.4	283	7.6	0.7	1.6
4DN	19.0	83.3	46.6	443	9.5	0.9	1.8
5DA	34.1	88.1	102	610	6.0	0.8	2.4
6ND	37.8	156.4	24.5	1580	64.8	4.2	1.3
7DZ	51.1	136.7	62.6	1102	17.6	0.7	2.3
8WC	58.2	103.7	27.1	1117	41.2	3.3	0.4

MPA, mycophenolic acid; MPAG, mycophenolic acid glucuronide.

Table IV Excretion of MPA in Urine and Bile

Initials	Bile MPA	Bile MPAG[a]	Urine MPA	Urine MPAG[a]	Percentage of MMF Dose Totally Excreted in Bile/Urine as MPA and MPAG[b]
1DS	0.5	116	NA	NA	NC
2SC	0.6	92	5.7	297	54
3WC	0.6	119	51.8	284	62
5AD	0.1	49	32.3	716	108
6ND	1.4	275	39.1	183	68
7DZ	0.6	88	90.7	577	102
8WC	0.6	616	7.4	79	95
Mean	0.6	194	37.8	356	82
SD	0.4	200	31.6	242	23
Median	0.6	116	35.7	291	82

MPA, mycophenolic acid; MPAG, mycophenolic acid glucuronide; MMF, mycophenolate mofetil; NA, complete sample collection not available; NC, not calculated.

a. Expressed as MPA equivalent.

b. Expressed as percentage of MMF dose.

consistent with a positive slope ($m = 0.04831$) when the MPA plasma concentrations in all these patients were regressed ($r = 0.51$; $n = 66$ observations; $p < 0.05$) against the number of days posttransplantation (Figure 3). The individual correlation coefficients ranged from 0.45 to 0.67 in 6 patients and near zero in 1 patient. There was also a significant ($p = 0.003$) correlation ($r = 0.73$) between the trough plasma MPA concentrations and the albumin concentrations ($n = 14$) in these patients. Figure 4 shows the changes in trough MPA concentrations, serum albumin concentrations, serum bilirubin concentrations, and unbound fraction of MPA in 1 patient over 4 weeks after transplantation. The increase in MPA trough concentrations parallels the increase in serum albumin concentrations in this patient. As the albumin concentrations increase, the unbound fraction of MPA decreases as well.

DISCUSSION

Limited information is available on the pharmacokinetics of MPA in liver transplant patients.[15-17] Most of the studies to date have been carried out in renal or pancreas transplant patients.[18-27] We present here our report on the pharmacokinetics of MPA in liver transplant patients treated with MMF, tacrolimus, and steroids. There was a large variation in the pharmacokinetics of MPA in liver transplant patients.

Table V Patient Demographics: Group II

Number	Age (years)/Gender	Diagnosis	Interval from LTx (days)	Number of Observations
1WR	55/F	PBC/HVC	1-27	13
2CM	39/M	HBV	3-19	10
3JL	56/M	PNC-E	2-31	13
4JA	40/F	PBC	4-39	6
5CW	53/M	PNC-E	5-49	11
6RM	54/F	FHF	2-24	7
7DM	65/F	PBC	5-43	7

PBC, primary biliary cirrhosis; HCV, hepatitis C virus; PSC, primary sclerosing cholengitis; PNC-E, ethanol-induced postnecrotic cirrhosis; FHF, fulminant hepatic failure; HBV, hepatitis B virus; LTx, liver transplantation.

Table VI Lowest and Highest Trough Concentrations of MPA in Patients from Group II

Number	Post LTx Days	TAC Dose (mg)	TAC Level (ng/ml)	MMF Dose (Gm)	Lowest Trough MPA Concentration (ug/ml)	Highest Trough MPA Concentration (ug/ml)	Total Bilirubin (mg/dl)	Albumin (Gm/l)	BUN (mg/dl)	Creatinine (mg/dl)
1WR	4	3 bid, po	< 5	1 bid	0.5		0.9	2.4	60	2.5
	24	4 bid, po	10.3	1 bid		4.5	0.8	5	38	2.6
2CM	4	8 bid, po	25.2	1 bid	< 0.3		1.6	2.2	22	1.7
	12	7 bid, po	14.5	1 bid		1.2	1.7	3.9	34	1.9
3JL	2	5 qd, iv	12.4	1 bid	< 0.3		1.8	2.3	9	0.7
	15	7 bid, po	10	1 bid		1.2	1.8	2.8	26	0.7
4JA	4	5 bid, po	7.6	1 bid	0.4		1.5	1.6	41	1.2
	35	5 bid, po	15.4	1 bid		1.9	1.3	3.6	59	1.6
5CW	5	3 qd, po	9.2	1 bid	< 0.3		0.5	1.9	107	3.7
	49	6 bid, po	< 5	1 bid		5.5	0.3	3.7	31	1.5
6RM	2	2 qd, iv	17.2	1 bid	< 0.3		3.4	2.4	34	0.8
	7	6 bid, po	7.2	1 bid		1.2	3.3	1.8	20	0.8
7DM	22	3 bid, po	15.6	1 bid	< 0.3		0.9	2.8	93	1.2
	43	13 qd, po	19.9	1 bid		3.3		3.0	60	1.2

MPA, mycophenolic acid; MMF, mycophenolate mofetil; TAC, tacrolimus; bid, twice a day; qd, once a day; iv, intravenous; po, oral; LTx, liver transplantation.

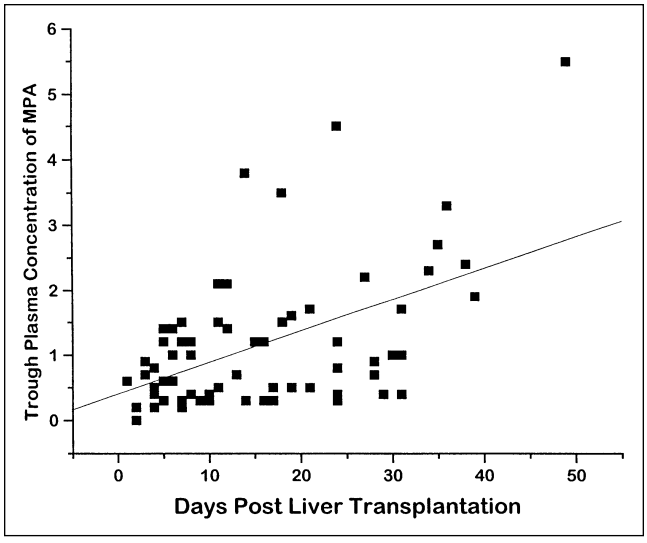

*Figure 3. Trough mycophenolic acid (MPA) plasma concentrations in 7 patients with time posttransplantation after a dose of 1 g mycophenolate mofetil (MMF) po bid (*n = *66; correlation coefficient = 0.51; slope = 0.04831).*

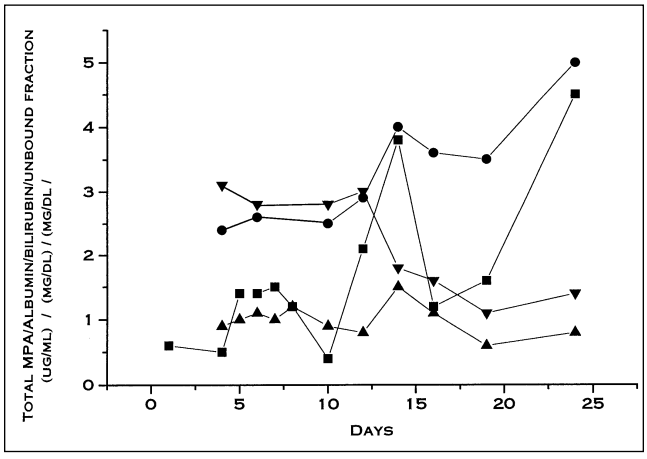

Figure 4. Serum albumin concentrations (circles), serum bilirubin concentrations (triangles), total mycophenolic acid (MPA) (squares), and free fraction of MPA (inverted triangles) in patient WR.

In theory, variations in absorption, distribution, or elimination can contribute to the observed interpatient variation in the pharmacokinetics of MPA. MMF is reported to be rapidly and completely absorbed and converted to MPA in healthy volunteers and in kidney transplant patients.[6,19,18-29] The occurrence of peak MPA plasma concentrations at a median time of 1.8 hours indicates that MMF is very rapidly absorbed after oral administration and is readily converted to MPA in liver transplant patients as well. The recovery of nearly 82% of the administered dose of MMF in the bile and urine suggests a fairly good absorption (if not complete) of MMF and conversion to MPA during the study period. Less than a twofold variation in this recovery between patients indicates that differences in absorption are not likely to contribute significantly to the differences between patients in the overall pharmacokinetics of MPA during the early postoperative period.

MPA is highly bound to albumin in plasma,[30] and it is known that the concentration of albumin changes after liver transplantation. This, in turn, might have caused a time-dependent increase in the trough MPA plasma concentrations in patients (Figure 4) and may also be responsible for the observed differences in the trough concentrations between patients during the early postoperative period. In support of this hypothesis, we observed a significant correlation ($r = 0.73$) between the trough MPA concentration and serum albumin concentrations in liver transplant patients. Since MPA is a low-clearance drug, an increase in the albumin concentration with time will lead to a decrease in the unbound fraction of MPA and a reduction in the total plasma clearance of MPA with a subsequent increase in the trough total MPA concentration and total MPA AUC.

The plasma protein binding of MPA varied nearly threefold in patients in group I, and this might have contributed to the observed differences in the pharmacokinetics of MPA between patients. Large variation in the pharmacokinetics has also been reported in kidney and liver transplant patients treated with cyclosporine and MMF.[6,15-27]

It is known that MPA is predominantly converted to a glucuronide conjugate.[19] Very high plasma concentrations of MPAG in comparison to MPA were observed in all the patients studied. The highest ratio of the AUC of MPAG to MPA was observed in a patient with highest serum creatinine. This is consistent with the information that MPAG is excreted primarily through the urine[19,28,29] and that delayed graft function in renal transplant patients is associated with increased AUC of MPAG.[20] In the present study, less than 5% of the dose was excreted as MPA in bile and urine. MPAG was the major metabolite in both bile and urine, accounting for nearly 75% of the dose of MPA. In general, more MPA and MPAG were recovered in the urine than in the bile. However, in the presence of renal dysfunction, more MPAG was recovered in bile than in urine. Enterohepatic recycling of MPA is also suggested by the presence of secondary peaks in 5 of the 8 patients.

The hepatic glucuronidation and enterohepatic recirculation are reported to be slightly decreased in patients with moderate hepatic impairment.[28] This is in

agreement with the positive correlation between serum bilirubin and the AUC of MPA observed in this study. In addition, the ratio of the AUC of MPAG to MPA was lowest in the patient with the highest serum bilirubin concentration, suggesting significant impairment in glucuronidation in this patient. Variation in the conjugation process could have also contributed to the observed differences in the pharmacokinetics of MPA in liver transplant patients.

The mean AUC of MPA/g dose in our patients (40 ug/ml/h) was higher than the published mean (± *SD*) AUC of MPA (27.3 ± 10.9 ug/ml/h) in kidney transplantation patients who were studied within 40 days after transplantation (n = 25), but this is comparable to the mean AUC of 44 ug/ml/h observed 3 months after kidney transplantation (n = 23) in patients on cyclosporine and MMF therapy.[6] Similarly, the AUC of MPA on day 28, reported in liver transplant patients on cyclosporine therapy, is lower than our observations (19.0 ± 5.2 ug/ml/min).[16] Recently, Zucker et al[21] have reported increased trough plasma concentrations and AUC of MPA in kidney transplant recipients receiving tacrolimus, when compared to those receiving cyclosporine. In our study, it was not possible to directly confirm this observation since all the patients in our study were receiving tacrolimus. This observation needs to be confirmed by further studies and, if substantiated, will necessitate the use of lower doses of MMF in patients on tacrolimus therapy as compared with those on cyclosporine therapy.

In summary, we have observed a time-dependent increase in the trough MPA plasma concentrations in liver transplant patients treated with tacrolimus, which is consistent with published information in kidney transplant patients treated with cyclosporine and MMF. In liver transplant patients, albumin concentration appears to significantly affect the plasma trough total MPA concentrations during the immediate postoperative period. There is a large intersubject variability in the pharmacokinetics of MPA in liver transplant patients. Elimination of MPA is decreased, and the formation of MPAG is reduced in patients with liver dysfunction. MPAG appears to accumulate in patients with renal dysfunction. While the large variability in the kinetics of MPA in liver transplant patients may suggest the need for therapeutic monitoring of MPA in liver transplant recipients, measurement of the trough total MPA plasma concentrations may not be appropriate to maintain the therapeutic effect and avoid MMF-related toxicity in liver transplant patients because of the variability in the binding of MPA to plasma proteins. This is illustrated in a recent report in which a pancreas transplant patient who exhibited signs of MMF toxicity had normal total MPA AUC but an elevated free MPA AUC.[22] An ideal therapeutic monitoring strategy must take into account the unbound MPA plasma concentrations rather than the total MPA concentrations in plasma. Further studies on the pharmacokinetics of MPA are warranted in transplant patients to evaluate various factors that influence the kinetics of MPA and to optimize MMF therapy in transplant patients. These studies should evaluate the time-dependent changes in the kinetics of MPA after intravenous and oral administration and attempt to relate unbound plasma concentrations or AUC of plasma-unbound concentrations versus time of MPA to clinical outcome using MMF therapy.

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