The Effect of Selective Bowel Decontamination on the Pharmacokinetics of Mycophenolate Mofetil in Liver Transplant Recipients

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Mycophenolate mofetil (MMF) is a prodrug immunosuppressant with a high oral bioavailability. Enterohepatic cycling of a glucuronide derivative of MMF contributes substantially to the bioavailability, but is dependent on bacterial deglucuronidation by intestinal flora. This study aims to determine whether an antibiotic regimen with activity against such organisms reduces the bioavailability of MMF by impairing enterohepatic cycling. In a prospective trial, 6 liver transplant recipients were administered MMF and a 21-day antibiotic regimen for selective bowel decontamination (SBD). Time-concentration profiles of the pharmacologically active metabolite, mycophenolic acid (MPA), were obtained during and after the SBD regimen. The bioavailability of MPA was reduced during compared with after the regimen (14.5 ± 3.5 *v* 21.1 ± 9.8 mg · h/mL; $P = .07$). The most pronounced contribution to this reduction was observed from 6 hours onward (2.4 ± 1.4 *v* 5.6 ± 4.4 mg · h/mL; $P < .05$). The presence of secondary maxima in the time-concentration profiles of MPA after, but not during, SBD indicates that enterohepatic cycling may be inhibited during SBD and restored afterward. Enterohepatic cycling may contribute 7% to 54% (mean, 29%) of the bioavailability of MPA. We conclude that the bioavailability of MMF may be reduced when SBD is used, and the reduction is likely to result from the interruption of enterohepatic cycling. This mechanism should be taken into consideration not only during SBD, but in any clinical setting combining MMF and broad-spectrum antibiotics. (*Liver Transpl 2001;7: 739-742.*)

Mycophenolate mofetil (MMF) has been investigated primarily in recipients of renal allografts.[1] Experience in liver transplant recipients is limited, but MMF has proven effective as rescue therapy and seems useful as adjuvant or even monotherapy in patients who poorly tolerate calcineurin inhibitors.[2-5]

MMF is a prodrug that undergoes rapid and essentially complete absorption after oral administration.[6,7] It is completely first-pass de-esterified into the pharmacologically active metabolite, mycophenolic acid (MPA), presenting as a sharp primary peak at approximately 1 hour postdose in the plasma concentration-time profile. The effective bioavailability of MMF as MPA is 100%. MPA is glucuronidated by the liver into a pharmacologically inactive phenolic glucuronide (MPAG), which is mainly excreted in the urine by active tubular secretion. However, a significant amount of MPAG is excreted into the bile and, after bacterial deglucuronidation, subsequently reabsorbed as MPA.[6,8] In the concentration-time profile of MPA, this enterohepatic cycling of MPAG is responsible for the occurrence of secondary maxima, usually approximately 6 to 12 hours postdose.[7,9,10] Consequently, mechanisms affecting enterohepatic cycling may potentially interact with the pharmacokinetics of MMF. In an interaction study, cholestyramine, which was expected to inhibit enterohepatic cycling by binding to MPA in the intestinal lumen, had a marked and highly significant effect on the profile of MPA.[6] The mean bioavailability of MPA was decreased by approximately 40% (range, 10% to 60%), which was almost entirely attributable to the reduction in MPA concentrations from 6 hours onward.

Enterohepatic cycling is dependent on the deglucuronidation of MPAG to MPA by intestinal flora, particularly colonic gram-negative anaerobes containing the majority of the glucuronidase activity.[6] Thus, antibiotics with activity against such organisms may significantly reduce the bioavailability of MMF by impairing enterohepatic cycling. This study aims to determine the effect of a regimen involving selective bowel decontamination (SBD) on the pharmacokinetics of MMF in liver transplant recipients.

Patients and Methods

Six recipients of hepatic allografts (median age, 52 years; range, 30 to 73 years) were included on the study (Table 1). MMF was administered orally as a 1-g capsule twice daily

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Table 1. Demographic and Clinical Data for the 6 Study Patients

Patient No.	Sex	Age (yr)	Indication for Transplant	MMF Start Day	Sample Day 1/2
1	F	52	Primary biliary cirrhosis	1	20/24
2	F	30	Budd-Chiari syndrome	3	20/26
3	M	52	Chronic autoimmune hepatitis	10	20/24
4	M	46	Chronic hepatitis C	2	19/26
5	M	56	Alcoholic cirrhosis	4	21/29
6	F	73	Primary sclerosing cholangitis	3	17/23

NOTE. Sample day 1/2 indicates days posttransplantation for measurement of the AUC of MPA.

from the time the patient could ingest oral medication. Dose modification or cessation of MMF would be considered in case of bone marrow suppression, gastrointestinal toxicity, or allergic reactions. Apart from MMF, all patients were administered microemulsion cyclosporine (Neoral; Novartis Healthcare A/S, Copenhagen, Denmark) at an initial dose of 5 mg/kg twice daily, with dose adjustment according to target trough blood levels of 250 to 350 mg/mL, and steroid at an initial daily dose of 200 mg tapered to 20 mg within 1 week. The regimen for SBD used an oral mixture consisting of mycostatin, 3 million international units; tobramycin, 0.6 g; and cefuroxim, 6 g, daily for 21 days after transplantation.[11]

The study was approved by the Ethics Committee of Copenhagen (J no. KF 02-144/97), and written informed consent was obtained from the patients.

A time-concentration profile of MPA was obtained on 2 separate occasions. The first (sample day 1) was obtained during SBD, and the second (sample day 2) was obtained a minimum of 4 days after cessation of SBD. Blood samples were collected at 0, 0.5, 1, 1.5, 2, 4, 6, 8, 10, and 12 hours postdose. The samples were analyzed for MPA concentration using high-performance liquid chromatography with UV detection at 254 nm.[12] The quantification limit of MPA was less than 0.1 mg/L, with linear ranges from the quantification limit up to 40 mg/L.

From the time-concentration profiles of MPA, the maximum concentration (C_{max}) and time to C_{max} (T_{max}) were observed. Bioavailability was expressed as the trapezoidal area under the curve (AUC). The AUC was calculated for the complete 12-hour sampling period as AUC_{12}, and for the 0- to 6-hour and 6- to 12-hour periods separately as AUC_6 and $AUC_{6\text{-}12}$, respectively. AUC_6 was taken as a measure of the primary absorption of MMF, whereas $AUC_{6\text{-}12}$ was assumed to reflect the contribution of enterohepatic cycling.

Results are presented as mean ± SD. Nonparametric statistical analysis was performed using Wilcoxon's test. *P* less than .05 is considered statistically significant.

Results

All patients completed the study and were administered the intended dose of MMF. The first sampling for the time-concentration profile was performed between days 17 and 20, at which time MMF had been administered for at least 10 days. The second sampling was performed between days 23 and 29, with an interval of 4 to 8 days from sample day 1. The time-concentration profiles of MPA for each of the 6 patients are shown in Figure 1. A sharp initial peak within 1 to 2 hours was

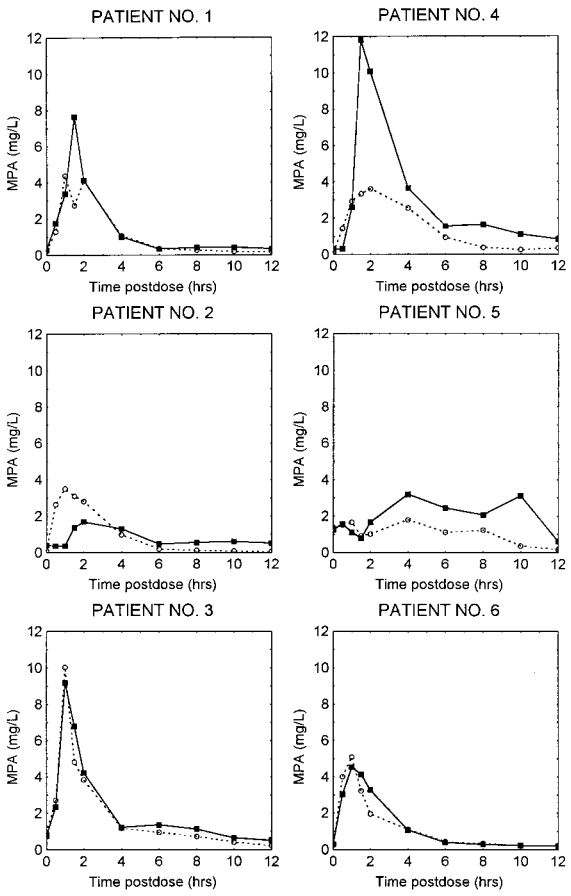

Figure 1. Time-concentration profiles of MPA during (○) and after (■) the SBD regimen.

Table 2. Individual Observed Parameters T_{max} and C_{max} and Estimated Variables AUC_{12}, AUC_6, and $AUC_{6\text{-}12}$ for the Time-Concentration Profiles of MPA

Patient No.	Day	T_{max} (h)	C_{max} (mg/L)	AUC_{12} (mg · h/mL)	AUC_6 (mg · h/mL)	$AUC_{6\text{-}12}$ (mg · h/mL)
1	1	1	4.37	13.2	11.8	1.4
	2	1.5	7.62	16.2	13.9	2.3
2	1	1	3.48	10.9	10.2	0.7
	2	2	1.67	9.5	6.3	3.3
3	1	1	10.01	20.5	17.0	3.4
	2	1	9.17	23.7	18.3	5.4
4	1	2	3.60	16.9	14.4	2.5
	2	1.5	11.79	36.7	28.8	7.9
5	1	4	1.78	12.7	8.3	4.4
	2	4	3.18	26.2	12.9	13.3
6	1	1	5.07	13.0	11.2	1.8
	2	1	4.51	14.0	12.5	1.6
Mean ± SD	1	1.7 ± 1.2	4.7 ± 2.8	14.5 ± 3.5*	12.2 ± 3.1	2.4 ± 1.4†
	2	1.8 ± 1.1	6.3 ± 3.9	21.1 ± 9.8*	15.4 ± 7.6	5.6 ± 4.4†

*$P = .07$.
†$P < .05$ (Wilcoxon's matched-pairs test).

seen in all except 1 patient (no. 5). A secondary maximum could be identified between 6 and 10 hours postdose on sample day 2 in all except 1 patient (no. 6) and was not detectable on sample day 1.

Results are listed in Table 2. No significant difference was shown in C_{max} or T_{max}. AUC_{12} was greater with marginal significance on sample day 2 than day 1 (21.1 ± 9.8 *v* 14.5 ± 3.5 mg · h/mL; Wilcoxon, $P = .07$). In the 5 patients with increases in AUC_{12} from sample day 1 to day 2, the increase constituted a mean of 29% (range, 7% to 54%) of the AUC_{12} on sample day 2. AUC_6 was insignificantly greater on sample day 2 than day 1 (15.4 ± 7.6 *v* 12.2 ± 3.1 mg · h/mL; P = not significant), whereas $AUC_{6\text{-}12}$ was significantly greater on sample day 2 than day 1 (5.6 ± 4.4 *v* 2.4 ± 1.4 mg · h/mL; Wilcoxon, $P < .05$; Fig. 2).

Discussion

Results indicate that the bioavailability of MMF expressed as the AUC_{12} of MPA may be reduced during a regimen of SBD in liver transplant recipients. In the majority of cases, the time-concentration profiles of MPA showed the expected configuration, with an initial sharp peak reflecting the primary absorption of MMF. Because no significant differences were shown in C_{max}, T_{max}, or AUC_6 of MPA between sampling days, the primary absorption of MMF must be considered unchanged by SBD. The presence of secondary maxima in the time-concentration profiles of MPA after cessation of SBD as opposed to during SBD indicates that enterohepatic cycling of MPA was inhibited by SBD and restored when SBD was withdrawn. The contribution of these secondary maxima is reflected by a significant increase in $AUC_{6\text{-}12}$. However, the secondary maximum never was very pronounced.

In this study, inhibition of enterohepatic cycling is assumed to be a consequence of the impaired bacterial

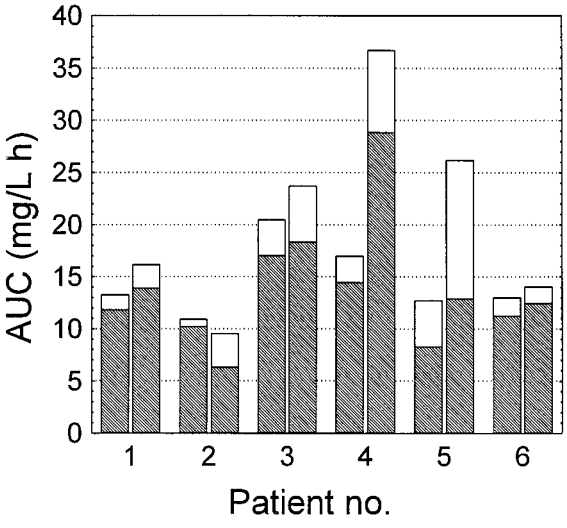

Figure 2. AUC_6 (▨) and $AUC_{6\text{-}12}$ (□) during and after the SBD regimen for each of the 6 patients.

deconjugation of MPAG caused by SBD. The antibiotic regimen used is not 100% efficient.[11] Because stool cultures were not performed, we cannot assume the sterility of feces during the regimen. However, direct interactions between MMF metabolism and the antibiotics are not expected, and any effect by SBD on the pharmacokinetics of MMF is likely to result from the proposed mechanism.[6]

The overall increase in AUC_{12} was only marginally significant. If the increase in AUC_{12} is assumed to result entirely from the restoration of enterohepatic cycling, then enterohepatic cycling may contribute 7% to 54% (mean, 29%) of the bioavailability of MPA. However, in 1 patient (no. 2), AUC_{12} showed a decrease from sample day 1 to day 2. These findings correspond well with the reports from the cholestyramine-interaction study, in which the mean contribution of enterohepatic cycling was estimated to 37%, but also with a substantial 6-fold interindividual variation.[6] As discussed earlier, variation in our data may further derive from varying degrees of failure of the antibiotic regimen.

The marginal significance of the AUC differences probably reflects the relatively small number of patients in the study. The disappearance of the second peak, together with the major contribution of the second half of the time-concentration profile to the differences in AUC, indicate that the observed differences in AUC are real and not a chance finding.

The proposed mechanism by which SBD interferes with the bioavailability of MMF could be active during any course of antibiotics that would have a similar impact on the resident intestinal flora responsible for the breakdown of MPAG. Consequently, the potential impact of the findings extends beyond the occasional use of SBD to the much more common use of broad-spectrum antibiotic therapy.

In conclusion, we find that the bioavailability of MMF seems to be reduced during SBD, and the reduction is likely to result from the interruption in enterohepatic cycling. This mechanism must be taken into consideration not only in organ transplant regimens combining the use of MMF and SBD, but in any clinical setting combining MMF and broad-spectrum antibiotics.

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