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 vs 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 vs 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)

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...
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.

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. 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 \( C_{\text{max}} \) and time to \( C_{\text{max}} \) \( T_{\text{max}} \) 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 \( \text{AUC}_{12} \), and for the 0- to 6-hour and 6- to 12-hour periods separately as \( \text{AUC}_0^6 \) and \( \text{AUC}_6^{12} \), respectively. \( \text{AUC}_0^6 \) was taken as a measure of the primary absorption of MMF, whereas \( \text{AUC}_6^{12} \) 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
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 vs 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 vs 12.2 ± 3.1 mg·h/mL; P = not significant), whereas AUC_{6-12} was significantly greater on sample day 2 than day 1 (5.6 ± 4.4 vs 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

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Day</th>
<th>T_{max} (h)</th>
<th>C_{max} (mg/L)</th>
<th>AUC_{12} (mg · h/mL)</th>
<th>AUC_{6} (mg · h/mL)</th>
<th>AUC_{6-12} (mg · h/mL)</th>
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<tbody>
<tr>
<td>1</td>
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<td>1</td>
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<tr>
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</tr>
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<td>4.51</td>
<td>14.0</td>
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<tr>
<td>Mean ± SD</td>
<td>1</td>
<td>1.7 ± 1.2</td>
<td>4.7 ± 2.8</td>
<td>14.5 ± 3.5*</td>
<td>12.2 ± 3.1</td>
<td>2.4 ± 1.4†</td>
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<tr>
<td></td>
<td>2</td>
<td>1.8 ± 1.1</td>
<td>6.3 ± 3.9</td>
<td>21.1 ± 9.8*</td>
<td>15.4 ± 7.6</td>
<td>5.6 ± 4.4†</td>
</tr>
</tbody>
</table>

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

![Figure 2. AUC_{6} (○) and AUC_{6-12} (■) during and after the SBD regimen for each of the 6 patients.](image)
deconjugation of MPAG caused by SBD. The antibi-
otic 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 antibi-
otics 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 AUC12 was only marginally
significant. If the increase in AUC12 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), AUC12 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 substi-
tial 6-fold interindividual variation.6 As discussed ear-
erlier, variation in our data may further derive from vary-
ing 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 reduc-
tion is likely to result from the interruption in entero-
hepatic cycling. This mechanism must be taken into
consideration not only in organ transplant regimens
combining the use of MMF and SBD, but in any clin-
ical setting combining MMF and broad-spectrum anti-
biotics.

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