Pharmacokinetics of Mycophenolate Sodium and Comparison with the Mofetil Formulation in Stable Kidney Transplant Recipients

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Background and objectives: The introduction of mycophenolate mofetil has improved graft survival after organ transplantation; however, its use may be limited by important adverse effects. For overcoming these problems, an enteric-coated formulation of mycophenolate sodium has been developed, but pharmacokinetic data of mycophenolic acid release from this formulation are scanty.

Design, setting, participants, & measurements: Pharmacokinetic studies in 32 kidney transplant recipients who were given the enteric-coated formulation of mycophenolate sodium (n = 12) or mycophenolate mofetil (n = 20) were performed. The profiles of mycophenolic acid from the two formulations at months 6, 12, 18, and 24 after transplantation were compared. Subsequently, all patients who were receiving the enteric-coated formulation were shifted to mycophenolate mofetil, and the pharmacokinetic evaluations were repeated.

Results: At month 6 after surgery, aberrant and variable pharmacokinetic curves were found in patients who were given the enteric-coated formulation, whereas those who were taking mycophenolate mofetil had regular mycophenolic acid kinetic profiles. Patients who were taking the enteric-coated formulation had mycophenolic acid time of occurrence for maximum drug concentration that ranged from 0 to 480 min and higher dosage-adjusted mycophenolic acid trough levels compared with patients who were given mycophenolate mofetil. Conversion from the enteric-coated formulation of mycophenolate sodium to mycophenolate mofetil resulted in an improvement of the mycophenolic acid kinetics profiles.

Conclusions: Given the emerging clinical benefit of mycophenolic acid monitoring in the transplant setting, therapeutic drug monitoring problems with the enteric-coated formulation of mycophenolate sodium should be taken into account.

months 6, 12, 18, and 24 after surgery; and (3) to investigate the MPA pharmacokinetic profiles before and after the conversion from EC-MPS to MMF in stable renal transplant recipients.

**Concise Methods**

**Patients**
In 2002 the Kidney Transplant Center of the Ospedali Riuniti Bergamo agreed to participate in a prospective, open-label, multicenter clinical trial aimed at evaluating the efficacy and safety of EC-MPS. Twelve adult kidney transplant recipients (eight men and four women) were enrolled from the Center of Bergamo. All renal transplant patients who were randomly enrolled in this trial were included in this study. They received induction therapy with basiliximab and were on maintenance immunosuppressive therapy with cyclosporine (CsA) and EC-MPS (corticosteroids were discontinued at week 6 after transplantation). For comparison, 20 adult renal transplant recipients (13 men and seven women), who underwent surgery in the same period (from December 2002 to January 2004) as those enrolled in the trial focusing on EC-MPS and were given MMF instead of EC-MPS and matched for concomitant immunosuppressive therapy (induction therapy with Campath-IH or the combination basiliximab plus low-dosage rabbit anti-thymocyte globulin, together with maintenance therapy with CsA and short-term steroids) were also included in the pharmacokinetic evaluations. Before surgery, eligible patients were allocated to EC-MPS or MMF treatment without a predefined criterion of choice. Bile acid-binding resins and/or any other drug that is able to affect MPA absorption or exposure were not allowed during the study. The full clinical details of this study have been described elsewhere (14). The study protocol was approved by the institutional review board (the Medical Ethics Committee of the Ospedali Riuniti, Bergamo), and patients gave written informed consent before study participation.

**Study Design**
The complete 12-h MPA pharmacokinetic profile was first evaluated at month 6 after transplantation. On the morning of the pharmacokinetic studies, blood samples were collected for routine hematologic evaluations. Patients gave written informed consent before study participation. Medical Ethics Committee of the Ospedali Riuniti, Bergamo), and patients underwent further pharmacokinetic evaluations. Thereafter, patients who were given EC-MPS were comparable to those who were given MMF as far as demographics (mean age 41 ± 14 and 47 ± 13 yr in EC-MPS and MMF groups, respectively) and hematocritical parameters during all of the 30-mo follow-up (Table 1). Two of the 12 patients discontinued EC-MPS as a result of leukopenia at months 15 and 20 after transplantation, respectively. None of the patients who were taking MMF discontinued the study drug.

**Results**

**Patient Demographics**
All patients who were enrolled in this study were white, adults, and recipients of first kidney transplant from cadaver donors. Mean HLA mismatch was 4.0 ± 1.4 in patients who were given EC-MPS and 4.0 ± 1.2 in those who were given MMF (NS). As shown in Table 1, at month 6 after surgery, all patients had stable renal function (EC-MPS serum creatinine 1.5 ± 0.4 mg/dl; MMF 1.6 ± 0.6 mg/dl) and normal liver function. Patients who were given EC-MPS were comparable to those who were given MMF as far as demographics (mean age 41 ± 14 and 47 ± 13 yr in EC-MPS and MMF groups, respectively) and hematocritical parameters during all of the 30-mo follow-up (Table 1). Two of the 12 patients discontinued EC-MPS as a result of leukopenia at months 15 and 20 after transplantation, respectively. None of the patients who were taking MMF discontinued the study drug.

**Pharmacokinetics of the Two MPA-Releasing Formulations**
The mean MPA pharmacokinetic parameters for the EC-MPS and MMF groups are shown in Table 2. The drug absorption was slower for EC-MPS than for MMF, consistent with a functional enteric coating for EC-MPS. Indeed, at month 6 after transplantation, mean time of occurrence for maximum drug concentration (t_{max}) was 159 min for EC-MPS and 54 min for MMF (P < 0.01). Dosage-normalized MPA trough levels were 3.6-fold higher in patients who were given EC-MPS than in those who were given MMF (6.1 ± 4.9 versus 1.7 ± 0.9 mg/L; P < 0.01). Despite these differences, mean MPA exposure, defined by the values of the dosage-adjusted area under the curve from 0 to 12 h (AUC_{0-12}), was not different between the two groups (Table 2). To dissect better potential differences in the MPA pharmacokinetic profiles between the two formulations, we considered the single kinetic curves for each patient. As shown in Figure 1, atypical MPA kinetic profiles in patients who were given EC-MPS were observed at month 6 after trans-
plantation. In particular, blunted profiles that did lack the early sharp peak that was observed in MMF recipients were documented. Some patients who were given EC-MPS showed multiple peaks of MPA. It is interesting that MPA $t_{\text{max}}$ ranged from 0 (basal) to 480 min after drug dosing. Conversely, patients who were treated with MMF had regular MPA pharmacokinetic profiles, with maximum MPA peak always within 2 h and a second, flat peak at 6 to 12 h after MMF dosing, corresponding to the enterohepatic recycling of MPA metabolites (17). Similar kinetic findings were shown at months 12, 18, and 24 after transplantation (Table 2).

Table 1. Clinical chemistry data of kidney transplant recipients who were given EC-MPS– or MMF-based immunosuppression

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Month 6</th>
<th>Month 12</th>
<th>Month 18</th>
<th>Month 24</th>
<th>Month 30</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EC-MPS ($n = 12$)</td>
<td>MMF ($n = 20$)</td>
<td>EC-MPS ($n = 12$)</td>
<td>MMF ($n = 20$)</td>
<td>EC-MPS ($n = 12$)</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.5 ± 0.4</td>
<td>1.6 ± 0.6</td>
<td>1.6 ± 0.6</td>
<td>1.5 ± 0.4</td>
<td>1.4 ± 0.4</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>66 ± 15</td>
<td>61 ± 19</td>
<td>69 ± 14</td>
<td>65 ± 22</td>
<td>74 ± 31</td>
</tr>
<tr>
<td>Serum urea (mg/dl)</td>
<td>64 ± 13</td>
<td>67 ± 29</td>
<td>59 ± 18</td>
<td>54 ± 19</td>
<td>63 ± 17</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>17 ± 4</td>
<td>18 ± 7</td>
<td>16 ± 4</td>
<td>20 ± 9</td>
<td>20 ± 9</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>18 ± 5</td>
<td>19 ± 15</td>
<td>15 ± 4</td>
<td>19 ± 11</td>
<td>18 ± 5</td>
</tr>
<tr>
<td>Serum albumin (g/dl)</td>
<td>3.8 ± 0.4</td>
<td>3.8 ± 0.4</td>
<td>3.6 ± 0.4</td>
<td>3.5 ± 0.3</td>
<td>3.7 ± 0.3</td>
</tr>
</tbody>
</table>

*ALT, alanine transaminase; AST, aspartate transaminase; EC-MPS, enteric-coated formulation of mycophenolate sodium; MMF, mycophenolate mofetil; RBC, red blood cells; WBC, white blood cells.

To investigate whether the atypical MPA pharmacokinetics in patients who were given EC-MPS could be influenced by the food intake, we compared MPA kinetic profiles that were drawn from three patients who remained under fasted conditions for 5 h after EC-MPS morning administration with those obtained in the same patients when they had a light breakfast 120 min after drug intake. As shown in Figure 2, breakfast avoidance was associated with only marginal improvement, if any, in the pharmacokinetic profiles, which were still irregular and extremely variable. Indeed, in patient 2016, prolonged fasted condition seemed to improve the kinetic profile. Con-

Table 2. Pharmacokinetic parameters of kidney transplant recipients who were given EC-MPS or MMF

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters</th>
<th>EC-MPS ($n = 12$)</th>
<th>MMF ($n = 20$)</th>
<th>EC-MPS ($n = 12$)</th>
<th>MMF ($n = 20$)</th>
<th>EC-MPS ($n = 12$)</th>
<th>MMF ($n = 20$)</th>
<th>EC-MPS ($n = 12$)</th>
<th>MMF ($n = 20$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>dosage (MPA eq/d)</td>
<td>960 ± 360</td>
<td>1040 ± 379</td>
<td>1000 ± 433</td>
<td>1000 ± 433</td>
<td>960 ± 360</td>
<td>1040 ± 379</td>
<td>1000 ± 433</td>
<td>1000 ± 433</td>
</tr>
<tr>
<td>$C_0$/dose (mg/L per MPA eq)</td>
<td>6.1 ± 4.9b</td>
<td>10.6 ± 9.6b</td>
<td>9.3 ± 13.3c</td>
<td>8.0 ± 11.5</td>
<td>6.1 ± 4.9b</td>
<td>10.6 ± 9.6b</td>
<td>9.3 ± 13.3c</td>
<td>8.0 ± 11.5</td>
</tr>
<tr>
<td>$C_{\text{max}}$/dose (mg/L per MPA eq)</td>
<td>18.3 ± 8.5</td>
<td>26.1 ± 19.0</td>
<td>24.4 ± 14.4</td>
<td>23.8 ± 10.8</td>
<td>18.3 ± 8.5</td>
<td>26.1 ± 19.0</td>
<td>24.4 ± 14.4</td>
<td>23.8 ± 10.8</td>
</tr>
<tr>
<td>$t_{\text{max}}$ (min)</td>
<td>159 ± 117b</td>
<td>90 ± 104</td>
<td>183 ± 159c</td>
<td>135 ± 70b</td>
<td>159 ± 117b</td>
<td>90 ± 104</td>
<td>183 ± 159c</td>
<td>135 ± 70b</td>
</tr>
<tr>
<td>$AUC_0$ to $t_{12}$/dose (mg/h per L/MPA eq)</td>
<td>59.9 ± 24.9</td>
<td>55.5 ± 22.1</td>
<td>61.1 ± 21.5</td>
<td>58.4 ± 18.5</td>
<td>59.9 ± 24.9</td>
<td>55.5 ± 22.1</td>
<td>61.1 ± 21.5</td>
<td>58.4 ± 18.5</td>
</tr>
</tbody>
</table>

*EC-MPS ($n = 20$) dosage (MPA eq/d) 1077 ± 392 1119 ± 350 1056 ± 300 1111 ± 220
*MMF ($n = 20$) dosage (MPA eq/d) 1.7 ± 0.9 1.9 ± 1.2 2.0 ± 0.9 2.5 ± 1.7
*EC-MPS ($n = 20$) $C_0$/dose (mg/L per MPA eq) 24.6 ± 10.8 23.8 ± 10.1 26.7 ± 9.8 21.8 ± 10.2
*EC-MPS ($n = 20$) $C_{\text{max}}$/dose (mg/L per MPA eq) 54 ± 26 41 ± 13 43 ± 20 54 ± 35
*EC-MPS ($n = 20$) $t_{\text{max}}$ (min) 48.5 ± 12.2 47.4 ± 13.1 50.0 ± 11.8 53.6 ± 18.3

*At the end of month 24, these patients were shifted from EC-MPS to MMF.
versely, breakfast avoidance in patient 1120 was associated with an irregular kinetic profile as compared with that observed in the same patient at month 6. No significant effect of breakfast was found in patient 2007. Again, these findings confirmed the extremely high variability in the MPA pharmacokinetic profiles after EC-MPS administration. Some regular profiles can be obtained randomly, a condition that is not affected by food intake.

Variability of MPA Pharmacokinetics Parameters

The coefficient of variation was calculated for main MPA pharmacokinetic parameters measured at 6, 12, 18, and 24 mo after transplantation in both groups of patients. As documented in Table 3, significantly higher intra- and interpatient variabilities of MPA pharmacokinetics were found in kidney transplant recipients who were given enteric-coated formulation of mycophenolate sodium (EC-MPS; n = 12) or mycophenolate mofetil (MMF; n = 20).

Conversion from EC-MPS to MMF

At the end of month 24, all patients who were given EC-MPS were switched to MMF, and the MPA pharmacokinetic evaluations were repeated at month 30 after transplantation. As shown in Table 4, this conversion was associated with a significant reduction in the MPA trough levels (from 8.0 ± 11.5 to 2.4 ± 0.7 mg/L per MPA equivalent; P < 0.01) and in t_{max} values (from 135 ± 70 to 47.8 ± 15.4 min; P < 0.01). Of note, conversion from EC-MPS to MMF resulted in a significant reduction in the variability of MPA C_{0} and t_{max} values (Table 4). Moreover, the replacement of EC-MPS with MMF induced an overall improvement in the daily MPA pharmacokinetic profiles and less dispersion of the MPA AUC values (Figure 4). As a consequence, at month 30 after transplantation, when all patients were on MMF, no differences in the daily MPA pharmacokinetic profiles were observed between transplant recipients who switched from EC-MPS to MMF and those who were on maintenance MMF since surgery. It is interesting that we found that some patients who showed a negligible MPA absorption while on EC-MPS therapy had a significant increase in MPA exposure when shifted to MMF. An example is given in Figure 5 (patient RP08, MPA AUC increased from 19.6 to 56.9 mg/h per ml).

Clinical Outcome

As shown in Table 5, no differences were observed between the EC-MPS and MMF groups on acute rejection episodes or graft function, expressed as GFR values, during the 24-mo follow-up period. The mean difference in the GFR values from month 24 to month 6 after transplant was −8.8 ± 26.8 ml/min per 1.73 m^2 (−14.8%) in the EC-MPS group and −4.1 ± 17.4 ml/min per 1.73 m^2 (−7.8%) in patients who were given MMF (NS). Similarly, no difference in proteinuria was found between the two groups (Table 5). No episodes of graft loss were recorded throughout the observational period. One patient per group developed CAN.

Discussion

This study shows that in stable kidney transplant recipients, the pharmacokinetics of MPA released from the new EC-MPS is extremely variable and unpredictable as compared with that after MMF dosing. Despite no significant differences in mean MPA exposure, expressed as dosage-adjusted MPA AUC_{0 to 24} and maximum concentration of drug (C_{max}), aberrant kinetic curves in individual patients were found, with an extremely high variability in MPA C_{0}, AUC_{0 to 24}, and t_{max}. Moreover, most patients who were given EC-MPS had multiple peaks of MPA in their pharmacokinetic profile, an effect that was not seen after long-term MMF administration.

These findings were at variance with those of Arns et al. (7), showing similar pharmacokinetic profiles after single EC-MPS or MMF administration to kidney transplant patients; however, single-drug administration is far from the clinical setting of transplant patients who are given long-term EC-MPS or MMF, as we did. The limitation of the observation by Arns et al. is underlined by the high variability of MPA exposure reported in a recent randomized, crossover study aimed at measuring the
Table 3. Intra- and interpatient variability of main MPA pharmacokinetic parameters in kidney transplant recipients who were given EC-MPS or MMF

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters</th>
<th>Intrapatient Variability (CV%)</th>
<th>Interpatient Variability (CV%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC-MPS (n = 12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C₀/dose (mg/L per MPA eq)</td>
<td>69.1</td>
<td>80.3b</td>
</tr>
<tr>
<td>C_max/dose (mg/L per MPA eq)</td>
<td>46.8</td>
<td>72.8</td>
</tr>
<tr>
<td>t_max (min)</td>
<td>82.8b</td>
<td>73.4</td>
</tr>
<tr>
<td>AUC₀ to 12/dose (mg/h per L/MPA eq)</td>
<td>26.9c</td>
<td>41.6</td>
</tr>
<tr>
<td>MMF (n = 20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C₀/dose (mg/L per MPA eq)</td>
<td>39.0</td>
<td>50.1</td>
</tr>
<tr>
<td>C_max/dose (mg/L per MPA eq)</td>
<td>28.3</td>
<td>45.5</td>
</tr>
<tr>
<td>t_max (min)</td>
<td>33.0</td>
<td>48.3</td>
</tr>
<tr>
<td>AUC₀ to 12/dose (mg/h per L/MPA eq)</td>
<td>13.5</td>
<td>25.1</td>
</tr>
</tbody>
</table>

*CV%, coefficient of variation.

bP < 0.01 versus MMF.

cP < 0.05 versus MMF.

Figure 2. MPA pharmacokinetic profiles performed in three patients (2016, 2007, and 1120) at months 6 and 12 after surgery under fasted conditions and allowing breakfast 90 to 120 min after EC-MPS administration. The last pharmacokinetic evaluation was repeated a few weeks after month 12 under prolonged fasted conditions (patients were fasted since the evening before and did not have access to food for 5 h after the morning drug dosage).
pharmacokinetics of co-administration of EC-MPS with CsA or tacrolimus in kidney transplant recipients (18). Our study extends this finding by comparing the pharmacokinetic profile of MPA in kidney transplant recipients who were given EC-MPS or MMF as part of their immunosuppressive therapy at different time points postoperatively.

Actually, only a few studies (7–12) have compared the pharmacokinetics of MPA released from EC-MPS with that from MMF in patients who were treated long term with these drugs. Some of them (9,10,12), however, provided data only about the minimum MPA concentration during the 12-h observation period, which may not necessarily reflect C0 values. In the remaining studies, pharmacokinetic analysis showed that the administration of EC-MPS at 720 mg and MMF at 1000 mg provided comparable MPA Cmax and AUC values. Similarly, we found no differences between EC-MPS and MMF in the previously mentioned pharmacokinetic parameters (7–12); however, examining the single MPA kinetic profiles, large differences among the two formulations were documented. In particular, patients who were given EC-MPS had MPA trough levels three- to five-fold higher than those that were found in patients who were given MMF, despite comparable MPA AUC0 to 12. Our results are at variance with recent observations (19) in which only a 30% increase in the median MPA predose levels were reported for patients who were given EC-MPS compared with those who were given MMF; however, in the latter investigation, cases of extremely high MPA C0 values were observed with EC-MPS but not with MMF, a condition that is consistent with a very prolonged release of MPA from this formulation. We extended these (19) and other findings limited to the early posttransplantation period (11) by documenting that MPA C0 levels were consistently higher with EC-MPS than with MMF during all of the pharmacokinetic evaluations performed within the 24-mo follow-up. Our results may have important clinical consequences when C0-based MPA monitoring is used to optimize MPA therapy, as suggested by International Consensus Conferences (20). Indeed, we and others previously showed that MPA trough levels in patients who were given MMF correlated with the clinical outcome, in terms of graft function (3), rejection episodes (2), and drug-related toxicity (21); however, the great variability of MPA C0 levels after EC-MPS administration compared with those observed after MMF intake would preclude the reliable implementation of C0-based therapeutic drug monitoring in patients who are given EC-MPS, which ultimately might translate in a suboptimal clinical outcome.

The enteric coating of MPA, which slows the release of the active compound and eventually delays the time to achieve MPA Cmax (5,6), was designed with the goal to improve the potential gastrointestinal toxic profile of MMF, which releases MPA in the small intestine. Overall, this trend was confirmed also by our study, showing that mean MPA tmax was longer in patients who were given MMF correlated with the clinical outcome, in terms of graft function (3), rejection episodes (2), and drug-related toxicity (21); however, the great variability of MPA C0 levels after EC-MPS administration compared with those observed after MMF intake would preclude the reliable implementation of C0-based therapeutic drug monitoring in patients who are given EC-MPS, which ultimately might translate in a suboptimal clinical outcome.

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under fasted conditions, and patients were allowed to eat only 90 to 120 min after drug administration, as recommended by the manufacturer. Moreover, the pharmacokinetic studies were performed under standardized conditions, with comparable light meals for both groups. To address this issue further, we repeated the pharmacokinetic analysis in a subgroup of patients who were not given breakfast. Fasting did not improve kinetic profiles, indicating that, if any, food is only negligibly implicated in the absorption of MPA after EC-MPS administration.

From a clinical point of view, it would have been interesting to know whether the high variability in MPA pharmacokinetics that was observed in patients who were given EC-MPS was associated with worse outcome compared with those who were given MMF. We did not find any statistical difference between the two groups on acute rejection episodes, renal function, and CAN. It must be considered, however, that this study was designed to test potential differences on the pharmacokinetics of release of MPA from EC-MPS or MMF; therefore, a large population may be required to test whether the difference in MPA pharmacokinetics between the two MPA-releasing formulations might affect clinical outcome.

This study certainly has some shortcomings. It was conducted using a limited number of patients. Moreover, we made a head-to-head comparison between the two MPA-releasing formulations, whereas the adoption of a crossover design could have limited the potential bias related to demographic imbalances between treatment groups. Indeed, a parallel treatment group design, as we did, would better mimic what usually happens in clinical practice and allow testing of intra- and interpatient variability of MPA pharmacokinetics in the long term. Nevertheless, to take into account potential bias related to the patient selection, we decided to switch at month 24 after transplantation all kidney transplant recipients who were given maintenance EC-MPS to MMF and repeat the MPA pharmacokinetics evaluations and month 30. In this way, we found that the conversion resulted in a significant reduction in the MPA $C_0$ levels, with values comparable to those measured in patients who were given MMF throughout the study period. Notably, in patients who were shifted from EC-MPS to MMF, the atypical daily MPA profile did normalize, being associated with less variability in the main pharmacokinetics parameters. Moreover, this switch resulted in a marked improvement of the MPA exposure in patients who previously experienced negligible MPA absorption when given EC-MPS. These findings further
Table 5. Clinical outcome of kidney transplant recipients who were given EC-MPS or MMF as part of their maintenance immunosuppression regimen

<table>
<thead>
<tr>
<th>MPA-Releasing Formulation</th>
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<th>GFR (ml/min per 1.73 m²)</th>
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<tr>
<td></td>
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<td>Month 18</td>
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<td>EC-MPS (n = 12)</td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>3</td>
<td>59.2 ± 18.9</td>
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<td>MMF (n = 20)</td>
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indicate that the variability in MPA absorption was just linked to the EC-MPS administration, confirming our previous results from the parallel study.

As an additional shortcoming, it must be considered that all of the patients in this study were given EC-MPS or MMF in combination with CsA. It is widely known that the two calcineurin inhibitors available, namely CsA and tacrolimus, exert different interactions on MPA (22); therefore, our findings on the pharmacokinetics of release of MPA from EC-MPS can be interpreted only when the drug is given in combination with CsA and cannot necessarily be translated also to patients who are given tacrolimus.

Conclusions
We have shown that, despite daily drug exposure, the pharmacokinetics of release of MPA from the new EC-MPS formulation is extremely variable as compared with that after MMF administration in stable kidney transplant recipients who are treated long term with these drugs in combination with CsA. Given the increasing evidence of the benefit of MPA monitoring in the kidney transplant setting to minimize toxicity and maximize its immunosuppressive property (2,3,21,23), therapeutic drug monitoring problems related to the enteric coating of EC-MPS should be taken into account.

Acknowledgments
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Disclosures
None.

References

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