Lack of an Effect of Oral Iron Administration on Mycophenolic Acid Pharmacokinetics in Stable Renal Transplant Recipients

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Study Objectives. To determine if coadministration of polysaccharide iron complex and slow-release ferrous sulfate alter the absorption of mycophenolic acid (MPA), and to examine the potential influence of dosing relative to mycophenolate mofetil (MMF) administration and the effect of immediate- versus sustained-release iron products on the steady-state pharmacokinetics of MPA.

Design. Prospective, open-label, three-phase, crossover, steady-state pharmacokinetic study.

Setting. National Institutes of Health–sponsored General Clinical Research Center at a university medical center.

Patients. Twelve adult (mean age 50 yrs) renal transplant recipients who were receiving concomitant iron and MMF maintenance therapy.

Intervention. Oral iron therapy was coadministered with MMF on days -6–0, MMF was administered alone on days 1–8 (control phase), then oral iron therapy was administered 2 hours after MMF administration on days 9–16.

Measurements and Main Results. Baseline demographics, concurrent drug regimens, and clinical laboratory values were assessed. Blood samples were obtained at baseline and at 1, 2, 3, 4, 6, 8, and 12 hours after MMF administration on days 0, 8, and 16. The MPA levels were measured by high-performance liquid chromatography. We found no significant differences in the dose-standardized area under the concentration-time curve from 0–12 hours (AUC_{0-12}) for MPA between the control phase (39.66 ± 8.70 mg•hr/L) and the concomitant ferrous sulfate or dose-separated ferrous sulfate (37.56 ± 9.95 or 32.84 ± 8.43 mg•hr/L, respectively, p>0.05) phases. Dose-standardized AUC_{0-12} values for MPA did not significantly differ after the concomitant administration of polysaccharide iron complex from that of the control phase (48.46 ± 9.68 and 43.80 ± 9.46 mg•hr/L, respectively, p=0.065). However, the AUC_{0-12} for MPA significantly increased when polysaccharide iron complex was administered 2 hours after MMF (53.41 ± 11.75 mg•hr/L, p=0.012). Maximum concentrations and times to reach maximum concentrations remained consistent across all study phases in each arm of the trial (p>0.05).

Conclusion. Multiple doses of iron therapy—slow-release ferrous sulfate, or polysaccharide iron complex—did not significantly reduce systemic exposure to MMF, as measured by using AUC_{0-12} values.

Key Words: mycophenolate mofetil, pharmacokinetics, renal transplantation, drug interactions, ferrous sulfate, polysaccharide iron complex.

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Mycophenolate mofetil (MMF) is a key component of modern immunosuppression and is routinely used to prevent rejection in transplant recipients. Several pivotal multicenter clinical trials involving kidney transplant recipients demonstrated a 50% reduction in acute rejection with MMF-based regimens compared with azathioprine-based regimens.[1–5] Evidence further demonstrated a significant correlation between the probability of rejection and the concentration-time curve for mycophenolic acid (MPA).[6–10] Investigators evaluating the relationship between rejection and systemic exposure to MPA reported thresholds that minimize the risk of rejection; the area under the concentration-time curve from 0–12 hours (AUC_{0-12}) for MPA was greater than 30 mg•hour/L, and the predose plasma concentration for MPA was greater than 1.0 mg/L.[7, 11] However, abbreviated MPA-sampling strategies have proven preferable over the use of predose concentrations, particularly in the early period after transplantation, owing to a strengthened correlation with the area under the concentration-time curve and with rejection in the case of AUC_{0-12}.[12, 13]

After oral administration, MMF is rapidly absorbed and presystemically hydrolyzed to its active form, MPA, in the liver.[14] Glucuronyl transferase then metabolizes MPA to MPA glucuronide, an inactive metabolite.[15] This metabolite also undergoes considerable enterohepatic recirculation, which possibly contributes to the biphasic pharmacokinetic profile of MPA.[16–18] Although MMF alone offers excellent bioavailability, it remains potentially susceptible to chelation interactions when it is coadministered with other drugs, including aluminum- and/or magnesium-containing antacids or cholestyramine.[15, 16, 19–21] In addition, data from a crossover, single-dose study of healthy volunteers suggested that the systemic exposure to MPA decreased by 89% after iron was concomitantly administered with a single dose of MMF.[20] This effect was attributed to the theoretical development of an insoluble iron-MMF complex. Given the concentration-efficacy relationship reported in the literature, transplant recipients receiving an MMF-based regimen who require iron supplementation may incur an increased risk for acute rejection secondary to reduced overall systemic exposure to MPA from such an interaction.

This study was designed to determine if coadministration of two commonly prescribed iron formulations—polysaccharide iron complex and sustained release ferrous sulfate—alter the absorption of MPA in stable renal transplant recipients. In addition, we examined the potential influence of timing of the dosing relative to MMF administration and the effect of immediate- versus sustained-release iron products on the steady-state pharmacokinetics of MPA.

Methods

The institutional review board of the University of Michigan approved the study protocol. All patients gave written informed consent before any study procedures were started.

Study Subjects

Patients were eligible for enrollment if they were at least 18 years old, if they received renal allografts from a living or deceased donor, if they were in stable condition, if at least 6 months had passed since transplantation, and if they were concomitantly receiving slow-release ferrous sulfate or polysaccharide iron complex with MMF maintenance therapy. Eligibility criteria also included no acute rejection in the 3 months before study entry, achievement of therapeutic trough levels of cyclosporine (usually 100–150 ng/ml) or tacrolimus (usually 5–10 ng/ml) as defined in the protocol of the transplant center, and no recent dosage adjustments to cyclosporine (United States Pharmacopeia, modified) or tacrolimus within 2 weeks before study entry.

Patients were excluded if they received other organ transplants in addition to kidney transplants or if they were pregnant or breastfeeding.

Immunosuppression consisted of a standard protocol: a calcineurin inhibitor, cyclosporine (Neoral, Novartis Pharmaceuticals Corp., East Hanover, NJ; or Gengraf, Abbott Laboratories, Abbott Park, IL), or tacrolimus (Prograf, Astellas Pharma US, Inc., Deerfield, IL) in combination with twice-daily MMF and daily prednisone. Previously prescribed formulations of slow-release ferrous sulfate (Slow-Fe; Novartis Consumer Health, Inc., Parsippany, NJ) or polysaccharide iron complex (Niferex-150; Ther-Rx, Bridgeton, MO) were maintained.

Study Design

This study was a prospective, open-label, three-phase, crossover, steady-state pharmacokinetic study. Patients were instructed to avoid drinking alcohol or taking any new drugs for 1 week before the study and throughout the trial.

Patients were assigned to study arms according to their previously prescribed iron formulation of slow-release ferrous sulfate or polysaccharide iron complex. In each arm, slow-release ferrous sulfate or polysaccharide iron complex was coadministered with the oral morning dose of MMF on days -6–0. On days 1–8, MMF was taken alone (washout period). On days 9–16, iron products were taken 2 hours after the dose of MMF.

The AUCs for MPA were measured on days 0, 8, and 16. Before each blood sampling day, patients fasted overnight for at least 10 hours, but water was allowed ad libitum.

After completion of the study, patients were eligible to cross over to the opposite study arm with the approval of their physician. Patients continued to fast 4 hours after the morning dose of MMF but were allowed to drink water ad libitum. All patients received standardized meals 5 and 10 hours after the administration of MMF. Each patient received the same oral MMF dose (500–1000 mg) twice/day throughout the trial.

Venous blood samples were drawn at baseline before the morning dose of MMF and at 1, 2, 3, 4, 6, 8, and 12 hours after the ingestion of MMF. Samples were immediately centrifuged, and plasma was frozen at -80°C until analysis.

Renal function was evaluated by measuring serum creatinine concentrations.

End Points

The primary end point was the $AUC_{0–12}$ for MPA. Concentrations of MPA and MPA glucuronide were measured by using validated high-performance liquid chromatography. The assay for MPA–MPA glucuronide in biologic specimens was developed in the Drug Laboratory at the Mayo Clinic, Rochester, Minnesota.

For each sample, two tubes were required. The test involved direct measurement of serum MPA levels and replicated analyses of serum treated with glucuronidase to measure total hydrolyzable MPA levels. The difference between unconjugated and total MPA results allowed us to calculate the concentration of MPA glucuronide. One tube labeled A was for MPA, and one tube labeled B was for MPA glucuronide. To tube A, 200 µl of the standards, controls, and samples were added, and to tube B, 50 µl and 150 µl of blank serum were added. To only tube B, 100 µl of 1:10 glusulase in sodium acetate buffer at pH 6.0 were added and incubated for 10 minutes at 37°C; 100 µl were pipetted into tube B. To both tubes, 100 µl of the internal standard (5 µg/ml zomepirac in acetonitrile) were added. Excess sodium sulfate was added and centrifuged, and the supernatant was removed. The extract was dried under nitrogen at 30°C and reconstituted in 200 µl of the mobile phase.

Using a chromatography system (Class-VP LC; Shimadzu Scientific Instruments, Columbia, MD), 30 µl of the reconstituted sample were placed onto an high-performance liquid chromatography guard column (2 cm x 4.6 mm, 5 µm) and an analytical column (5 cm x 4.6 mm, 5 µm) (both Discovery C18; Supelco, Sigma-Aldrich, Bellefonte, PA) at ambient temperature. Chromatographic separation was achieved by delivering isocratic solvent with a mobile phase of 20% acetonitrile and 80% triethylamine-phosphate buffer at pH 7.0 (final concentration 25% triethylamine and 1.875 mmol/L potassium phosphate buffer) with a flow rate of 2.0 ml/minute. Detection was achieved by monitoring the absorbance at 213 nm. We eluted MPA at 2.8 minutes and the internal standard at 6.75 minutes.

Concentrations were calculated by comparing peak-height ratios of the drug with those of the internal standard. The lower limit of quantification was defined as 0.5 µg/ml. Intraday variability was defined as less than 10%, and interday variability was not applicable. Secondary end points were the maximum concentration (C_{max}) and the time to reach C_{max} (T_{max}). Both C_{max} and T_{max} were determined directly from measured values.

Table 1. Baseline Demographic Characteristics

Characteristic	Polysaccharide Iron Complex Group (n=7)	Slow-Release Ferrous Sulfate Group (n=5)
	Mean ± SD	
Age (yrs)	50.28 ± 8.71	51.00 ± 14.45
Time after transplantation (mo)	47.00 ± 45.22	51.00 ± 29.29
Weight (kg)	87.11 ± 18.57	108.54 ± 29.29
	No. (%) of Patients	
Sex		
Male	3 (43)	4 (80)
Female	4 (57)	1 (20)
Caucasian	6 (86)	5 (100)
Deceased donor transplant	3 (43)	3 (60)
First transplant	6 (86)	5 (100)
Diabetes mellitus	1 (14)	3 (60)
Cause of end-stage renal disease		
Diabetes mellitus	1 (14)	2 (40)
Polycystic kidney disease	2 (29)	0 (0)
Glomerulonephritis	4 (57)	2 (40)
Other	0 (0)	1 (20)
Cyclosporine-based regimen[a]	6 (86)	5 (100)

[a]Cyclosporine U.S. Pharmacopeia, modified.

Statistical Analysis

The patients' characteristics were summarized by using descriptive statistics. Individual AUC_{0-12} values were calculated by using the linear trapezoidal and logarithmic trapezoidal approximation for increasing and decreasing plasma concentrations, respectively. Values were dose normalized to MMF 1 g. A paired *t* test was used to compare experimental-phase AUCs for MMF plus iron products taken concomitantly or 2 hours apart were compared with those from the control phase of MMF alone. Prospective power calculations indicated that a minimum of eight patients in each arm were required to detect a 30% difference in AUC_{0-12} values for MPA with 80% likelihood if we assumed a two-sided α of 0.05. Statistical analyses were performed by using software (Statistical Package for the Social Sciences for Windows, version 11.0; SPSS Inc., Chicago, IL).

Results

Twelve patients were screened and enrolled in the study. One subject was prematurely withdrawn from the study because of a marked change in renal function after day 8 of the pharmacokinetic study. After the sequence for slow-release ferrous sulfate was completed, one patient consented to switch iron formulations and completed the sequence for polysaccharide iron complex. Data from seven patients in the arm for polysaccharide iron complex and five in the arm for slow-release ferrous sulfate were analyzed.

Effect of Polysaccharide Iron Complex on the Pharmacokinetics of MPA

Table 1 summarizes the patients' baseline demographics. Immunosuppressive therapy consisted of primarily cyclosporine (Neoral in five patients and Gengraf in one), MMF, and prednisone. One patient received tacrolimus, MMF, and prednisone. Each patient received 150 mg of elemental iron. The patient population was primarily Caucasian and first-time transplant recipients. Serum creatinine concentration measurements remained constant between each study phase (p=0.407), with a maximum difference of 0.2 mg/dl between study phases.

Table 2 shows the calculated pharmacokinetic parameters reflecting coadministration of MMF and polysaccharide iron complex. During the control phase, calculated AUC_{0-12} values for MPA were greater than 30 mg•hour/L for all subjects (range 35.4–56.4 mg•hr/L) but one, whose value was 27.8 mg•hour/L. The value of 30 mg•hour/L is an established threshold for a diminished risk of acute rejection.[7, 11] The mean estimated AUC_{0-12} value for MPA when MMF was coadministered with polysaccharide iron complex

Table 2. Pharmacokinetic Parameters from the Polysaccharide Iron Complex Study

Parameter	MMF Alone	MMF + Polysaccharide Iron Complex	
		Coadministered	2 Hours Apart
		Median (Range)	
MPA AUC_{0-12} (mg•hr/L)	45.26 (27.84–56.73)	51.91 (36.33–57.75)	57.59 (33.24–69.21)
		Mean ± SD	
MPA AUC_{0-12} (mg•hr/L)	43.80 ± 9.46	48.46 ± 9.68	53.41± 11.75[a]
MPA C_0 (mg/L)	2.51 ± 1.05	2.84 ± 1.83	2.39 ± 2.00
C_{max} (mg/L)	9.53 ± 5.12	12.46 ± 5.90	12.6 ± 3.77
T_{max} (hrs)	1.70 ± 1.24	1.57 ± 1.13	1.57± 0.98

MMF = mycophenolate mofetil; AUC_{0-12} = area under the concentration-time curve from 0–12 hours; MPA= mycophenolic acid; C_0 = predose plasma concentration; C_{max} = maximum concentration; T_{max} = time to reach C_{max}.
[a]p=0.012 versus MMF alone.

Table 3. Pharmacokinetic Parameters from the Slow-Release Ferrous Sulfate Study

Parameter	MMF Alone	MMF + Slow-Release Ferrous Sulfate	
		Coadministered	2 Hours Apart
		Median (Range)	
MPA AUC_{0-12} (mg•hr/L)	38.30 (30.44–54.04)	36.37 (27.14–53.22)	37.77 (23.53–41.21)
		Mean ± SD	
MPA AUC_{0-12} (mg•hr/L)	39.66 ± 8.70	37.56 ± 9.95	32.84 ± 8.43
MPA C_0 (mg/L)	1.80 ± 0.78	1.54 ± 1.28	1.48 ± 0.54
C_{max} (mg/L)	14.10 ± 5.18	10.88 ± 4.00	9.40 ± 3.16
T_{max} (hrs)	1.04 ± 0.98	1.99 ± 2.24	1.00 ± 0.00

MMF = mycophenolate mofetil; AUC_{0-12} = area under the concentration-time curve from 0–12 hours; MPA= mycophenolic acid; C_0 = predose plasma concentration; C_{max} = maximum concentration; T_{max} = time to reach C_{max}.

(48.46 ± 9.68 mg•hr/L) was similar to the control value for MMF alone (43.80 ± 9.46 mg•hr/L). Although the difference was not significantly different (p=0.065), we observed an 11.8% mean increase in the AUC_{0-12} for MPA during the concomitant-dosing phase versus the MMF-alone phase. In addition, mean AUC_{0-12} values were significantly greater when polysaccharide iron complex was administered 2 hours after MMF than in the control phase (p=0.012). This difference resulted in an observed mean increase of 22.7% for MPA exposure. Observed C_{max} and T_{max} were similar between the control arm and the concomitant or dose-separation arm; mean C_{max} values were slightly increased in both the concomitant and dose-separation phases.

Effect of Slow-Release Ferrous Sulfate on the Pharmacokinetics of MPA

Tables 1 and 3 summarize the patients' characteristics and calculated pharmacokinetic parameters, respectively, in the slow-release ferrous sulfate study. The mean ± SD dose of elemental iron was 83.0 ± 42.7 mg. Renal function, as evaluated by using serum creatinine concentrations, remained stable throughout all study phases (p=0.47), with no change exceeding 0.6 mg/dl. All subjects received immunosuppression based on cyclosporine (Neoral in three and Gengraf in two) with MMF and prednisone.

All calculated AUC_{0-12} values for MPA in the control phase were therapeutic and ranged from 30.4–54.0 mg•hour/L. No difference was observed in mean AUC_{0-12} values between the control phase and the concomitant phase (p=0.716). The mean AUC_{0-12} value for the dose-separation phase was similar to the control value (p=0.236). Results for C_{max} and T_{max} remained consistent between study phases (control vs concomitant or separation arm); C_{max} values were slightly reduced in both the concomitant and dose-separation phases (p=0.32 and p=0.241, respectively).

Discussion

The impetus for this trial came from a previous report that demonstrated an 89% reduction in the AUC_{0-12} for MPA after MMF 1000 mg was

administered with ferrous sulfate (210 mg elemental iron) in healthy volunteers.[20] The investigators theorized that the decrease was secondary to the development of an insoluble iron-MMF complex. However, results of a later in vitro investigation did not support this theory.[22] Our study was designed to investigate the effect of two iron formulations—slow-release ferrous sulfate and polysaccharide iron complex—on the pharmacokinetics of MPA to determine true steady-state concentrations of each drug in renal transplant recipients.

Slow-Release Ferrous Sulfate

Overall systemic exposure to MPA was not altered with concomitant slow-release ferrous sulfate and MMF in stable renal transplant recipients. In addition, 2-hour dosing separation had no effect on the relative bioavailability of MMF. These results are strikingly dissimilar from those previously reported.[20] These differences were possibly due to the previous trial's evaluation of a healthy population, use of twice the dose of elemental iron, or, most likely, use of a single-dose design.[20] Our study reflected steady-state MPA exposure in renal transplant patients (at least 6 mo after transplantation) who received concomitant or dose-separated ferrous sulfate with MMF 1000 mg twice/day.

While our study was ongoing, other researchers tested hypotheses in renal transplant recipients similar to ours.[23, 24] One group measured AUC_{0-12} values for MPA on day 5 after de novo renal transplantation.[24] Another group created a single-dose design and measured AUC_{0-12} values for MPA in renal transplant recipients at least 6 months after transplantation.[23] Both evaluated a formulation of ferrous sulfate iron. Our trial was effectively a hybrid of these two studies. Although we enrolled somewhat fewer patients than the others did, our conclusions regarding ferrous sulfate were similar to theirs.

Investigators recently repeated the nonfed-state study design previous researchers used[20] by administering MMF 1 g alone or with oral slow-release ferrous sulfate to healthy volunteers.[25] Their aim was to confirm the reported interaction between ferrous sulfate and MMF. However, the results were dissimilar to the previous findings. Like us, they found no notable alteration in the pharmacokinetic profile of MMF when it was coadministered with iron. Given the similar designs of the two trials, the authors suggested that the difference might have been attributable to confounders associated with bioanalytic assays used in the original study.[20, 25]

Our trial and the above-mentioned trials add to the body of robust evidence demonstrating the lack of interaction when ferrous sulfate is coadministered with MMF.

Polysaccharide Iron Complex

The results surprisingly demonstrated a significant increase in overall systemic exposure of MPA during the dose-separation phase with polysaccharide iron complex. In addition, mean AUCs for MPA increased in the concomitant-administration phase, although the changes were not statistically significant. The magnitude of the difference was similar for the mean and median values of those groups as well. A peculiar observation was that the interaction was enhanced during the dose-separation phase. This finding was inconsistent with those of our investigation of a ferrous sulfate product and with the results of three published reports.[20, 23, 24] The increased exposure may be attributed to chemical differences in the polysaccharide iron complex compared with the ferrous sulfate salt, to alterations in the gastric environment that benefited MMF absorption of this product, to interpatient variability, or, most likely, to the small sample size.

Most important, our data suggested that overall exposure to MPA was not decreased after the concomitant or delayed administration of ferrous sulfate and polysaccharide iron complex. Further in vitro studies may be required to elucidate the pathway responsible for the influence of polysaccharide iron complex on the absorption of MPA.

Study Limitations

Limitations of this trial include the relatively small sample size, the primarily Caucasian population, the unavailability of the area under the concentration-time curve for cyclosporine when the pharmacokinetics of MPA were being studied, and the nonfed-state study design. The limited sample affected the statistical power for the two pharmacokinetic studies. These flaws may limit overall generalizability of the results to the renal transplant population.

Because we did not study cyclosporine pharmacokinetics, we cannot rule out effects of cyclosporine on concentrations of MPA. However, of note, the same dosage regimens for

calcineurin inhibitors, MMF, prednisone, and any other drugs were maintained in all patients throughout the study.

Finally, during this study, three other groups of investigators reported the lack of potential effect of ferrous sulfate on the pharmacokinetics of MPA.[23–25] However, previous investigations focused on the effect of a single dose of ferrous sulfate or reflected the pharmacokinetics of MPA 5 days after transplantation. By contrast, our trial reflected true steady-state pharmacokinetics for MPA and iron. In addition, we investigated the influence of two commonly prescribed products in the United States.

Conclusion

In stable renal transplant recipients, oral absorption of MMF was not reduced with polysaccharide iron complex or slow-release ferrous sulfate administered with or 2 hours after MMF ingestion.

Acknowledgments

References

1. **European Mycophenolate Mofetil Cooperative Study Group**. Placebo-controlled study of mycophenolate mofetil combined with cyclosporin and corticosteroids for prevention of acute rejection. Lancet 1995;345(8961):1321–5.
2. **Halloran P, Mathew T, Tomlanovich S, Groth C, Hooftman L, Barker C**. Mycophenolate mofetil in renal allograft recipients: a pooled efficacy analysis of three randomized, double-blind, clinical studies in prevention of rejection. The international mycophenolate mofetil renal transplant study groups. Transplantation 1997;63(1):39–47.
3. **Sollinger HW**. Mycophenolate mofetil for the prevention of acute rejection in primary cadaveric renal allograft recipients. U.S. renal transplant mycophenolate mofetil study group. Transplantation 1995;60(3):225–32.
4. **Kobashigawa JA, Meiser BM**. Review of major clinical trials with mycophenolate mofetil in cardiac transplantation. Transplantation 2005;80(2 suppl):S235–43.
5. **Hebert MF, Ascher NL, Lake JR, et al**. Four-year follow-up of mycophenolate mofetil for graft rescue in liver allograft recipients. Transplantation 1999;67(5):707–12.
6. **Pawinski T, Durlik M, Szlaska I, Urbanowicz A, Majchrnak J, Gralak B**. Comparison of mycophenolic acid pharmacokinetic parameters in kidney transplant patients within the first 3 months post-transplant. J Clin Pharm Ther 2006;31(1):27–34.
7. **Pillans PI, Rigby RJ, Kubler P, et al**. A retrospective analysis of mycophenolic acid and cyclosporin concentrations with acute rejection in renal transplant recipients. Clin Biochem 2001;34(1):77–81.
8. **Takahashi K, Ochiai T, Uchida K, et al**. Pilot study of mycophenolate mofetil (RS-61443) in the prevention of acute rejection following renal transplantation in Japanese patients. RS-61443 investigation committee—Japan. Transplant Proc 1995;27(1):1421–4.
9. **van Gelder T, Hilbrands LB, Vanrenterghem Y, et al**. A randomized double-blind, multicenter plasma concentration controlled study of the safety and efficacy of oral mycophenolate mofetil for the prevention of acute rejection after kidney transplantation. Transplantation 1999;68(2): 261–6.
10. **Weber LT, Shipkova M, Armstrong VW, et al**. The pharmacokinetic-pharmacodynamic relationship for total and free mycophenolic acid in pediatric renal transplant recipients: a report of the German study group on mycophenolate mofetil therapy. J Am Soc Nephrol 2002;13(3):759–68.
11. **Armstrong VW, Shipkova M, Schutz E, Weber L, Tonshoff B, Oellerich M**. Monitoring of mycophenolic acid in pediatric renal transplant recipients. Transplant Proc 2001;33(1–2): 1040–3.
12. **Oellerich M, Shipkova M, Schutz E, et al**. Pharmacokinetic and metabolic investigations of mycophenolic acid in pediatric patients after renal transplantation: implications for therapeutic drug monitoring. German study group on mycophenolate mofetil therapy in pediatric renal transplant recipients. Ther Drug Monit 2000;22(1):20–6.
13. **Nicholls AJ**. Opportunities for therapeutic monitoring of mycophenolate mofetil dose in renal transplantation suggested by the pharmacokinetic/pharmacodynamic relationship for mycophenolic acid and suppression of rejection. Clin Biochem 1998;31(5):329–33.
14. **Bullingham R, Monroe S, Nicholls A, Hale M**. Pharmacokinetics and bioavailability of mycophenolate mofetil in healthy subjects after single-dose oral and intravenous administration. J Clin Pharmacol 1996;36(4):315–24.
15. **Roche Laboratories Inc**. CellCept (mycophenolate mofetil) package insert. Nutley, NJ; 2005.
16. **Bullingham RE, Nicholls AJ, Kamm BR**. Clinical pharmacokinetics of mycophenolate mofetil. Clin Pharmacokinet 1998;34(6):429–55.
17. **Meiser BM, Pfeiffer M, Schmidt D, et al**. Combination therapy with tacrolimus and mycophenolate mofetil following cardiac transplantation: importance of mycophenolic acid therapeutic drug monitoring. J Heart Lung Transplant 1999;18(2):143–9.
18. **van Gelder T, Meur YL, Shaw LM, et al**. Therapeutic drug monitoring of mycophenolate mofetil in transplantation. Ther Drug Monit 2006;28(2):145–54.
19. **Bullingham R, Shah J, Goldblum R, Schiff M**. Effects of food and antacid on the pharmacokinetics of single doses of mycophenolate mofetil in rheumatoid arthritis patients. Br J Clin Pharmacol 1996;41(6):513–16.
20. **Morii M, Ueno K, Ogawa A, et al**. Impairment of mycophenolate mofetil absorption by iron ion. Clin Pharmacol Ther 2000;68(6):613–16.
21. **Campbell NR, Hasinoff BB**. Iron supplements: a common cause of drug interactions. Br J Clin Pharmacol 1991;31(3): 251–5.
22. **Lidgate D, Brandl M, Holper M, Abubakari A, Wu X**. Influence of ferrous sulfate on the solubility, partition coefficient, and stability of mycophenolic acid and the ester mycophenolate mofetil. Drug Dev Ind Pharm 2002;28(10): 1275–83.
23. **Lorenz M, Wolzt M, Weigel G, et al**. Ferrous sulfate does not affect mycophenolic acid pharmacokinetics in kidney transplant patients. Am J Kidney Dis 2004;43(6):1098–103.
24. **Mudge DW, Atcheson B, Taylor PJ, et al**. The effect of oral iron administration on mycophenolate mofetil absorption in renal transplant recipients: a randomized, controlled trial. Transplantation 2004;77(2):206–9.
25. **Ducray PS, Gerber M, Boutouyrie B, Zandt H**. Absence of an interaction between iron and mycophenolate mofetil absorption. Br J Clin Pharmacol 2006;62(4):492–5.