

CASE REPORT

Probable Drug Interaction Between Intravenous Ciprofloxacin and Mycophenolate Mofetil in a Bone Marrow Transplant Recipient

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Several studies have reported that oral antibacterials, including ciprofloxacin, administered during mycophenolate mofetil therapy may reduce mycophenolic acid (the active drug moiety) exposure. To our knowledge, however, this effect has never been described with antibiotics administered by the parenteral route. We describe a 17-year-old female who received intravenous mycophenolate mofetil after bone marrow transplantation, with therapeutic drug monitoring performed during therapy. On day 2 of mycophenolate mofetil therapy, the mycophenolic acid area under the plasma concentration–time curve was 30.3 mg•hour/L. On day 8, although her mycophenolate mofetil dosage had remained unchanged, the mycophenolic acid area under the plasma concentration–time curve was unexpectedly lower at 10.7 mg•hour/L. A drug interaction was suspected. Three intravenous anti-infective drugs had been introduced after initial therapeutic drug monitoring had been performed—ciprofloxacin, trimethoprim-sulfamethoxazole, and caspofungin. The patient subsequently developed severe graft-versus-host disease during mycophenolate mofetil therapy and died. Use of the Horn drug interaction probability scale indicated a probable interaction between intravenous mycophenolate mofetil and intravenous ciprofloxacin in this patient. The available literature does not support the role of either trimethoprim-sulfamethoxazole or caspofungin in a drug interaction with mycophenolate mofetil. Published studies have shown that ciprofloxacin is partially excreted by transintestinal elimination after intravenous administration and that it may greatly reduce the levels of enterobacteria of gastrointestinal flora, which are responsible for mycophenolic acid enterohepatic recirculation. Clinicians should be aware that ciprofloxacin, even administered intravenously, may modify the pharmacokinetics of mycophenolate mofetil. Ciprofloxacin should be used with caution in patients receiving mycophenolate mofetil; if this anti-infective must be used, therapeutic drug monitoring should be performed to guide dosage adjustments.

Key Words: mycophenolate mofetil, ciprofloxacin, drug interaction, enterohepatic cycling, therapeutic drug monitoring, graft-versus-host disease. (Pharmacotherapy 2011;31(1):36e–40e)

Mycophenolate mofetil is an immunosuppressant drug commonly used in solid organ transplantation. It was first introduced in renal transplantation and has shown beneficial effects on acute graft rejection and graft survival when

combined with corticosteroids and cyclosporine regimens.^{1,2} As the introduction of mycophenolate mofetil in bone marrow transplantation has been more recent, its role has not yet been fully established in this setting.³

The pharmacokinetics of mycophenolate mofetil have been well described.⁴ Mycophenolate mofetil is the ester prodrug of mycophenolic acid (MPA), which is the active drug moiety. After intravenous administration, mycophenolate mofetil is rapidly and almost fully hydrolyzed to MPA by blood esterases. This also occurs after oral administration, resulting in extensive presystemic biotransformation. Mycophenolic acid acts as an inhibitor of inosine monophosphate dehydrogenase involved in the *de novo* purine biosynthesis. Mycophenolic acid is metabolized to the stable and pharmacologically inactive mycophenolic acid glucuronide (MPAG) by uridine diphosphate glucuronosyltransferase enzymes. Both MPA and MPAG are largely bound to albumin in the blood. Mycophenolic acid glucuronide is excreted in bile and urine. Both MPAG and MPA undergo significant enterohepatic cycling processes. It is thought that MPAG excreted in bile is then metabolized to MPA in the intestine due to the action of glucuronidases produced by the endogenous bacteria of the gastrointestinal flora. It has been suggested that this enterohepatic recirculation causes a secondary peak of the MPA plasma concentration usually observed 6–12 hours after administration of an oral dose.⁴ Based on an oral interaction study with cholestyramine, the contribution of enterohepatic cycling to MPA exposure was estimated to be 40%.⁵ Finally, 90% of a mycophenolate mofetil dose is excreted in the urine, mainly as MPAG.

In this case report, we describe an adolescent bone marrow transplant recipient whose exposure to intravenous mycophenolic acid was likely decreased by the receipt of intravenous ciprofloxacin.

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Case Report

A 17-year-old female (height 5'3", weight 60 kg) came to our pediatric hematology unit for bone marrow transplantation. She had been diagnosed with paroxysmal nocturnal hemoglobinuria 3 years earlier. The severity of her disease, including aplastic anemia and thrombotic complications, eventually indicated the need for bone marrow transplantation.

Before undergoing the transplantation, the patient received a conditioning regimen of intravenous busulfan 11.1 mg/kg (therapeutic drug monitoring–guided total dose), cyclophosphamide 200 mg/kg (total dose), and equine antilymphocyte globulins 100 mg/kg (total dose). During the conditioning treatment, she developed a fever (39–40°C), and intravenous antibiotic therapy with vancomycin, amikacin, and piperacillin-tazobactam was started. As no source of infection was found, vancomycin and amikacin were discontinued after 3 and 5 days of therapy, respectively; piperacillin-tazobactam 12 g/day was continued.

The bone marrow graft was infused on hospital day 1. Immunosuppressant monotherapy with intravenous cyclosporine 100 mg twice/day was started the day before transplantation. Posttransplantation treatment included parenteral administration of patient-controlled analgesia with morphine, ketamine 30 mg/day, as-needed acetaminophen (up to 3600 mg/day), alizapride 300 mg/day, omeprazole 80 mg/day, hydroxyzine 50 mg/day, and furosemide 40 mg/day. The patient also received oral ursodeoxycholic acid 500 mg/day and valaciclovir 1000 mg/day. Selective bowel decontamination was performed with gentamicin 240 mg/day and amphotericin B 3 g/day. Mouthwashes were administered 4 times/day with sodium bicarbonate and antifungal and antiseptic agents, and twice/day with vancomycin.

Approximately 24 hours after bone marrow transplantation (48 hrs after cyclosporine therapy was started), the patient developed renal failure (serum creatinine concentration > 2.3 mg/dl) associated with acute pulmonary edema and a 4-kg weight gain. Cyclosporine-induced thrombotic microangiopathy was suspected, and cyclosporine therapy was replaced with intravenous corticosteroids and mycophenolate mofetil on day 5. The acute pulmonary edema rapidly resolved with furosemide and potassium canreonate. Treatment with defibrotide was also started on day 5 for prophylaxis of venoocclusive disease.

The initial dose of intravenous mycophenolate mofetil was 1800 mg/day (30 mg/kg [1100 mg/m²]), administered as a 2-hour infusion of 600 mg every 8 hours. Therapeutic drug monitoring was performed 4 times during therapy. Plasma concentrations of MPA were measured by an automated enzyme-multiplied immunoassay technique (EMIT) using the Cobas Mira Chemistry Analyzer (Roche Diagnostics Systems, Basel, Switzerland) analyzer. The patient's MPA exposure was controlled by using the area under the plasma concentration–time curve from 0–12 hours (AUC_{0–12}). Four plasma concentrations of MPA, determined at time 0 (predose [trough] level) and 0.5, 1.5, and 3 hours after the end of mycophenolate mofetil infusion, were used to estimate the AUC_{0–8} by using the trapezoidal method. The AUC_{0–12} was then derived from AUC_{0–8} by linear extrapolation. Because, to our knowledge, no AUC therapeutic range has yet been defined for bone marrow transplantation, we used the therapeutic range used in solid organ transplantation (30–60 mg•hr/L) as the reference range for MPA AUC_{0–12}.^{4,6,7}

Figure 1 shows the evolution of the MPA AUC_{0–12} and trough and 30-minute postdose concentrations during mycophenolate mofetil

therapy. The MPA AUC measured on day 7 (30.3 mg•hr/L) was close to the lower limit of the therapeutic range. On day 13, however, although the mycophenolate mofetil dosage had remained unchanged, both the MPA AUC_{0–12} and trough level had decreased to approximately one third of their initial values. Three intravenous anti-infective drugs had been introduced after the initial therapeutic drug monitoring had been performed because of fever recurrence observed on day 8. Ciprofloxacin was administered on days 8–15, as 800 mg/day on days 8–13 and 1200 mg/day on days 13–15. Because the fever persisted, trimethoprim 240 mg–sulfamethoxazole 1200 mg every 48 hours and caspofungin 70 mg/day were initiated on days 10 and 11, respectively. Both drugs were continued throughout mycophenolate mofetil therapy. The mycophenolate mofetil dose was subsequently increased to 4500 mg/day (1500 mg every 8 hrs); this 2.5-fold increase resulted in a quantitatively similar rise of the MPA AUC measured on day 18 (26 mg•hr/L). Because the patient developed diarrhea, however, her mycophenolate mofetil dose was decreased to 3000 mg/day on day 18, and the drug was eventually discontinued on day 33 due to the persistence of gastrointestinal adverse effects. Therapeutic drug monitoring was last performed

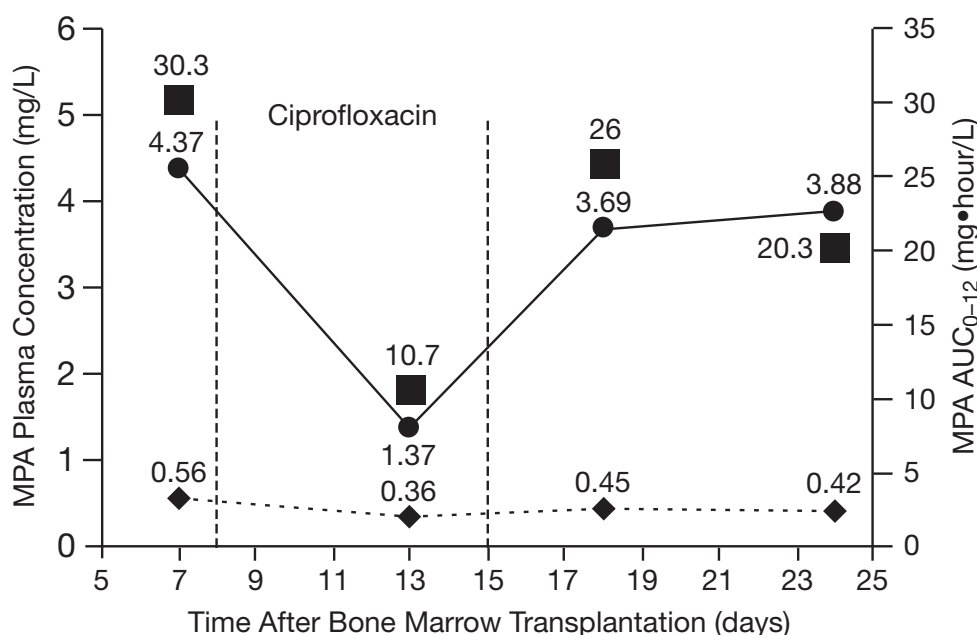


Figure 1. Time course of mycophenolic acid (MPA) area under the plasma concentration–time curve from 0–12 hours (AUC_{0–12}; squares), trough concentrations (diamonds), and 30-minute postdose concentrations (circles) measured during mycophenolate mofetil therapy after the patient's bone marrow transplantation. The mycophenolate mofetil dose was 1800 mg/day on days 1–13, 4500 mg/day on days 13–18, and 3000 mg/day on days 18–33. Ciprofloxacin therapy was administered on days 8–15, represented by the vertical dashed lines.

on day 24 and showed persistent MPA under-exposure.

On day 18 of mycophenolate mofetil therapy, the patient developed grade III cutaneous graft-versus-host disease. Cyclosporine was briefly reintroduced, but the graft-versus-host disease worsened to a grade IV gastrointestinal form, and another episode of thrombotic microangiopathy developed secondary to cyclosporine. Despite the subsequent use of various immunosuppressant drugs, including daclizumab, infliximab, methotrexate, and corticosteroids, the patient died from severe graft-versus-host disease 62 days after bone marrow transplantation.

Discussion

Our patient's MPA exposure was characterized by a large, unexplained decline between days 7 and 13, although no changes in the mycophenolate mofetil dosage had been made. In addition, no specific medical conditions were identified to explain this decline in MPA exposure. The patient's renal function greatly improved during this time period from a creatinine clearance of 37 ml/minute on day 7 to 104 ml/minute on day 13. All drug therapy had been administered appropriately, confirmed by review of the patient's medical record.

The possible role of the three anti-infective agents introduced between days 7 and 13 was investigated. Several studies have reported that antibacterials administered by the oral route may reduce MPA exposure. In renal transplant recipients, concomitant administration of oral amoxicillin–clavulanic acid, metronidazole, or ciprofloxacin with mycophenolate mofetil was associated with significant decreases in MPA trough concentrations.^{8,9} In another study, the association of oral norfloxacin and metronidazole significantly reduced the AUC of MPA and MPAG by 33% and 41%, respectively.¹⁰ An increase in the MPA AUC was reported after bowel decontamination with mycostatin, tobramycin, and cefuroxime, especially 6–12 hours after dosing.¹¹

According to the manufacturer's data, trimethoprim-sulfamethoxazole does not significantly influence the AUC of MPA⁴ and, to our knowledge, no published study has reported a possible drug interaction between mycophenolate mofetil and caspofungin. Finally, of the three anti-infectives our patient was receiving, only ciprofloxacin has been shown to reduce MPA concentrations.^{8,9} However, ciprofloxacin was

given by the oral route in those studies, whereas the intravenous route was used in our patient.

Ciprofloxacin is a fluoroquinolone with both renal and nonrenal elimination pathways. Renal elimination accounts for two thirds of its total clearance.¹² Ciprofloxacin is also partially metabolized, and part of the administered dose is secreted in the gastrointestinal tract and eliminated in the feces. Actually, 18% of an intravenous dose of ciprofloxacin is eliminated through the intestine, and this proportion is increased to as much as 40% in patients with renal failure.^{13,14} It has been demonstrated that the transintestinal elimination of ciprofloxacin involves an active secretion mechanism.¹⁵

Because of this transluminal secretion, ciprofloxacin may interfere with MPA and MPAG enterohepatic cycling, even when administered intravenously. One study provided interesting results that support this hypothesis.¹⁶ In 16 subjects, a rapid and large decrease of the bacterial counts in stool samples was observed during 4 days of therapy with intravenous ciprofloxacin. In most subjects, fecal flora returned to their normal levels within 10 days after the last dose of ciprofloxacin. In addition, high concentrations of the drug were found in the feces, confirming intestinal elimination of the drug.

Thus, the available literature suggests that a drug interaction between mycophenolate mofetil and ciprofloxacin, both administered intravenously, is possible. Ciprofloxacin, which undergoes partial transintestinal elimination, may decrease the levels of intestinal flora responsible for the enterohepatic cycling of MPA and thus might alter MPA disposition in patients receiving the drug.

The Horn drug interaction probability scale¹⁷ indicated a probable interaction between intravenous mycophenolate mofetil and intravenous ciprofloxacin. In addition, the Pharmacovigilance Center of the University Hospitals of Lyon (Lyon, France) was consulted to evaluate the potential influence of the patient's drugs administered on her fatal outcome. The role of an interaction between mycophenolate mofetil and ciprofloxacin was found to be plausible.

As substantial and largely unexplained intraindividual variability of mycophenolate mofetil pharmacokinetics has been described,^{18,19} other factors contributing to the decrease in MPA concentrations cannot be excluded. Of note, after ciprofloxacin was discontinued on day 15,

MPA concentrations never achieved the level measured the day before ciprofloxacin was started on day 8, despite significant mycophenolate mofetil dosage increases. It is difficult to interpret the ciprofloxacin dechallenge because the patient had many complications and was administered several drugs to treat acute graft-versus-host disease after day 18. However, the sequence of the events during the patient's hospitalization and published data support the probable role of the drug interaction.

Conclusion

This case report suggests that intravenous ciprofloxacin may reduce plasma MPA concentrations during mycophenolate mofetil therapy. Additional clinical studies are necessary to confirm this drug interaction as well as the magnitude of its potential effect. The proposed mechanism for this interaction may also apply to other antibiotics. Clinicians should be aware that some antibacterials, even when administered intravenously, may reduce MPA exposure, and they should be used with caution in patients treated with mycophenolate mofetil. If antibacterials must be used—and ciprofloxacin in particular—therapeutic drug monitoring should be performed to guide dosage adjustments.

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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. The Tricontinental Mycophenolate Mofetil Renal Transplantation Study Group. A blinded, randomized clinical trial of mycophenolate mofetil for the prevention of acute rejection in cadaveric renal transplantation. *Transplantation* 1996;61(7):1029–37.
3. Basara N, Blau WI, Kiehl MG, et al. Mycophenolate mofetil for the prophylaxis of acute GVHD in HLA-mismatched bone marrow transplant patients. *Clin Transplant* 2000;14(2):121–6.
4. Bullingham RE, Nicholls AJ, Kamm BR. Clinical pharmacokinetics of mycophenolate mofetil. *Clin Pharmacokinet* 1998;34(6):429–55.
5. Baxter K, ed. *Stockley's drug interactions*, 8th ed. London: Pharmaceutical Press, 2008.
6. del Mar Fernandez De Gatta M, Santos-Buelga D, Dominguez-Gil A, Garcia MJ. Immunosuppressive therapy for paediatric transplant patients: pharmacokinetic considerations. *Clin Pharmacokinet* 2002;41(2):115–35.
7. van Gelder T, Le Meur Y, Shaw LM, et al. Therapeutic drug monitoring of mycophenolate mofetil in transplantation. *Ther Drug Monit* 2006;28(2):145–54.
8. Borrows R, Chusney G, James A, et al. Determinants of mycophenolic acid levels after renal transplantation. *Ther Drug Monit* 2005;27(4):442–50.
9. Borrows R, Chusney G, Loucaidou M, et al. The magnitude and time course of changes in mycophenolic acid 12-hour predose levels during antibiotic therapy in mycophenolate mofetil-based renal transplantation. *Ther Drug Monit* 2007;29(1):122–6.
10. Naderer OJ, Dupuis RE, Heinzen EL, Wiwattanawongsa K, Johnson MW, Smith PC. The influence of norfloxacin and metronidazole on the disposition of mycophenolate mofetil. *J Clin Pharmacol* 2005;45(2):219–26.
11. Schmidt LE, Rasmussen A, Norrelykke MR, Poulsen HE, Hansen BA. The effect of selective bowel decontamination on the pharmacokinetics of mycophenolate mofetil in liver transplant recipients. *Liver Transpl* 2001;7(8):739–42.
12. Karabalut N, Drusano GL. Pharmacokinetics of the quinolone antimicrobial agents. In: Wolson JS, ed. *Quinolone antimicrobial agents*, 2nd ed. Washington, DC: American Society for Microbiology, 1993:195–224.
13. Rohwedder R, Bergan T, Thorsteinsson SB, Scholl H. Transintestinal elimination of ciprofloxacin. *Chemotherapy* 1990;36(2):77–84.
14. Sorgel F, Naber KG, Jaehde U, Reiter A, Seelmann R, Sigl G. Gastrointestinal secretion of ciprofloxacin. Evaluation of the charcoal model for investigations in healthy volunteers. *Am J Med* 1989;87(suppl 5A):625–5.
15. Griffiths NM, Hirst BH, Simmons NL. Active secretion of the fluoroquinolone ciprofloxacin by human intestinal epithelial Caco-2 cell layers. *Br J Pharmacol* 1993;108(3):575–6.
16. Krueger WA, Ruckdeschel G, Unertl K. Influence of intravenously administered ciprofloxacin on aerobic intestinal microflora and fecal drug levels when administered simultaneously with sucralfate. *Antimicrob Agents Chemother* 1997;41(8):1725–30.
17. Horn JR, Hansten PD, Chan L-N. Proposal for a new tool to evaluate drug interaction cases. *Ann Pharmacother* 2007;41:674–80.
18. Fernandez A, Martins J, Villafrauela JJ, et al. Variability of mycophenolate mofetil trough levels in stable kidney transplant patients. *Transplant Proc* 2007;39(7):2185–6.
19. van Hest RM, Mathot RA, Pescovitz MD, Gordon R, Mamelok RD, van Gelder T. Explaining variability in mycophenolic acid exposure to optimize mycophenolate mofetil dosing: a population pharmacokinetic meta-analysis of mycophenolic acid in renal transplant recipients. *J Am Soc Nephrol* 2006;17(3):871–80.