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Severe Mycophenolate Intoxication in a Solid Organ Transplant Recipient—No Intervention Actually Needed

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INTRODUCTION

Following solid organ transplantation, mycophenolate mofetil (MMF) and enteric-coated mycophenolate sodium (EC-MPS) are immunosuppressants commonly used in combination with other immunosuppressive agents to prevent rejection. Additionally, they are also used in the treatment of some autoimmune diseases.[1] Both MMF and EC-MPS deliver the immunosuppressive substance mycophenolate (MPA). The effect and clinical pharmacokinetics and -dynamics of MPA have previously been covered in comprehensive reviews.[2,3] In short, MPA is a selective, reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH). IMPDH is the rate-limiting enzyme in the de novo synthesis of guanosine nucleotides. The potent cytostatic effect of IMPDH-inhibition by MPA is most pronounced in cells with a rapid turnover, such as activated T- and B lymphocytes, enterocytes, and bone marrow cells.

MPA therapy is generally safe in therapeutic doses. The most frequently reported side effects of MPA are dose-dependent gastrointestinal (GI) symptoms (diarrhea, abdominal cramps, nausea, vomiting). Reversible and dose-dependent bone marrow effects such as anemia, leukopenia, and thrombocytopenia are also common.

Following oral administration, MMF is rapidly absorbed and hydrolyzed to MPA, showing a high-absolute oral bioavailability of MPA.[4] EC-MPS is dissolved at pH 5.5 and hence, readily absorbed in the small intestine.[5] The systemic exposure of the 2 different drugs is similar when dosed in equimolar doses, with comparable peak concentrations, but EC-MPS generally shows a slower absorption rate.[6] This results in proportionate inhibitory effects on IMPDH and clinical efficacy.[6] MPA is metabolized by liver UDP-glucuronosyltransferases to a major 7-O-glucuronide metabolite (MPAG) and 2 minor metabolites, MPA-acyl-glucuronide and MPA-phenyl-glucoside (glucoside-MPA).[3] MPAG and glucoside-MPA are inactive while MPA-acyl-glucuronide is pharmacologically active.[4] MPA is subjected to enterohepatic recirculation (EHC); MPAG is excreted into bile, and ß-glucuronidases produced by gut bacteria hydrolyzes it to MPA, which is reabsorbed. Approximately 90% of the glucuronide metabolites are finally renally excreted.[3] Accumulation of MPAG in plasma, that is, in patients with reduced renal function, has been shown to reduce clearance of MPA.[3] The mean half-life of MPA presented in the literature is in the range of 18 ± 4 hours, but accurate determination is hampered by the described and well-known EHC.[3,4]

Supratherapeutic overdoses are not common. Ceschi et al[7] present a review of overdose cases found in the literature up until now, in addition to the one from Alex et al.[8] In transplant recipients, the highest MMF dose presented so far is 25 g, and the highest measured plasma concentrations of MPA is 44.1 mg/L (5 h after ingestion of 10 g MMF). Even therapeutic doses may, however, in rare circumstances, lead to high MPA trough values. Doi et al published findings from a patient with lupus nephritis who, after 1 week of MMF 1 g/day, developed seizures, leukopenia, thrombocytopenia, and renal failure. The symptoms were initially thought to be lupus related but turned out to be due to severe MPA intoxication with a measured concentration of 88 mg/L.[9] The patient experienced a complete recovery without any complications after MMF withdrawal.

In this case report, we present serial plasma MPA concentrations and discuss treatment alternatives and the clinical

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K.M., G.M., M.H.B., and A.V.R. were actively treating the patient. A.Å., G.M., K.M., M.H.B., and A.V.R. outlined the theoretically intervention for increased MPA elimination. S.B. measured MPA concentrations, and I.R. replicated the MPA measurements and also measured MPAG concentrations. A.Å. wrote the article, and all authors actively edited the article.

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outcome after an ingestion of 60 g MMF in a solid organ transplant recipient.

CASE DESCRIPTION

A young adult patient (170 cm, 70 kg), with >10 years of diabetes mellitus type 1, previously successfully transplanted with a solid organ presented at our emergency room following consumption of 60 g (120 tablets of 500 mg) MMF approximately 9 hours earlier.

The immunosuppressive therapy consisted of once daily prednisolone 5 mg and BID tacrolimus (Prograf®) 4 mg and MMF (CellCept®) 1 g. The graft was functioning perfectly with normal laboratory results. In the weeks and months before the event, the patient had stable tacrolimus and MPA concentrations with unchanged doses.

Following ingestion of 60 g MMF at 09:00 p.m. on day 0, the patient presented at the emergency room in the early morning of day 1 (06:00 a.m.) with severe GI pain. The patient had vomited at midnight and again at 04:00 and 05:50 a.m. without any visible tablet residues being observed in the vomit as reported by next of kin. At admission, the patient was alert but nervous and complaining of GI pain. There was a normal physical examination with blood pressure of 135/100 mm Hg, heart rate of 90 min^{-1}, and temperature of 35.5°C. The patient had a slight skin erythema and received acute treatment consisting of pantoprazole 80 mg IV, metoclopramide dihydrochloride 10 mg IV, and dexchlorpheniramine 10 mg IV. Maintenance medication at admittance, in addition to immunosuppressive drugs, consisted of once daily acetylsalicylic acid 75 mg, pantoprazole 40 mg, calcium with D-vitamin, and iron(II)-sulphate sustained release 100 mg as well as BID magnesium 350 mg and lamotrigine 25 mg. There was no suspicion of overdose of any other medication than MMF. A thorough tablet count was later performed verifying this.

The 9-hour plasma MPA concentration, obtained at presentation at the transplant center (day 1 at 06:00 a.m.), was 295 mg/L and showed a rapid decline as seen in Figure 1. The second and third samples were obtained on day 1 at 11:30 a.m. and 02:00 p.m. These MPA concentrations were, however, not available for the treating clinicians until 2 days later. The measured MPA concentrations were later also confirmed at an independent research laboratory, at which also MPAG concentrations were determined.

At noon day 1, ciprofloxacin 500 mg BID was initiated to reduce EHC by inhibiting conversion of MPAG to MPA by intestinal ß-glucuronidases.[10,11] Active charcoal was also considered but never administered. Further, cholestyramine 4 g thrice daily was initiated the same afternoon (to bind MPAG/MPA in the intestinal compartment of the EHC loop[4]) and tacrolimus was substituted by cyclosporine (200 mg BID) the same evening for cyclosporine's properties to inhibit MPAG transport into the bile.[12]

The nadir leukocyte count during the follow-up was 3.6×10^9 cells/L (Figure 1). Hemoglobin averaging 10 g/dL and platelets averaging 250×10^9/L were stable with virtually no changes from values taken 1 week before intoxication and the following month. In the evening on day 3, the first 3 MPA concentrations were available (C_9 = 295 mg/L, $C_{17.5}$ = 25.9 mg/L, C_{20} = 10.1 mg/L). This corresponds to a half-life of only 1.7 hours, and the pharmacokinetic evaluation indicated that the day 4 morning plasma concentrations would be close to zero. Because of the increased risk of acute rejection, the patient was started on 500 mg MMF in the evening of day 4, and both cholestyramine and ciprofloxacin were withdrawn (Figure 1). From the evening on day 5, normal MMF doses of 1 g BID was reinstalled, and cyclosporine was withdrawn, and tacrolimus restarted at 4 mg BID.

The patient was discharged from the hospital after 2 days and was followed closely at our out-patient clinic for several weeks. The MMF-induced GI symptoms slowly improved and eventually normalized during the first week. Four months later, no sequelae were detected, and the transplanted organ remained fully functioning.

Retrospective inspection of all measured MPA plasma concentrations shows that the half-life calculated from the first 3 concentrations, all above 10 mg/L, was significantly lower than the half-life of about 12 hours estimated from the other concentrations obtained before starting the patient on MMF again.

The patient has given informed consent that the case is presented.

DISCUSSION

The current case report presents a solid organ transplant recipient ingesting a supratherapeutic dose of 60 g MMF, 30 times the individual daily steady-state dose, resulting in a 9-hour plasma MPA concentration just below 300 mg/L. To our knowledge, no previous report has shown this high systemic exposure of MPA in a human before. Despite the extreme plasma concentrations, the patient did not suffer from any clinically relevant bone marrow depression; nadir leukocyte count was 3.6×10^9 cells/L. As expected from ingesting this number of tablets, the patient did, however, have significant GI pain for some days.

Literature regarding treatment of acute MPA intoxication is sparse. There are, however, several theoretical approaches that may reduce systemic MPA exposure. In general, in case of oral intoxications, activated charcoal is often recommended to inhibit absorption of the ingested substance. In this case, the time between ingestion and presentation at our clinic was too long (approximately 9 h) for any relevant effect, and it was never administered.[13] Our patient had also reported recurrent vomiting, which also is a contraindication. Theoretically, active charcoal could inhibit the EHC of MPA also hours after intoxication. There is, however, no published data supporting this intervention for MPA, and activated charcoal would most likely lead to reduced "detoxification" effects of the more specific inhibitors of MPA EHC, that is, ciprofloxacin and cholestyramine, which we introduced instead.

Oral ciprofloxacin reduces the activity of intestinal β-glucuronidase activity in gram-negative bacteria and hence reduce the conversion of MPAG to MPA, leading to less available MPA for recirculation. EHC-reabsorbed MPA accounts for up to 60% total systemic exposure of MPA.[4,14–16] The effect of ciprofloxacin on MPA elimination is thought to be moderate. Other antibiotics affecting the intestinal bacterial flora have also been described to have a similar minor to moderate effect on MPA elimination.[11] Case reports have shown a 35%–63% reduction in MPA AUC with, for example, amoxicillin clavulanate.[17]

The lipid-lowering drug cholestyramine is a bile acid sequestrant that binds anionic compounds like bile and MPA,

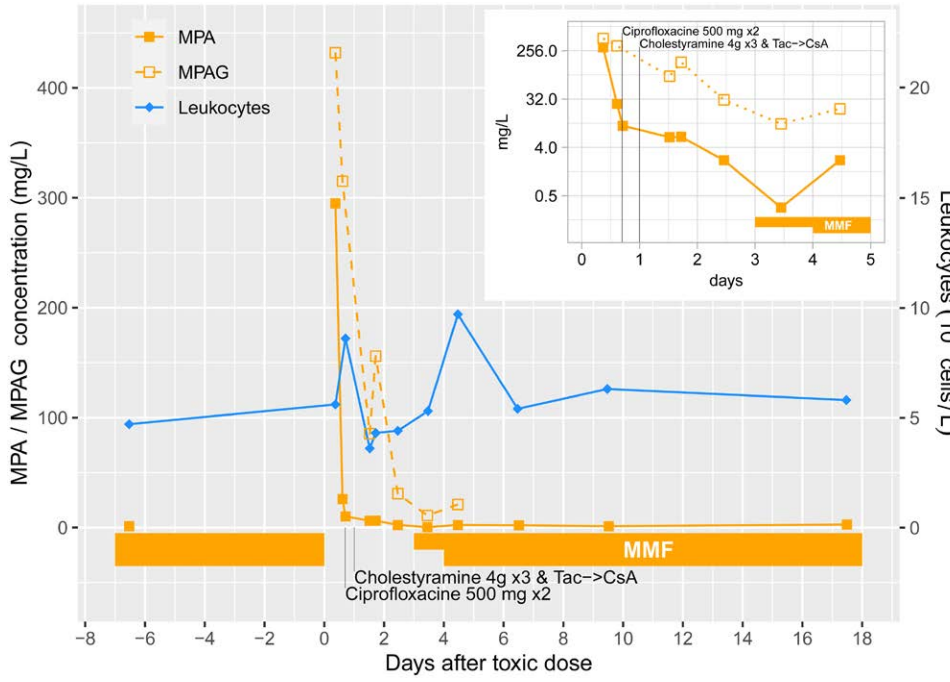

FIGURE 1. Plasma concentrations of MPA (solid orange), MPAG (dashed orange), and leukocytes (solid blue) is shown in relation to the day of ingestion of 60 g MMF in this solid organ–transplanted patient. MPA/MPAG concentrations are scaled on the left y axis, and leukocyte counts are on the right y axis. Doses of MMF are indicated as blocks under the graph and initiation of EHC reducing intervention is marked with vertical black line. The inserted graph in the upper right corner show the magnified early phase plotted semi logarithmically. MPA, mycophenolate; MPAG, 7-O-glucuronide metabolite; MMF, mycophenolate mofetil; EHC, enterohepatic recirculation

in the GI tract and prevent absorption.[18] Cholestyramine may decrease MPA exposure by 10%–60%.[4]

Switch from tacrolimus to cyclosporine was performed to augment MPA elimination by the cyclosporine-specific inhibition of ATP-binding cassette transporter, for example, MRP-2[19], mediated hepatic extraction of MPAG into bile. This leads to both reduced EHC of MPA, because less MPAG reaches the intestine, and it also increases the free MPA plasma concentration from the MPAG-induced displacement of MPA from plasma albumin binding sites and hence, may increase plasma clearance of MPA.[12,15,16]

The exact mechanism observed in our patient leading to the very efficient elimination of MPA while the plasma concentrations were high is not known. Ciprofloxacin was initiated 2 hours before the third MPA concentration was measured and the initiation of cholestyramine and switch to cyclosporine after the third measurement. Therefore, we claim that the potential inhibition of EHC by those interventions does not explain the efficient initial MPA elimination. The pharmacokinetic mechanism is hence unknown. Increased free MPA concentrations can maybe partly explain the observed rapid initial elimination, but we did unfortunately not have enough plasma to pursue this hypothesis by free concentration measurements.[14,15] It actually seems like the intervention to inhibit EHC in our patient, starting >15 hours after ingestion, had an overall limited effect on the MPA elimination.

The widespread use of MMF caries the risk of being deliberately misused by patients for self-harms and, if trough concentrations are not measured on a regular basis, may lead to intoxication even on recommended doses.[9] In severe acute overdose situations, expected events would be GI problems, leukopenia, anemia, and thrombocytopenia and if long-lasting, possible overimmunosuppression leading to increased susceptibility to infections. With timely withdrawal of additional MMF/EC-MPS doses, rapid initiation of EHC inhibiting therapy, it is possible to reduce and sometimes avoid excessive bone marrow depression, and other adverse outcomes may be minimized.

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