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EXPERT OPINION

Do we need to worry about mycophenolate overdose?

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Introduction: To discuss the significance of the recent observational case series from the Swiss Toxicological Information Centre (STIC). Mycophenolic acid (MPA) and its prodrug mycophenolate mofetil are immunosuppressive agents that are frequently prescribed in renal transplant recipients, and their safety profiles must be established.

Areas covered: This case series and systemic literature analysis consists of 15 cases of MPA overdose from the STIC and a systemic analysis of the literature over the past 18 years. This study focuses on acute overdosing, the effects of which are presumably mild. In contrast, the effects of long-term overdosing may be much more severe. Substantial underreporting is likely. The pharmacokinetic monitoring of MPA is rarely performed, which is both striking and does not coincide with findings in academic literature. The scant data on pharmacokinetic monitoring presented demonstrated that MPA has a short terminal half-life, which suggests that decontamination and activated charcoal treatment in acute overdose may not be necessary.

Expert opinion: The case series and systematic literature analysis of acute mycophenolate overdose represent an important contribution toward increasing the safety of MPA therapy.

Keywords: human toxicity, mycophenolate mofetil, mycophenolate sodium, mycophenolic acid, overdose

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Mycophenolate mofetil (MMF), a prodrug of mycophenolic acid (MPA), is the most widely prescribed immunosuppressive agent for preventing rejection following kidney transplantation in many countries [1]. Up to 80% of transplant recipients undergo long-term therapy using some form of MPA.

Both MMF and enteric-coated mycophenolate sodium (EC-MPS) therapy are associated with frequent adverse drug reactions (≥ 1% of patients) that include diarrhea, nausea, vomiting, infections, leukopenia and/or anemia. Other adverse events include fatigue, headache and/or cough. Less frequent adverse effects (0.1 – 1% of patients) include esophagitis, gastritis, gastrointestinal tract hemorrhage and/or invasive cytomegalovirus (CMV) infection. Intravenous (i.v.) administration of MMF is commonly associated with thrombophlebitis and thrombosis. The US FDA recently issued an alert concerning the increased risk of developing opportunistic infections in patients taking MMF and MPA, particularly new or reactivated viral infections, including shingles, other herpes infections, CMV, and BK virus-associated nephropathy. Moreover, the FDA is currently investigating 17 cases of progressive multifocal leukoencephalopathy, a rare and usually fatal neurological disease, which developed in patients taking the drug [2].

Literature describing the acute toxicity of MPA is sparse. MPA can be administered either intravenously or orally, with the latter being available in various formulations such as the prodrug MMF or as mycophenolate sodium. In fact, although there is a substantial amount of evidence supporting considerable

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interpatient and intrapatient variability in responses to the drug [3,4]; manufacturer guidelines endorse fixed dosing.

In this edition of *Expert Opinion on Drug Safety*, we are delighted to see a systematic analysis of all reported acute overdoses from the Swiss Toxicological Information Center (STIC) as well as a literature review of MPA overdose cases over an 18-year period [5]. Most adult cases occurred as a result of attempted suicide, whereas children were subject to accidental poisoning in the home. The authors should be congratulated for this work as it includes all available data, including the sparsely available pharmacokinetic monitoring data suggesting that MPA has a short terminal half-life (between 2.6 and 7.4 h). Although most of the symptoms were mild and included abdominal pain, vomiting, headache, dizziness and/or a drop in blood pressure, they worsened in a dose-dependent manner. The authors clearly discuss limitations and emphasize the issue of underreporting.

MPA is available as i.v. MMF, as oral MMF and now as non-innovator generic formulations, such as the Teva formulation [6]. It is also available as EC-MPS. Most of the reports in the STIC database involve MMF.

One of the striking findings this manuscript highlights is the paucity of data surrounding the monitoring of MPA blood levels in these patients. The clinical utility of therapeutic drug monitoring of MPA is still controversial. However, the pharmacokinetics of MMF is highly variable [3,4]. This can be attributed to drug–drug interactions between MMF and both of the calcineurin inhibitors (cyclosporine or tacrolimus [7]) and with steroids [8]. Cyclosporine augments MPA clearance, whereas tacrolimus may reduce it. Ontogeny of drug disposition [9] and variable degrees of renal impairment [10] also significantly contribute to the substantial interpatient variability, which can reach 100%. There is good evidence that an AUC > 30 mg × h/l is required to prevent rejection [11]. Recent consensus guidelines have, therefore, increased the dosing recommendation depending on the concomitant calcineurin inhibitor being administered to avoid underdosing [3,4]. The upper therapeutic window of MPA is not as well defined, and limited sampling strategies are necessary to determine AUC as there is poor correlation between the trough level and the AUC [12]. It should be pointed out that these limited sampling strategies only apply for the oral MMF. The pharmacokinetics of MMF and EC-MPS are very different [13]. Limited sampling strategies for EC-MPS vary in estimating AUC [14,15].

Other advantages of therapeutic drug monitoring of MPA include safer therapy in patients who are treated with protocols that explore calcineurin inhibitor minimization, withdrawal or even complete avoidance. This also applies to steroid withdrawal or steroid avoidance regimens. These patients might, therefore, benefit from therapeutic drug monitoring of MPA, especially when unexplained side effects occur. MPA pharmacokinetic monitoring may also help in identifying nonadherence in the adolescent population.

A recent crossover study comparing equivalent exposure of MMF with two different formulations of tacrolimus suggests a high prevalence of both underdosing and overdosing [16]. Despite this evidence, MMF and EC-MPS therapies are not usually subject to pharmacokinetic monitoring, as is clearly indicated by the authors of the study addressed in this editorial. Pharmacokinetic monitoring is widely available, either through immunological assays such as the EMIT 2000 MPA assay from Siemens Healthcare, Inc., through the high-performance liquid chromatography reference method or through mass spectrometry – the most cost-effective method.

The substantial prevalence of underreporting should be emphasized, since it may suggest that side effects are usually mild. MPA is commonly administered concomitantly with multiple agents, and it is these other medications that may be causing adverse events. As MMF is the single-most commonly prescribed immunosuppressant for renal transplantation in the pediatric population in North America [17], it is critically important that physicians be mindful of overdosing. This is especially crucial in children who require life-long immunosuppression since they are at a substantially higher risk of malignancies such as post-transplant lymphoproliferative disease and other forms of cancer [18]. In the article, patients were only subject to overdosing for a maximum of 5 days. This may explain why there was only one case of myelosuppression. Given the relationship between drug exposure and myelosuppression, and the prevalence of myelosuppression in patients who have undergone transplantation, there are most likely more cases of overdosing that go unnoticed [3]. We were able to identify the extent of overdosing in our own case report (included in the study) because of pharmacokinetic monitoring [19].

In view of the benefits of pharmacokinetic monitoring of MPA for MMF or EC-MPS therapy, which was omitted in most of the cases reported by the manuscript, the infrequent use of this clinical tool is surprising. Although there is good evidence showing that a minimum AUC of 30 mg × h/l prevents rejection, there is a complete lack of good data defining the upper limit of the therapeutic window, especially as the resurgence of viral illnesses increases with increasing exposure to the agent. We would like to draw attention to the possibility that many patients are being treated with doses surpassing the therapeutic level for a prolonged period of time, and that this goes unnoticed because of a lack of pharmacokinetic monitoring. Chronic overdosing may have far more serious effects than the acute short-term overdosing as described by the authors. Further, as renal function often declines following renal transplantation and as retransplantation is often necessary, monitoring the accumulation of the main glucuronide metabolite, MPA-G, may become increasingly important with worsening renal function. MPA-G is formed in the liver, excreted in the bile and subjected to enterohepatic recirculation and renal excretion [10].

Conclusion

We would like to congratulate the authors of the recent manuscript in *Expert Opinion on Drug Safety* once more for their important work. We agree that more data are needed to determine the effects of decontamination and activated charcoal treatment. The relatively short half-life of MPA suggests that charcoal treatment may not be necessary in patients with reasonably good kidney function. Cognizance of the effects of and consequent avoidance of acute and chronic overdosing is of particular importance in young patients requiring life-long immunosuppression. Pharmacokinetic monitoring of MPA in patients receiving MMF or EC-MPS therapy should be encouraged, and the upper limit of the therapeutic window should be more clearly defined. This may be especially true in view of the recent FDA warning concerning new or reactivated viral infections which can be associated with a fatal neurological disease. The manuscript described in this editorial constitutes an important step toward improved drug safety of MMF and EC-MPS therapies.

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Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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