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Proton Pump Inhibitors and Their Interaction with the Immunosuppressant Mycophenolate

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Abstract

This review aims to provide an overview of the literature dealing with the interactions between proton pump inhibitors and the antiproliferative immunosuppressant mycophenolate in solid organ transplantation. Currently, two mycophenolate compounds are available: mycophenolate mofetil and enteric-coated mycophenolate sodium. So far, only a few studies have investigated the impact of proton pump inhibitors on mycophenolate mofetil pharmacokinetics. To date, there are no studies regarding the interactions between enteric-coated mycophenolate sodium and proton pump inhibitors.

Following oral administration, mycophenolate mofetil is extensively hydrolyzed to its active constituent mycophenolic acid, which acts as a potent and specific inhibitor of T- and B-cell proliferation by reversibly inhibiting inosine monophosphate dehydrogenase. Mycophenolic acid reaches maximum plasma concentration within one hour in most transplant recipients. A second peak is seen in the plasma mycophenolic acid profile between four and 12 hours after oral administration induced by enterohepatic recirculation.

All studies evaluated that mycophenolic acid plasma concentration in the first hours after dosing were significantly reduced by co-medication with proton pump inhibitors, e.g. pantoprazole or lansoprazole, but not the mycophenolic acid plasma concentration 3-10 hours thereafter. The data suggest that the first pass of mycophenolic acid was markedly reduced by proton pump inhibitors. However the reabsorption of mycophenolic acid through enterohepatic recirculation was not influenced.

Causal for the proton pump inhibitor-induced reduction of mycophenolic acid plasma concentration seems to be the aqueous solubility profile of mycophenolate mofetil, which shows greater solubility at pH < 5 and poor solubility at pH > 6. More precisely, the mofetil part of the drug formulation is separated from the mycophenolic acid part in a pH-dependent mechanism. The gastric acid secretion inhibitory effect of proton pump inhibitors with a gastric pH > 4.5 might decrease the elution and hydrolysis of mycophenolate mofetil, subsequently diminishing the plasma concentration of mycophenolic acid.

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Because gastrointestinal side effects are common in patients after solid organ transplantation, and a considerable proportion of transplant recipients receive proton pump inhibitors, this is an important drug interaction between a widely used immunosuppressive agent and a class of drugs frequently used in transplant patients. This interaction results in a decreased mycophenolate mofetil drug exposure, which may lead to patients having a higher risk for acute rejection and chronic transplant failure. We have to take into account that patients with proton pump inhibitor co-medication need higher mycophenolate mofetil dosages to reach equal immunosuppressive effects. **(Trends in Transplant. 2010;4:11-8)**

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Key words

Mycophenolic acid. Mycophenolate mofetil. Pantoprazole. Organ transplantation. Pharmacokinetics. Drug interaction.

Introduction

Mycophenolate was developed in the 1960s as a potential antibiotic, antineoplastic, and antipsoriatic drug. Because of its immunosuppressive properties, mycophenolate has gained widespread acceptance as the antiproliferative immunosuppressant of choice and has proven to be effective in preventing allograft rejection after organ transplantation[1-3]. Currently, two mycophenolate compounds are available: mycophenolate mofetil (MMF) and enteric-coated mycophenolate sodium (EC-MPS). Following oral administration, both are rapidly metabolized to the active constituent mycophenolic acid (MPA), which acts as a potent and specific inhibitor of T- and B-cell proliferation by reversibly inhibiting inosine monophosphate dehydrogenase (IMPDH), the key enzyme of the *de novo* purine synthesis in activated lymphocytes[3]. Mycophenolate mofetil is used in almost 76% of patients after heart and lung transplantation, in 79% after kidney transplantation, and in 48% after liver transplantation[3-5].

Several drug interactions with MPA have been reported, including cyclosporine, corticosteroids, rifampicin, norfloxacin, metronidazole, antivirals like acyclovir, phosphate binder like sevelamer, and metal ions like calcium ions[3,6-8]. So far, only a few studies have investigated the impact of proton pump inhibitors (PPI) on MPA pharmacokinetics[9-11]. To date, there are no studies regarding the interactions between EC-MPS and PPI.

Absorption, distribution, metabolism, and excretion of mycophenolate mofetil

Following oral administration, MMF and EC-MPS are extensively hydrolyzed to MPA by esterases in the stomach, small intestine, blood, liver, and tissues[12]. Mycophenolic acid reaches maximum plasma concentration (C_{max}) within one hour in most transplant recipients and is extensively bound to albumin, with an average protein binding of 97.5% in patients with normal kidney and liver function[13]. Only free (unbound) MPA is capable of inhibiting IMPDH.

Mycophenolic acid is mainly inactivated in the liver via first-pass glucuronidation. The resulting phenolic glucuronide of MPA (MPAG) is not pharmacologically active and a significant portion is secreted into the bile and recycled to the liver via enterohepatic recirculation. Its clearance is highly dependent on protein

binding, and a second peak is seen in the plasma MPA profile between 4-12 hours after oral administration induced by enterohepatic recirculation. It has been estimated that enterohepatic recycling contributes approximately 40% to MPA exposure[3].

Over 90% of the administered MMF dose is excreted in the urine, mostly as MPAG, while 6% is recovered in the feces[14-16]. Significant renal dysfunction, hypoalbuminemia, or liver impairment can alter MPA and MPAG serum albumin binding, changing the fraction of free MPA available[3].

Gastrointestinal side effects in patients after organ transplantation

Gastrointestinal side effects are common in patients after solid organ transplantation, and a considerable proportion of transplant recipients receive PPI. The Mitos Study Group, including 1,788 heart transplant recipients, reported that almost 40% of all patients suffered from gastrointestinal complications, of which 86.3% were treated with gastrointestinal-protective co-medication[17].

Effectiveness of proton pump inhibitors

Proton pump inhibitors have emerged as the most effective class of drugs for the treatment of gastroesophageal reflux disease, as well as several other acid-related disorders[18]. Proton pump inhibitors that inhibit gastric acid secretion through binding with H^+/K^+-adenosine triphosphatase (ATPase) in gastric parietal cells can modify the intragastric release of other drugs by elevating the pH value. For pantoprazole, lansoprazole, and omeprazole, this binding is irreversible, while rabeprazole exhibits reversible binding to the proton pump. Thereby, they can influence drug absorption and metabolism by interacting with adenosine triphosphate-dependent P-glycoprotein or with the cytochrome P450 (CYP) enzyme system[19]. The P450 CYP enzyme system seems to be important for the interactions with MMF[9,20]. In this review, we focus on the interaction with the PPI pantoprazole 40 mg and MMF. Previous studies have shown that pantoprazole 40 mg has a stable $AUC_{0\text{-}24h}$ of 9.93 µmol/h/l, which correlates with the degree of acid suppression. Moreover, the bioavailability of 77% after the first dose does not change after repeated dosing[21,22].

Discussion

Drug interactions between PPI and tacrolimus have been reported. However, little is known about the interaction between PPI and MMF[9,20,23].

For the first time in 1996, Bullingham, et al. performed a study in patients with rheumatoid arthritis given a single dose of MMF (2,000 mg)[7]. They evaluated that feeding decreased the maximum plasma concentration (C_{max}) of MPA and increased the time to reach C_{max} (t_{max}), but did not affect MPA area under the curve (AUC) consistent with delay in gastric emptying in the fed state. With antacid containing aluminum and magnesium hydroxides (Maalox®) MPA AUC was lowered about 15% and C_{max} was decreased by 37%, but t_{max} was not affected. Bullingham, et al. supposed that these effects are simply explained by reduced absorption in both the initial phase and during the enterohepatic circulation. They suggested that the drug interaction was due to chelation rather than interference with metabolism or recycling. Increase in gastric pH seemed an alternative, but this should not affect re-circulatory absorption. They expected that this lowering in MPA AUC would not have any clinically major effect[7].

Eleven years later, in 2007, Miura, et al. published the second article describing a

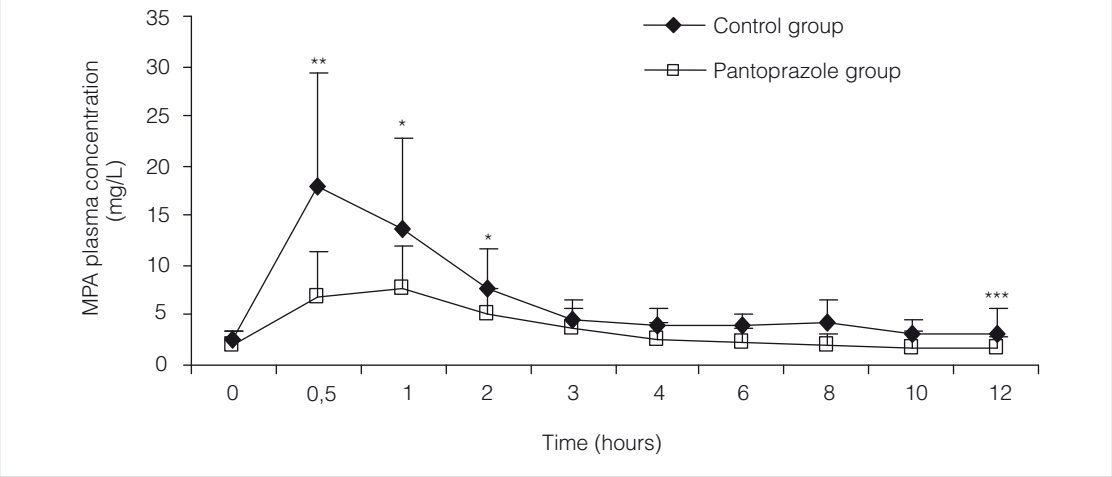

Figure 1. *Mycophenolic acid (MPA) blood concentration-time profile in controls (n = 12) and patients administered 40 mg of pantoprazole (n = 21). Values are reported as mean ± standard deviation or percent. Each parameter was statistically compared with the control group. Significant differences are indicated by asterisks (*p < 0.05, **p < 0.001, ***p < 0.0001 vs. control). In a subgroup of patients (6 patients in the control group and 15 patients in the proton pump inhibitor [PPI] group) MPA concentrations between 3 and 12 hours were also measured[10].*

negative influence of PPI co-medication on MPA AUC in renal transplant recipients[9]. The MPA plasma concentrations were significantly decreased by 30 mg lansoprazole but not by 10 mg rabeprazole, especially in recipients having the CYP 2C19 or the multidrug resistance-1 C3435T polymorphisms. Patients with these polymorphisms had higher plasma concentrations of lansoprazole and therefore a greater inhibition in gastric acid secretion. They hypothesized that the greater gastric acid secretion-inhibitory effect of lansoprazole might decrease the elution and hydrolysis of MMF and consequently diminish the plasma concentration of MPA. Lansoprazole reduced only the first pass of MPA, but the reabsorption of MPA through enterohepatic circulation was not reduced[9].

We carefully evaluated our therapy regime in heart transplant patients and we stopped PPI therapy in patients without any anamnesis of gastrointestinal side effects, and observed that patients after PPI withdrawal had higher MPA levels with necessity of MMF dose reduction. Based on this observation, we retrospectively analyzed MPA plasma concentrations (C_0, $C_{0.5}$, C_1, C_2 hours) in 21 patients with pantoprazole 40 mg daily in the PPI group and 12 patients without pantoprazole in the control group. In a subgroup, MPA $C_{4\text{-}12h}$ were measured to evaluate full MPA AUC measurements. The MPA concentrations were obtained by high-performance liquid chromatography[10,24,25].

Thirty minutes, one, and two hours after the morning dose of MMF, the MPA plasma concentrations were significantly lower in the PPI group than in the control group. At the next five time points, MPA plasma concentrations did not differ significantly in the subgroup. Twelve hours after dosing, the PPI group revealed a significantly lower MPA level (1.6 ± 1.3 mg/l; $p < 0.05$) than the control group (3.3 ± 2.4 mg/l; Fig. 1). As expected, the PPI group revealed a significantly lower total AUC, with 45% reduction compared to the control group. The C_{max} was 4.5-fold lower in the PPI group than in the control group. However, t_{max} showed no difference in both groups.

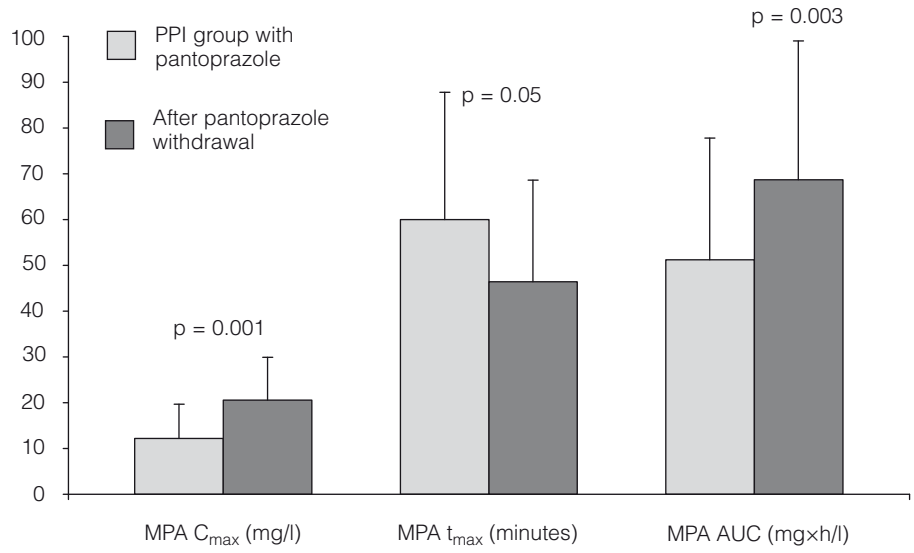

Figure 2. *Prospective analysis in patients receiving 40 mg of pantoprazole and 1 month after pantoprazole withdrawal (n = 22). Values are reported as mean ± standard deviation. Significant differences are indicated by symbol (p vs. control). Maximal mycophenolic acid (MPA) plasma concentration (C_{max}), time to reach C_{max} (t_{max}) and total MPA-AUC are demonstrated[11]. PPI: proton pump inhibitor; AUC: area under the curve.*

The MPA plasma concentration 0.5, one, and two hours after dosing was significantly reduced by co-medication with pantoprazole, but not the MPA plasma concentration 3-10 hours after dosing. The data suggest that the first pass of MPA was markedly reduced by pantoprazole. However, the reabsorption of MPA through enterohepatic recirculation was not influenced.

Based on this these observations, we started a prospective study in heart transplant recipients receiving MMF and tacrolimus in a standardized setting[11]. Mycophenolic acid plasma concentrations (C_0, $C_{0.5}$, C_1, C_2 hours) were obtained in 22 patients with pantoprazole 40 mg daily and mycophenolate mofetil 1,000 mg twice daily. Measurements were repeated one month after pantoprazole withdrawal. A four-point limited-sampling strategy was applied to calculate MPA AUC[25].

This prospective study showed that the usual therapeutic dose of pantoprazole had a significant influence on C_{max} (1.9-fold higher after PPI withdrawal) and the total MPA AUC could be increased by 34% after PPI withdrawal (Fig. 2). The MPA plasma concentrations 0.5 and one hour after dosing were significantly reduced by co-medication with pantoprazole 40 mg, but not the MPA plasma concentration two hours after dosing.

Bullingham, et al. suggested that the drug interaction with PPI was due to chelation of MMF rather than interference with metabolism or recycling[7]. However, Lidgate, et al. demonstrated that the aqueous solubility profile of MMF shows greater solubility at pH < 5 and poor solubility at pH > 6[8]. The mofetil part of the drug formulation is separated from the MPA part in a pH-dependent mechanism[9,26]. The intragastric pH elevation under PPI treatment is a long-lasting effect due to the irreversible inhibition of the gastric proton pump. Somberg, et al. showed that pantoprazole provides a mean gastric pH > 4.5 in intensive

care unit patients in 24 hours[27]. The gastric acid secretion-inhibitory effect of PPI might decrease the elution and hydrolysis of MMF, subsequently diminishing the plasma concentration of MPA. Tomiyama, et al. could show in rats that two hours after administration of PPI, K^+-ATPase activity is inhibited by about 40% and the acid secretory rate by about 94%[28]. Therefore, within two hours after dosing, pantoprazole almost completely inhibited the gastric acid secretion and subsequently the absorption of the MPA with reduced plasma concentrations in the first hour. Furthermore, the peak of the MPA time-concentration curve is reached 0.5 or one hour after intake in the majority of patients throughout the literature[13,29]. This peak represents the main contributor to total MPA AUC. The IMPDH activity and therefore the immunosuppressive effect of MMF reveal a very good correlation with the total AUC, as reported[30]. When the main contributors to the total AUC ($C_{0,5h}$ and C_{1h}) are reduced due to PPI, this should result in a significant decrease in the immunosuppressive effect. The C_{2h} has less impact on total AUC and therefore on IMPDH activity. An additional interesting question is whether the mechanism of altered MMF kinetics under PPI treatment can be modulated through the use of histamine H2 blockers. In three patients treated with H2 blockers (ranitidine 300 mg/day) we found the same decreased MPA plasma concentration at $C_{0.5h}$ and C_{1h} and MPA C_{max}. However, we have to confirm this preliminary result with a larger number of patients. Until now, there are no other data regarding this drug interaction.

In our prospective study, but not in the retrospective study, t_{max} was significantly longer in patients with PPI than without PPI medication. Naesens, et al.[31] demonstrated that a delayed gastric emptying rate in renal patients was associated with a significantly longer MPA t_{max} and a significant decrease in MPA C_{max}. Therefore, one might assume that our data with reduced MPA C_{max} and longer t_{max} under PPI are possibly also induced by a delayed gastric emptying rate. A counterargument to this assumption would be that the C_{2h} values do not reveal a significant difference after PPI withdrawal. Further investigations are necessary to prove this.

Mycophenolate mofetil kinetics are influenced by many factors such as renal function, liver function, and co-medications such as steroids[5,29,32]. Renal and liver function in our patients showed normal values and did not differ between the two measurement points. Half of the patients were on a maintenance dose of low-dose steroids (0.1 mg/kg prednisolone) and had the same prednisolone dose at both time points. Comparing both groups (with and without steroids), there is no difference in MPA plasma concentrations and MPA C_{max}. Therefore, we presume that steroids did not influence our results. Cattaneo, et al.[5] showed that high-dose steroids in kidney transplantation induce the hepatic glucuronyl transferase (GT) expression, enhancing the activity of uridine diphosphate GT, the enzyme responsible for MPA metabolism. Therefore, high-dose steroids are another factor responsible for decreasing MPA AUC. Cattaneo, et al. performed AUC measurements the first month with high-dose steroids and six months after transplantation with low-dose steroids. However, our patients did not receive high-dose steroids. In addition, the effects of low-dose steroids on MMF kinetics did not differ between each patient. We therefore feel that the effects of low-dose steroids in this study are marginal and not an explanation for the differences between the groups.

Of central clinical interest in transplanted patients are the rates of acute rejection episodes and the development of chronic transplant failure. The study by Galiwango, et al. showed that MMF dose reduction, e.g. for gastrointestinal intolerance, was associated with a significantly increased rate of sustained rejection in heart transplant patients[33]. Kaczmarek, et al. and Meiser, et al. evaluated that

lower therapeutic drug concentrations of MMF correlate not only with increased rates of acute rejection episodes, but also with development of transplant vasculopathy in heart transplant recipients[34,35]. However, in our study, acute rejection episodes and transplant vasculopathy occurred in seven patients during their PPI treatment with lower MPA plasma concentrations. The observation period after the PPI withdrawal was only one month, therefore to fully examine this phenomenon a more extensive study including a larger number of patients and a longer follow-up is necessary. However, as previously mentioned, in our retrospective study with 21 patients a trend for more acute rejection episodes and transplant vasculopathy was found in the PPI group[10]. The follow-up in both groups (control group 34.5 ± 42 months and PPI group 21 ± 32 months) was not significantly different. Therefore, it is of central interest to further examine the mechanisms of PPI-induced lower MPA levels and to design a strategy for using PPI and MMF to preserve MPA plasma concentrations to increase safety in terms of freedom from acute rejection episodes and transplant vasculopathy.

Not only increased rates of acute rejection episodes and transplant vasculopathy, but also cost effectiveness are important issues in posttransplant therapy. One year of pantoprazole therapy (40 mg/d) costs € 470 when prescribed in Germany. Regarding the necessity of lower MMF doses for the patients after PPI withdrawal, average MMF costs of more than € 2,000 per year can be saved in patients who are no longer on PPI. Increased laboratory costs for therapeutic drug monitoring are thereby "reimbursed"[10].

Several clinical trials have documented an increase in MPA AUC under fixed-dose regimens during the first months after transplantation and this is widely accepted[36,37]. Therefore, some transplant centers react to this phenomenon by increasing the initial MMF dose. Considering that we achieved an average increase in MPA AUC of 34% after withdrawal of the PPI co-medication, the widely accepted concept of increasing MPA AUC over time might have to be looked at from a different angle. The PPI might have contributed to this phenomenon in previous investigations because they were withdrawn in the previous study populations over time, resulting in increasing MPA AUC[36,37].

We conclude that the usual therapeutic dose of pantoprazole (40 mg) has a significant inhibitory influence on MPA C_{max}, the total MPA AUC, and t_{max}. The MPA plasma concentrations 0.5 and one hour after dosing were significantly reduced by co-medication with pantoprazole. These are the few studies to document an important drug interaction between a widely used immunosuppressive agent and a class of drugs frequently used in transplant patients. This interaction results in a decreased MMF drug exposure, which may lead to patients having a higher risk for acute rejection and chronic transplant failure. In addition, transplant physicians have to take into account that patients with PPI co-medication need higher MMF dosages to reach equal immunosuppressive effects.

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