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Different Routes of Proton Pumps Inhibitors Co-Administration have Significant Impact on Mycophenolate Acid (MPA) Serum Levels in Heart Transplant Recipients

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Antiproliferative drugs including mycophenolate mofetil (MMF) are widely accepted part of an immunosuppressive therapy following heart transplantation. Proton pump inhibitors (PPIs) are routinely administered after cardiac surgery procedures including transplantation. They may also have impact on mycophenolate acid (MPA) serum levels.

Material/Methods: There were 30 consecutive patients (28 male and 2 female patients) with a mean age of 45±12 years who were enrolled into this study. MPA serum levels were studied; PPIs were intravenously and orally administered.

Results: The mean MPA plasma concentrations were statistically significantly different between parenteral group (2.3±1.4 umg/mL) and oral group (3.1±2.2 umg/mL) (P=0.036) before immunosuppressive drug administration (C-0 time). There was a statistically significant different drug concentration at the second sample time C-30 (30 minutes after drug intake) reaching 4.4±2.8 umg/mL versus 7.9±4.5 umg/mL (P<0.05). There was no statistically significant difference in MPA plasma concentration at the 3rd measurement C-120 (10.7±4,9 umg/mL versus 9.8±5 umg/mL) (P=0.3). There is a statistically significant different MMF serum concentration after oral intake and intravenous infusion at C-30 (2.4±1.4 in group 1 versus 3.3±2.5 in group 2, P<0.036) but not at C-120 time interval (8.9±5.0 versus 9.8±5.3 in group 1 and 2, respectively) (P=0.3).

Conclusions: Our study was the first study that compared different routes of PPI co-administration on MPA serum levels in a transplant recipient group. Our study revealed that the parenteral route of administration only slowed not decreased MPA pharmacokinetics within 120 minutes following MMF administration.

MeSH Keywords: **Drug Interactions • Heart Transplantation • Mycophenolic Acid • Proton Pump Inhibitors**

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Background

Antiproliferative drugs including mycophenolate mofetil are widely accepted part of an immunosuppressive therapy following heart transplantation [1,2]. Although the most common regimen is based on calcineurin inhibitors, mycophenolic acid (MPA) is a commonly added drug to reduce the risk for rejection episodes and allograft vasculopathy [3]. It is a reversible inhibitor of guanine nucleotides synthesis key enzyme called inosine monophosphate dehydrogenase (IMPDH), blocking cytotoxic and B lymphocyte proliferation. Among anti-proliferation drugs, mycophenolate mofetil (MMF) is chosen in a majority of immunosuppressive regimens worldwide nowadays [4]. MMF is a prodrug that is transformed into MPA in the stomach at low pH.

Proton pump inhibitors (PPIs) are routinely administered after cardiac surgery procedures including transplantations. They lower gastric acid secretion and increase stomach pH to prevent stress ulcerations. PPI prophylaxis usually includes parenteral administration for at least 3 postoperative days followed by oral prescription. PPIs modify drug release by increasing the gastric pH values, so they interfere with the hydrolysis of MMF to MPA.

The aim of this study was to compare the bioavailability (defined by area under the curve [AUC] 0-2) of MPA after MMF intake based on 450 blood samples obtained during co-administration of oral and parenteral forms of PPIs.

Material and Methods

Material

There were 30 consecutive patients (28 male and 2 female patients) with a mean age of 45±12 years who were enrolled in this study. There were 21 patients (70%) and 9 patients (30%) diagnosed with dilated and ischemic cardiomyopathy, respectively.

All patients were transplanted using the Lower-Shumway (biatrial) technique. Mean donor age was 35±11 years. Preservation methods included cold crystalloid cardioplegia (Custadiol HTK solution) and topical cooling. Mean cold ischemia time was 223±18 minutes.

Triple-drug immunosuppressive therapy including tacrolimus, MMF, and prednisolone were used in all patients. There were 450 blood samples examined during the study including 180 blood samples taken during parenteral co-administration of PPI and MMF and 270 during oral intake. Surveillance endomyocardial biopsies were scheduled weekly within the first month following surgery.

Methods

All patients enrolled into the study received standard immunosuppressive therapy including tacrolimus, steroids, and MMF. The MMF was administered in fixed dose of 3000 mg per day during the study period.

MMF was administered orally at 8: 00 to 8: 30 A.M. All patients received pantoprazole 40 mg at 6: 00 A.M., given parenterally for 3 days and continued orally for the proceeding 14 days during the study. All patients fasted till 10: 00 A.M. Standardized low fat, low sodium meals were provided. All anti-hypertensive drugs were administered after 1.5 hours following mycophenolate intake.

Blood samples (7 mL) were collected 30 minutes prior to MMF administration (C-0) and 30 minutes (C-30) and 120 minutes (C-120) thereafter. Clinical laboratory tests and tacrolimus troughs were analyzed in our hospital laboratory. Mycophenolate acid (MPA) post-dose plasma concentrations were obtained by high-performed liquid chromatography in patients on pantoprazole 40 mg per day.

The area under the curve (AUC) was calculated according to formula most commonly used in clinical practice, limited sampling, under the curve area: AUC=(7.75+(6.49×C-0)+(0.76×C-30)+(2.43×C-120) [5].

Assay methodology

The methodology of MPA was based on a homogeneous particle enhanced turbidimetric inhibition immunoassay named Petinia technique. The Petinia technique is based on rate of aggregation between MPA samples and synthetic particle-mycophenolic acid conjugate. Both particles compete for monoclonal MPA specific antibody. The rate of aggregation is measured using biochromatic turbidimetric readings at 340 nm and 700 nm.

Calculated parameters for MPA were based on simplified AUC composed of the samples: 30 minutes before MMF intake and 30 and 120 minutes thereafter.

Statistical analysis

Nonparamentric test were used. The relationship between analyzed parameters was assessed by U-Mann Whitney and Spearman rang tests. Tests were considered significant at $P<0.05$. The analysis was performed with the use of statistical package Statistica (StatSoft Inc.)

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Results

There were 30 patients enrolled in the study who underwent heart transplantation at the Cardiac Surgery and Transplantology Department in Poznan, Poland. There were 450 blood samples examined during the study, including 180 blood samples taken during parenteral co-administration of PPI and MMF and 270 more during oral intake. They were treated with standard triple immunosuppressive therapy including calcineurin inhibitor (tacrolimus), anti-lympho-proliferative drugs drug (MMF), and steroids. During the first 5 postoperative days, PPIs were administered parenterally in daily dose of 40 mg. The PPIs were continued orally thereafter.

The was no statistical difference in renal function tests between both groups: serum creatinine concentration was 128.4±33 versus 124±53 umol/L in the parenteral group and the oral group, respectively (*P*=0.13). We found no correlation between MPA C-30 and tacrolimus levels in both groups by Spearman tests (R=–0.08, *P*=0.54 and R=0.14, *P*=0.2). There was no interference between tacrolimus concentration and MPA C-120 by Spearman tests (R=0.004 (*P*=0.98) and R=0.05 (*P*=0.6) in group 1 and group 2, respectively).

Liver function tests were also comparable regarding APT: 41.8±47 U/L versus 37.3±41 U/L in group 1 and group 2, respectively (*P*=0.6). The MPA level C-30 was not related to route of PPI administration estimated by Spearman test (R=–0.09, *P*=0.5 versus R=–0.17, *P*=0.1). No correlation between ALAT serum activity and C-120 MPA concentration was found as R was 0.2 (*P*=0.1) and R=0.1 (*P*=0.3) in parenteral and oral group, respectively. Detailed information is presented in Table 1.

There was a significant difference in tacrolimus concentration between both groups 11.2±4 ng/mL versus 17.1±25 (*P*=0.01) The was no correlation observed between tacrolimus concentration and C-30 in Spearman tests R=–0.29 (*P*=0.06) in group 1 and R=0.06 (*P*=0.6) in group 2. Tacrolimus concentration did not interfere with MPA C-120 levels which was calculated in Spearman correlation tests R=0.004 (*P*=0.98) in group 1 and R=0.05 (*P*=0.6) in group 2.

The mean MPA plasma concentrations were statistically significant between parenteral group (2.3±1.4 umg/mL) and the oral group (3.1±2,2 umg/mL) (*P*=0.036) before immunosuppressive drug administration (C-0 time). There was a statistically significant different drug concentration in the second sample C-30 (30 minutes after drug intake) reaching 4.4±2,8 umg/mL versus 7.9±4.5 umg/mL (*P*<0.05). There was no statistically significant difference in MPA plasma concentration on the 3rd measurement C-120 (10.7±4.9 umg/mL versus 9.8±5 umg/mL) (*P*=0.3). There was a statistically significant different MMF serum concentration after oral intake and intravenous infusion at C-30 (2.4±1.4 in group 1 versus 3.3±2.5 in group 2, *P*<0.036) but not at C-120 time interval (8.9±5.0 versus 9.8±5.3 in group 1 and group 2, respectively) (*P*=0.3). Results are presented in Figure 1.

Table 1. Comparison of data in both group of parenteral and oral MPA routes administration.

Parameter	Oral administration	Parentral administration	p
Creatinine	124±53	128±33	ns
ALT	35±38	37±20	ns
AST	38±41	41±42	ns
Tacr	17±25	11±4	<0.03

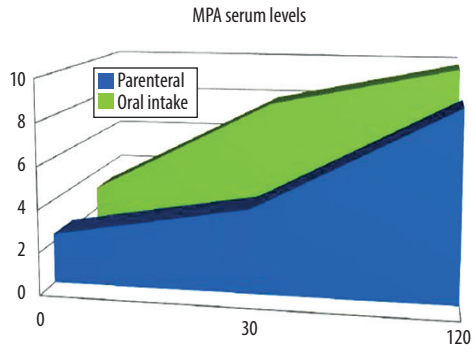

Figure 1. Comparison of MPA levels during parenetral and oral PPI's administration within time.

There was a statistical difference between C-0, C-30, and C-120 in both groups estimated by ANOVA Friedman tests.

All patients survived the surgery and there was no death in the following year of observation. One patient required permanent pacemaker implantation due to AV block, 3rd degree. The endomyocardial biopsies performed within the first postoperative year revealed only 3 patients (10%) at risk for acute rejection, who were successfully treated with glycol-corticosteroid infusions. There was 5 cases (14%) with infectious episodes within the 1-year study period including 2 cases (7%) of bacterial pulmonary infection, successfully treated with antibiotics (piperacillin/tazobactam), 1 case (3.5%) with CMV treated with foscarnet, and 1 case (3.5%) with pulmonary aspergillosis successfully treated with micafungin. In the postoperative period, kidney function deterioration was observed in 5 cases (17%), with serum creatinine 148±12 umol/L to 173±18 umol/L, *P*<0.05). New onset diabetes after transplantation (NODAT) was diagnosed in 12 patients (40%) and treated with insulin. Detailed information is presented in Table 2.

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Table 2. Postoperative immediate and 1-year follow up period.

Postoperative data	No=30
Survival	30 (100%)
– PPM implantation	1 (3%)
Hospitalisation time	28±3 days
– ICU stay	6±1 day
Rejections:	
– EMB results	4 (14%) (3a stage)
– Therapy	glicocorticosteriods
Kidney deterioration	5 (17%)
– Preoperative (umol/l)	148±12
– Postoperative (umol/l)	173±18
NODAT	12 (40%)
Infections:	
– Pulmonary (bacterial)	2 (7%)
• Therapy	Piperacillin/Tazobactam
– CMV infection	1 (3.5%)
• Therapy	Foscarnet
– Asperillosis	1 (3.5%)
• Therapy	Micafungin

ICU – Intensive Care Unit; EMB – enomyocardial biopsy; NOTAD – new onset diabetes after transplantation.

Study limitations

The study included a relatively small group of patients undergoing heart transplantation at a single center. There was no control group as all the patients undergoing heart transplantation required PPIs. We focused on different routes of PPI administration and its impact on MPA concentration with maximal dose of MPA (adjusted to AUC) and high dose of PPI (80 mg/daily) as the routine postoperative protocol at our center.

Discussion

Immunosuppression following heart transplantation includes standard triple therapy based on calcineurin inhibitors, antiproliferative drugs, and corticosteroids. Antiproliferative drugs added to calcineurin inhibitors increase patient survival, reduce rejection rate, and decrease the risk of cardiac allograft vasculopathy [6]. They block cytotoxic T lymphocytes mediating acute cellular rejection and lymphocytes B proliferation that are linked to antibody-mediated rejection [7]. Its uncompetitive inhibition of inosine monophosphate dehydrogenase cause depletion of *novo* purine synthesis [8].

Previous reports have highlighted the risk of interaction between MPA and PPIs [9]. Problems with co-administration of both drugs and the risk of MPA lowering serum levels have also been reported [10,11]. Our study focused on different routes of PPI administration. This was the first study comparing the influence of different routes (parenteral and oral) of PPI co-administration with MMF on its resulting pharmacodynamics. Moreover, our study results were contrary to common clinical beliefs and previous reports regarding to MPA serum concentration with PPIs therapy [12]. We focused on the AUC curve, which is more accurate for evaluation of MPA serum concentration as previous reported in studies of kidney transplantation patients [13].

The results of nonsignificant association between oral intake of PPIs and MPA serum plasma concentration have been previously presented [13]. The most commonly administered dose of pantoprazole (40 mg/day) was chosen for the study. As MPA is characterized by complex metabolisms, such factors like race, sex, age, and renal and liver function may interfere with its activity [14].

PPIs are routinely applied as preventive gastrointestinal (GI) tract complication therapy following surgery. The incidence of GI bleeding and ulcerations had been reported to be relatively high (up to 16% versus 12%) [15].

In previous studies, lower levels of MPA (C-0, C-30, C-90) were observed during PPI administration, without statistical significance [16]. A reduction in absorption was observed but without the influence of MPA trough level (C-0). Therapeutic doses of pantoprazole have been proven to influence maximal MPA concentration as MMF hydrolysis is reduced due to an increased gastric pH environment. Impairment of MPA exposure following MMF administration has been demonstrated previously but without statistical significance [17,18]. According to the study by Doesch et al., the trend for reduced plasma MPA concentration was observed and correlated with AUC results [6]. The results obtained from co-administration of MMF and pantoprazole-Na were not shown to reveal any significant changes [19,20].

There are results from *in vitro* and *in vivo* studies indicating inadequate dissolution but not hydrolysis [21,22]. According to the aforementioned results, the absorption was continued in the small intestine. In our study, we focused on AUC (0-2) to measure MPA exposure and effectiveness despite PPIs co-administration. We compared MPA-AUC with parenteral PPI administration (47.8±20 U) and oral administration (57.9±21 U) (P<0,05).

The results of our study indicated significant differences in AUC between oral and parenteral administration for MMF. The mean AUC was calculated to be 47.7±20 in group 1 versus 59±23 in group 2, (P=0.004). There is a statistically significant different MMF serum concentration after oral intake and intravenous infusion in C-30 (2.4±1.4 in group 1 versus 3.3±2.5 in group 2, P<0.036) but not in C-120 time interval (8.9±5.0 versus 9.8±5.3 in group 1 and group 2, respectively) (P=0.3). The

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mean serum MMF concentration in both groups are presented in Figure 1. There was no difference in serum creatinine concentration and ALT activity between both groups.

In the presented study, there were significant MPA serum concentrations differences in C-0 and C-30 time but not C-120. Under the curve concentration (AUC) was different between both groups, as well (Figure 1). This study revealed impaired MPA serum concentrations secondary to MMF hydrolysis and stomach absorption related to PPI administration. Interestingly, there was no difference in C-120 MPA serum concentration that supported the hypothesis of prolong MPA digestion.

In our study, there was a significant difference in AUC between both groups despite fixed MPA dose. Although the first 2 blood samples revealed impaired MPA concentration indicating decreased digestion, there was no difference in MPA concentrations at C-120 time. At C-120 time, MPA concentration reached comparable levels, and there was a significant difference in overall AUC estimations.

The study results support the hypothesis that MMF hydrolysis is decreased by PPI co-administration. Our study revealed differences by route of PPI administration. The maximum MPA level evaluated in C-120 time was comparable between both groups. This indicated that MMF impaired pharmacokinetics within the study time but had the ability to reach comparative levels within 120 minutes after MMF intake.

We believe that impairment in MPA pharmacokinetics was not related to liver and kidney function but related to different routes of PPI administration. Our study indicated that neither liver function tests (ALT) nor kidney parameters (serum creatinine) influenced C-30 and C-120 MPA concentrations.

There was no difference between ALT tests results between both groups estimated by the U Mann-Whitney test. The potential correlation between ALT serum activity and MPA concentrations were observed in C-30 and C-120. The MPA level C-30 was not related to route of PPI administration estimated by the Spearman test (R=–0.09, *P*=0.5 versus R=–0.17, *P*=0.1). No correlation between ALT serum activity and C-120 MPA concentration was found as R was 0.2 (*P*=0.1) and 0.1 (*P*=0.3) in the parenteral group and the oral group, respectively.

Creatinine serum levels were not related to MPA ingestion. We found no correlation between MPA C-30 and tacrolimus levels in both groups using the Spearman tests (R=–0.08, *P*=0.54 and R=0.14, *P*=0.2). There was no interference between tacrolimus concentration and MPA C-120 in the Spearman tests (R=0.004 (*P*=0.98) and R=0.05 (*P*=0.6) in group 1 and group 2, respectively).

There was a significant difference in tacrolimus concentration between both groups. We correlated tacrolimus concentration within MPA blood samples related to C time. There was no correlation observed between tacrolimus concentration and C-30 in the Spearman test R=–0.29 (*P*=0.06) in group 1 and R=0.06 (*P*=0.6) in group 2. Tacrolimus concentration did not interfere with MPA C-120 levels, which was calculated in Spearman correlation tests R=0.004 (*P*=0.98) in group 1 and R=0.05 (*P*=0.6) in group 2. These results revealed that tacrolimus does not impair MPA digestion.

Conclusions

Our study was the first that compared different routes of PPI co-administration on MPA serum levels in transplant recipient groups. The statistically significant diversity in MPA AUC, at C-0, C-30, and C-120 was observed between patients treated by parenteral and oral PPIs intake. Our study revealed that the parenteral route only slowed not decreased MPA pharmacokinetics within 120 minutes following MMF administration.

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