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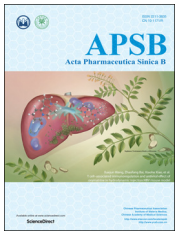

ORIGINAL ARTICLE

Nonlinear relationship between enteric-coated mycophenolate sodium dose and mycophenolic acid exposure in Han kidney transplantation recipients

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Human plasma

Abstract The aim of the research was to investigate the pharmacokinetics (PK) of enteric-coated mycophenolate sodium (EC-MPS) by quantification of the active metabolite of mycophenolic acid (MPA) after multiple escalating oral doses in Han kidney transplant recipients. A total of 28 Han postoperative kidney transplant recipients were given a multiple-dose of 540, 720 or 900 mg of EC-MPS two times a day in combination with tacrolimus for 6 days. Blood specimens were collected at each time point from 0 to 12 h after EC-MPS administration. MPA plasma concentrations were measured by UPLC–UV. The relationship between the EC-MPS dose and its PK parameters was assessed. In the range from 540 to 900 mg, C_{max} and AUC_{0-12h} did not increase with dose escalation. The AUC_{0-12h}, C_{max}, C_0 and T_{max} for the 540 720 and 900 mg doses were not significantly different, respectively ($P > 0.05$). $AUC_{0-12\,h}$ and C_{max} were increased less than proportionally with increasing EC-MPS dose levels. Inter-individual variability in AUC_{0-12h}, C_{max} and C_0 were considerable. Nonlinear PK relationships were found from the doses of 540–900 mg of EC-MPS.

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1. Introduction

The enteric-coated mycophenolate sodium (EC-MPS), a formulation of mycophenolic acid (MPA) is a standard immunosuppressive drug widely used in the renal transplant patients. Chemical structures of mycophenolate sodium and MPA are shown in Fig. 1. As compared with mycophenolate mofetil (MMF), EC-MPS shows the potential to reduce the incidence of adverse gastrointestinal effects by delaying MPA release until gastric emptying yet maintaining efficacy equivalent to that of MMF[1]. Although EC-MPS was used clinically as a fixed-dose drug, therapeutic drug monitoring (TDM) of the MPA area under the concentration–time curve (AUC) was found to improve clinical outcome[2-4]. MMF or EC-MPS, together with calcineurin inhibitors (either cyclosporine or tacrolimus) and steroids have become standard immunosuppressive therapy worldwide. A cyclosporine-based research project reported that treatment with 2724 mg of EC-MPS resulted in an AUC of MPA which was only 37% higher than treatment with 1440 mg of EC-MPS ten days after transplantation[5]. de Winter BC et al.[6] reported a nonlinear relationship between MMF dose and MPA AUC in renal transplant patients. There are limited PK data of EC-MPS in early Chinese kidney transplant recipients. A better understanding of the pharmacokinetic (PK) characteristics of EC-MPS in renal transplant recipients will improve the clinical effectiveness and safety profile of this medication. To increase our understanding of the PK characteristics of EC-MPS, we choose 3 dose groups in our research. The aim of the study was to test the PK behavior of EC-MPS over a range of 3 doses.

2. Materials and methods

2.1. Determination of plasma MPA concentrations

The method of UPLC–UV was used to analyze the MPA concentration in plasma. The validated UPLC–UV method was simple, accurate and successfully applied to the PK of EC-MPS study.

2.2. Chemicals

MPA, the reference standard (99.53% purity, Sigma, USA). EC-MPS was purchased from Novartis Pharma Schweiz AG. The internal standard of carbamazepine (IS) was purchased from the National Institute for Control of Pharmaceutical and Biological Products. Acetonitrile, which was HPLC-grade, was purchased from Merck Company, Inc. (Darmstaelt, Germany). Ultra-pure grade water was prepared using the Millipore Milli-Q purification system (Bedford, MA, USA). Hydrochloric acid, of HPLC-grade, was obtained from Tedia Company, Inc. (Fairfield, Ohio, OH, USA). Potassium dihydrogen phosphate is analytical pure.

2.3. Ultra performance liquid chromatography spectrometry

A UPLC-H-Class system (Waters Corporation) with Acquity UPLC and Acquity TUV detector (Waters Corporation), was used to determine the compounds. The samples were separated on an ACQUITY.UPLC BEH C18 column (50 mm × 2.1 mm, 1.7 μm, Waters, USA); the mobile phase consisted of water (20 mmol/L potassium dihydrogen phosphate) and acetonitrile (69.5:30.5, *v/v*) at a flow rate of 0.25 mL/min; the UV detective wave length was 254 nm and column temperature was 35 °C.

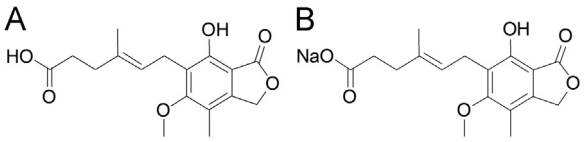

Figure 1 The chemical structures of (A) mycophenolic acid (MPA) and (B) mycophenolate sodium.

2.4. Sample preparation

Human plasma samples were thawed at room temperature. For each sample, an aliquot of 200 μL was added into 1.5 mL Eppendorf tubes with 400 μL IS (1 μg/mL) acetonitrile solution. After the tube was vortex mixed for 2 min, the mixture was centrifuged at 12,000 × *g* at 4 °C for 5 min, all of the supernatant was transferred into another Eppendorf tube and dried with nitrogen in a 40 °C water bath. Mobile phase (100 μL) was then added, followed by a thorough vortex mixing for 2 min, centrifuged at 12,000 × *g* at 4 °C for 3 min, and the upper layer (5 μL) was injected into the UPLC system.

2.5. Method validation

The validation of the UPLC–UV method for the determination of MPA in plasma samples was performed according to Food and Drug Administration (FDA) Guidelines. The lower limit of quantification (LLOQ), carryover effect, precision, accuracy, matrix effect, extraction recovery and stability tests were carried out to assess the method validation.

Specificity was evaluated by comparing the chromatograms of blank plasma from 6 different sources with the blank human plasma sample spiked with MPA and IS. Linearity of MPA was evaluated over the range of 0.10–40.00 μg/mL. The calibration curves were established by plotting the peak area ratio of MPA to IS *versus* the theoretical concentration of MPA, and fitted with by least square weighted linear regression. The sensitivity of the analytical procedure was expressed as LLOQ that can be quantitatively determined with acceptable accuracy and precision and should be with a signal–noise (*S/N*) ratio at least of 10.

The carryover effect was evaluated by injecting blank sample after the 40.00 μg/mL sample. Carryover in the blank sample following the 40.00 μg/mL sample should not be greater than 20% of the LLOQ for MPA and 5% for IS.

The matrix effects were determined by comparing the peak areas obtained from samples where the extracted matrix was spiked with standard solutions to those of the pure samples prepared in mobile phase containing equivalent amounts of the analyte in quality control (QC) samples. Recovery was calculated by comparing the peak area obtained from an extracted sample with that obtained from unextracted standard solution prepared with the same solvent.

Intra- and inter-day precision and accuracy were assessed by analysis of the QC samples. QCs at three levels (0.20, 5.00 and 32.00 μg/mL) were analyzed on 6 replicates during the same day and on 3 different days. The mean accuracy (%) was determined by comparing the measured concentrations against the theoretical concentration (mean concentrations/theoretical concentration × 100) for the QC samples.

The plasma samples and stock solutions stability tests were assessed at three QC levels in different conditions. Freeze and thaw stability were evaluated by four freeze–thaw cycles. Frozen samples were allowed to thaw at 25 °C for 12 h. Short-term stability was assessed by thawing at 25 °C and keeping at 25 °C

for 24 h. Long-term stability was assessed by storing at −80 °C or 4 °C for 30 days. At last the processed samples were stored in the autosampler (4 °C) for 24 h before analyzed.

2.6. Patients selection

Consecutive, prospective patients who were over 18 years and received the first kidney transplant were enrolled to assess the PK behavior of EC-MPS in this single-center study. Patients were recruited after passing a physical examination and laboratory tests, which included blood biochemistry, hematology, and urine analysis. Patients with cancer, hematologic abnormality, hepatic, or gastrointestinal or any acute disease, and patients with allergy to EC-MPS were excluded. All patients underwent the same therapeutic schemes of EC-MPS with tacrolimus and steroids. All participants were informed of the details and procedure of the research before they signed a written informed consent.

2.7. Study design

This research was carried out in the Clinical Nephrotransplantation Center of the First Affiliated Hospital of Zhengzhou University (People's Republic of China). This study was conducted according to the principles of the Declaration of Helsinki. The clinical protocol and the informed consent form were approved by the Ethics Committees of the Zhengzhou University. In the study, 720 mg was selected as the reference dose. The *de novo* kidney transplant recipients were divided into 3 groups on the basis of the doses. All participants received EC-MPS, tacrolimus and corticosteroids as concomitant immunosuppressive therapy. All the *de novo* renal transplant recipients received dose of 540, 720 or 900 mg of EC-MPS (180 mg/Tab) at fasted state 2 times a day for 6 days with water. The starting tacrolimus dose was 0.06–0.08 mg/kg 2 times a day. The tacrolimus dosage was adjusted on the basis of clinical evaluations. All patients received two intraoperative corticosteroid doses of 500 mg of methylprednisolone. Maintenance methylprednisolone dose was tapered to 500 mg on day 2, followed by a stepwise reduction to 375 mg on day 3, 250 mg on day 4, and 120 mg on day 5. Then methylprednisolone tablets of 16 mg/day were administered. On day 7, patients fasted overnight before dosing and until 1.5 h after EC-MPS administration, serial blood samples (2 mL each) were drawn at 0, 0.5, 1, 1.5, 2, 4, 6, 8, 10 and 12 h after oral intake of EC-MPS. The blood samples were centrifuged at $3000 \times g$ at 4 °C for 5 min, and plasma samples were separated and analyzed by the validated UPLC.

2.8. Pharmacokinetic analysis

The PK analysis was performed using Drug and Statistic software version 2.1.1 (Beijing, China). Noncompartmental PK analysis was used to determine the data obtained from individual patients. The following PK parameters were obtained directly from the observed data for each patient: trough concentrations prior to oral dosing (C_0), peak plasma concentration (C_{max}), time to reach C_{max} (T_{max}), the area under the concentration–time curve 0 to time (AUC_{0-t}) calculated by linear trapezoid method, and total body clearance (CL) was calculated by dose/$AUC_{0-\tau}$ (τ was administration interval).

2.9. Statistical analysis

All results were presented as mean ± standard deviation (SD). Data analysis was performed by using SPSS version 11.5 (SPSS Inc., Chicago, IL, USA). The dose linearity of AUC and C_{max} for MPA was evaluated by using one-way analysis of variance (ANOVA). ANOVA was also used to perform any differences in T_{max} and CL between the study dose groups. $P < 0.05$ was considered statistically significant. Inter-individual variability was assessed using coefficients of variation (CV).

3. Results

3.1. Method validation

Chromatographic results showed that the retention time of IS and MPA were 2.1 and 5.2 min, respectively. There were no interfering peaks at the retention time of either MPA or IS. The standard calibration curve was linear from 0.10 to 40.00 μg/mL for MPA ($r = 0.999\ 7$, $n = 7$). The LLOQ was 0.10 μg/mL with $S/N > 10$. The carryover of MPA was less than 15% of average peak area of LLOQ. The carryover of IS was less than 1% of average peak area. The extraction recovery of MPA at 0.20, 5.00 and 32.00 μg/mL ranged from 89.76% to 97.50% and the IS value was 99.38%. The matrix effect at three QC levels for the MPA ranged from 87.88% to 100.97%. The precision, presented by relative standard deviation (RSD) of intra- and inter-day for MPA was less than 9.67% at the three QC levels. The accuracy for MPA ranged from 95% to 101%. Stability tests showed that the plasma samples and stock solutions were stable (RSD < 8.7%) after the 24 h at 25 °C storage, 24 h in the autosampler (4 °C), 4 freeze–thaw cycles (–80 to 25 °C) and long-term storage (30 days, –80 or 4 °C). Technically, the method for determination of MPA from human plasma was sensitive, robust and precise.

3.2. Patients

A total of 28 patients were enrolled in the study. Table 1 summarizes the characteristics of the patients.

3.3. Pharmacokinetic parameters

A total of 28 patients participated in the PK study. The mean MPA plasma concentration–time curves of EC-MPS after multiple oral doses of 540, 720, and 900 mg are shown in Fig. 2. Table 2 shows the PK parameters. Due to enterohepatic circulation, most of the patients (24/28) revealed a second small peak 4–12 h after taking EC-MPS in the three different dose groups. Bioavailability increased with decreasing EC-MPS doses. Compared with the reference dose of 720 mg (100%), the relative bioavailability was 130.4% and 93.3% in patients receiving EC-MPS doses of 540 and 900 mg.According tothe numerically decreasing relative bioavailability, MPA AUC increased less than proportionally with increasing EC-MPS doses. In the range of 540 to 900 mg, C_{max} and $AUC_{0-12\ h}$ did not increase with dose escalation. The $AUC_{0-12\ h}$, C_{max}, C_0 and T_{max} for the 540, 720 and 900 mg doses were not significantly different across the doses. Inter-individual variability in $AUC_{0-12\ h}$ (540 mg, 55.5%; 720 mg, 41.6%; 900 mg, 27.3%), C_{max} (540 mg, 77.0%; 720 mg, 75.5%; 900 mg, 63.0%) and C_0 (540 mg, 70.1%; 720 mg, 75.9%; 900 mg, 46.4%) values were considerable. Nonlinear PK properties were discovered for EC-MPS in renal

Table 1 Demographic data and clinical parameters.

Parameter	EC-MPS(mg)		
	540	720	900 mg
Gender (male/female)	9 (9/0)	11 (8/3)	8 (6/2)
Age (years)	24.56±5.57	32.73±7.62	33.13±6.33
Race (Han/other)	9 (9/0)	11 (11/0)	8 (8/0)
Weight (kg)	59.00±7.37	61.73±10.85	67.38±10.32
Serum creatinine (μmol/L)	112.89±23.38	131.91±37.81	124.63±30.16
Alanine amino transferase (U/L)	15.00±4.39	16.27±10.13	11.75±7.09
Aaspartate amino transferase (U/L)	12.22±2.54	10.55±3.05	11.38±6.67
Albumin (g/L)	43.44±3.21	40.42±6.11	38.49±3.94

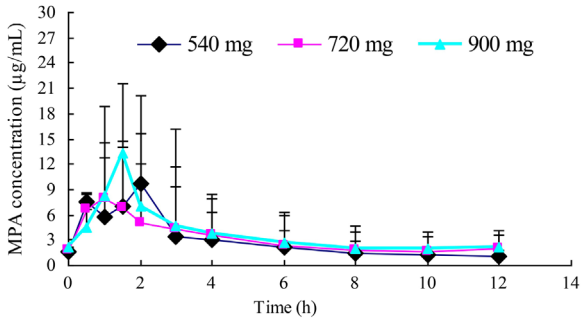

Figure 2 Mean plasma concentration–time curve of MPA after oral dose of 540 mg ($n=9$), 720 mg ($n=11$), and 900 mg ($n=8$) of enteric-coated mycophenolate sodium (EC-MPS, two times a day for 6 days) in kidney transplant recipients ($n=28$).

transplant recipients after multiple dose administration at doses of 540 to 900 mg on day 7.

3.4. Tolerability

No serious adverse effects (AEs) were observed during the PK study. The most common AEs were diarrhea (4/28; 14.3%), eructation (5/28; 17.9%) and nausea (7/28; 25.0%) in the three dose groups. All these gastrointestinal symptoms were mild. Results of vital signs, clinical laboratory assessments and physical examinations were within normal limits for all participants and no clinically meaningful differences were found.

4. Discussion

The aim of our research was to assess the PK properties of MPA in renal transplant recipients treated with EC-MPS, tacrolimus and steroids within 7 days after the transplantation. At day 7 after transplantation the daily doses of EC-MPS were 1080, 1440 and 1800 mg and the corresponding MPA AUC_{0-12h} values were 37.14 (20.62), 37.96 (15.80) and 44.29 (12.09) μg h/mL, respectively. Previous studies suggest that plasma MPA AUC is an important risk factor for rejection[7,8]. An appropriate $AUC_{0-12\,h}$ after drug administration (between 30–60 μg · h/mL) was associated with significant decrease in acute graft rejection in kidney transplant patients[9]. Compared with the other two dose groups (720 mg twice daily or 900 mg twice daily), the lower dose of EC-MPS (540 mg twice daily) also can achieve target MPA exposure rapidly in Han renal transplant patients. This finding is consistent with published results showing that lower doses of EC-MPS (540 mg twice daily) can provide enough MPA exposure for Chinese live-donor kidney transplant patients[10-13]. The other support for our discoveries comes from a study reporting that lower dosing (500 mg twice daily) of MMF can provide enough MPA exposure for most Thai kidney transplant patients with the mean AUC value 39.49 μg · h/mL[14]. The current recommended oral doses in adult renal transplant recipients are 720 mg twice daily for EC-MPS and 1000 mg twice daily for MMF[15]. The 720 mg of EC-MPS delivered bioequivalent mean MPA exposure compared with 1000 mg of MMF[16]. Based on this information, we compared the previous studies of MMF dose and MPA AUC with the present study. Armstrong et al.[17] found that the oral MMF formulation shows high and consistent bioavailability (mean 95%) based on comparison with the intravenous formulation in heart transplant recipients. In an early study, the authors compared MMF of 1000 mg with MMF of 1500 mg, both two times daily, in cyclosporine-treated patients, and found MPA AUC and MMF dose presented a linear relationship[18]. However, de Winter et al.[6] reported that the bioavailability decreased with increasing MMF doses. The authors found the relative bioavailability was 176%, 133%, 85% and 76% in patients treated with MMF doses of 250, 500, 1500 and 2000 mg in combination with tacrolimus, compared with an MMF dose of 1000 mg (100%). The MMF exhibits nonlinear PK character. In our study, we found that the bioavailability decreased significantly with escalating EC-MPS doses, which supports nonlinear PK property for EC-MPS.

After oral administration, EC-MPS is rapidly and completely hydrolyzed into MPA. MPA is primarily metabolized to an inactive metabolite 7-*O*-mycophenolic acid glucuronide (MPAG), which undergoes enterohepatic recirculation[11,19]. In our study, most of the patients revealed a second small peak in the 4–12 h after taking EC-MPS due to the enterohepatic circulation, which agrees with other findings[19,20]. It has been estimated that the enterohepatic circulation contributes approximately 40% (10%–60%) to MPA exposure[21]. The saturable absorption process of MPA from the gut may cause the decrease in bioavailability with higher dose. The enterohepatic circulation is responsible for the reabsorption of MPAG in the gut as MPA. At higher dose, saturation of enterohepatic circulation may lead to less MPAG recirculated and more will be excreted by the kidney, producing less MPA exposure.

MPA clearance is correlated with the calcineurin inhibitor that is co-administered and time post-transplantation[6,22]. In the published reports, the mean MPA CL values ranged from 10.9 to 33.0 L/h[11,23–24]. In our study, at day 7 post-transplantation, mean MPA CL increased from 7.80 to 54.30 L/h for tacrolimus-cotreated patients. This may be caused by a combination of

Table 2 PK parameters of MPA after multiple dose of 540, 720 and 900 mg EC-MPS in 28 kidney transplant recipients.

Parameter	EC-MPS (mg)			*P* value
	540	720	900	
$AUC_{0-12\,h}$ (μg · h/mL)	37.14 ± 20.62	37.96 ± 15.80	44.29 ± 12.09	0.633
C_{max} (μg/mL)	18.06 ± 13.91	13.32 ± 10.06	15.86 ± 10.00	0.652
C_0 (μg/mL)	1.53 ± 1.00	1.79 ± 1.36	2.13 ± 0.99	0.519
T_{max} (h)	1.89 ± 1.65	1.32 ± 0.72	1.63 ± 1.03	0.558
CL (L/h)	20.76 ± 11.57	22.71 ± 9.22	23.26 ± 12.67	0.880

$P < 0.05$ was considered statistically significant ($n = 28$).

improving renal function during the first weeks post-transplantation[25].

In the present study, we observed interindividual variability in AUC_{0-12h}, C_{max} and C_0 were considerable in the three dose groups, with the CV ranging from 27.3% to 77.0%, which is in line with previous findings in solid organ transplant patients[26]. It is known that MPA exposure is significantly influenced by renal function[12]. Differences in the activity of the metabolizing enzymes or phenotype may result in altered effectiveness in some individuals[14,27]. Although EC-MPS is recommended as a fixed-dose drug, TDM of the MPA exposure was found to improve clinical outcome without adding any extra costs[28-30]. The large interpatient variability in MPA PK at the three dose groups suggeststhat individualization of EC-MPS dose based on TDM are needed to ensure a favorable impact on the prognosis of recipients.

This study has several limitations. We have focused on the PK study of MPA using EC-MPS. The studied population comprised patients with a disease, and the average age of the participants is young; the number of patients enrolled in the study is relatively small.

5. Conclusions

In this PK study of EC-MPS in the Han renal transplant recipients, nonlinear PK properties were discovered at doses ranging from 540 to 900 mg after multiple-dose administration. This may have important contributions to clinical practice.

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