Pharmacokinetics of Mycophenolic Acid in Kidney Transplant Recipients Treated with a Low Dose (1 gram/day) of Mycophenolate Mofetil

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Abstract

Pharmacokinetic studies of mycophenolic acid (MPA) were performed in 16 stable Thai kidney transplant recipients treated with 1 g/d of mycophenolate mofetil (MMF). The complete area under the blood concentration-time curve (AUC) of MPA was determined using the linear trapezoidal rule from 8 concentrations at, 0, 1, 2, 3, 4, 6, 8, and 12 h after MMF administration. The mean values of AUC_{0-12} were 37.54 $\pm$ 0.80 $\mu g \bullet h/ml$. MPA concentrations at 8 h after dosing, not the trough or maximum levels, showed the best correlation with AUC_{0-12} ($r^2 = 0.72$). The equation model of abbreviated AUC of MPA, derived by multiple linear regression analysis, that had the highest correlation (r^2) and lowest absolute prediction error (APE) was : $AUC = 0.6\ C_1 + 1.9\ C_3 + 8.68\ C_8 + 4.65$ ($r^2 = 0.92$, APE = 2.05 $\pm$ 0.32%). The best abbreviated AUC equations obtained by linear trapezoidal rule were : $AUC = 4.5\ C_0 + C_1 + 1.5\ C_2 + 5\ C_4$ ($r^2 = 0.78$, APE = 5.78 $\pm$ 1.14%) and $AUC = 5\ C_0 + C_1 + C_2 + 5\ C_3$ ($r^2 = 0.76$, APE = 6.21 $\pm$ 1.46%)

Key word : Pharmacokinetic Studies, Mycophenolic Acid, Mycophenolate Mofetil

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Mycophenolate mofetil (MMF), a morpholinoethyl ester derivative of mycophenolic acid (MPA), is an effective immunosuppressive drug that can reduce acute graft rejection in kidney transplant patients[1-5]. Prescription of MMF dosage, however, is not determined by the amount of the drug per body weight. In Western countries, the dose of MMF used in kidney transplantation is in the range of 1-1.5 g twice daily or 2-3 g/day[6]. Several kidney transplant recipients including Thais, however, could not tolerate the gastrointestinal adverse drug effects when such doses were prescribed. The usually tolerated dose of MMF prescribed in Thai kidney transplant recipients is approximately 1 g/day.

Several pharmacokinetic studies have demonstrated the importance of AUC (area under the blood concentration-time curve) of MPA in therapeutic monitoring of MMF in renal transplantation[7-9]. Several recent studies from Western countries have shown that MMF at the dose of 1 g/day can provide acceptable pharmocokinetic profiles of MPA when compared with higher doses[10,11]. There are no available pharmacokinetic data of MMF in Thai renal transplant recipients.

The present study was conducted to perform pharmacokinetic studies of MPA in Thai kidney transplant recipients treated with MMF 1 g/day.

PATIENTS AND METHOD

The pharmacokinetic studies of MPA were conducted in 16 (male = 9, female = 7) Thai renal transplant recipients receiving MMF at the dose of 1 g/day. Other immunosuppressive drugs consisted of cyclosporine A and prednisolone. The study was approved by the Ethic Committee of the Faculty of Medicine, Chulalongkorn University Hospital, Bangkok, Thailand. Each participating patient gave written informed consent. The inclusion criteria were as follows 1) recipients with more than 3 months of follow-up, 2) recipients within the age range of 15-65 years, 3) recipients with stable and normal renal function, and 4) recipients with total bilirubin less than 5 mg/dL.

The recipients were excluded if they received cholestyramine, non steroid anti-inflammatory drugs, salicylate, antacids with magnesium and aluminum hydroxides, and furosemide.

For at least 1 week before the study, each recipient took MMF, 500 mg twice daily, with the exact interval of 12 hours. Basic demographic, clinical, and blood as well as laboratory data were determined in each recipient. Regarding pharmacokinetic profiles, the complete AUC (area under the blood concentration-time curve) or AUC_{0-12} was studied for a duration of 12 hours. On the experimental day, blood samples (3 ml) were obtained before the morning dose of MMF and then at 1, 2, 3, 4, 6, 8, and 12 h after dosing. All the samples were centrifuged and the serum samples were separated and stored at the temperature of -80°C. The concentrations of MPA were assayed by high peformance liquid chromatography (HPLC) using Shimadzu high performance liquid chromatograph version LC-3A with LDC 4100-UV detector 324.0 mm × 250 mm 5-μm particle syl (Lichrocart C_{18} Merck) reverse phase column.

The highest measured blood concentrations and the corresponding sampling time were defined as C_{max} and t_{max}, respectively. Two trough levels were measured, before drug administration (C_0) and 12 h after drug dosing (C_{12}). As described in the authors' previous pharmacokinetic studies, the complete AUC, AUC_{0-12}, for each patient was determined by using the linear trapezoidal rule from the eight concentrations (C_0, C_1, C_2, C_3, C_4, C_6, C_8 and C_{12}) (12).

Pearson product-moment correlation coefficients were calculated to evaluate the linear relations between the AUC_{0-12} and the blood concentration at a given time. The formulations of abbreviated AUC, as previously described, were derived from multiple linear regression analysis and linear trapezoidal rule. The accuracy of predicting the complete AUC by the abbreviated AUC was evaluated by using correlation coefficient (r^2) and the percentage of absolute prediction error (APE) calculated as follows :

$$APE = \frac{(\text{Predicted AUC} - \text{Measured AUC}) \times 100\%}{\text{Measured AUC}}$$

The former, r^2, represents only the strength of a relationship between two variables whereas the latter, APE, assesses the agreement of the relationship between the two parameters[12]. As such, APE per cent has more statistical impact than the values of r^2. The criteria of acceptable accuracy of abbreviated AUC were APE per cent $\leq$ 10 per cent and $r^2 \geq 0.9$.

All the data in the tables and figures are expressed as mean $\pm$ SE or percentage. Statistical significance was attained when p-value was < 0.05.

RESULTS

The mean values of demographic and clinical data were as follows : patient age = 44.8 $\pm$ 2.0 years, duration after kidney transplantation = 28.9 $\pm$ 5.5 months, body weight = 64.5 $\pm$ 2.4 kg, height = 165.4 $\pm$ 1.9 cm, body surface area = 1.7 $\pm$ 0.1 m^2, body mass index = 23.5 $\pm$ 0.7 kg/m^2. Basic laboratory data included : serum creatinine = 1.4 $\pm$ 0.1 mg/dL, creatinine clearance = 58.9 $\pm$ 4.3 ml/min, urine protein = 0.5 $\pm$ 0.2 g/d, urine volume = 3,678 $\pm$ 361 ml/d. The results of liver function test were in normal range.

Fig. 1 depicts the mean MPA concentrations at different time points. The values of C_{max} and T_{max} were 5.72 $\pm$ 0.29 (ranged 4.42 - 8.66) µg/ml and 1.38 $\pm$ 0.21 h, respectively. The trough concentrations of C_0 were not statistically different from C_{12} (2.75 $\pm$ 0.07 *vs* 2.58 $\pm$ 0.06 µg/ml). The values of AUC_{0-12} of MPA were 37.54 $\pm$ 0.80 µg•h/ml.

Table 1. Correlation coefficients (r^2) between MPA levels and AUC_{0-12}.

MPA levels	AUC_{0-12} (mg•h/ml)
	r^2 (p)
C_0	0.24 (NS)
C_1	0.18 (NS)
C_2	0.25 (NS)
C_3	0.36 (< 0.01)
C_4	0.18 (NS)
C_6	0.49 (< 0.01)
C_8	0.72 (< 0.001)
C_{12}	0.27 (NS)

NS = not significant

There was no statistical correlation between AUC_{0-12} and demographic, clinical as well as basic laboratory data (data not shown). As seen in Table 1, the concentrations of MPA at 8 hours after dosing, C_8, had the highest correlation (r^2 = 0.72) with AUC_{0-12}. Of interest, the trough concentrations, C_0 and C_{12}, provided much lower statistical correlations (r^2 = 0.24 and 0.27, respectively).

Table 2 illustrates various formulae of abbreviated AUC derived by multiple linear regression analysis. It is obvious that equation 3, AUC = 0.6 C_1 + 1.9 C_3 + 8.68 C_8 + 4.65 was the best least time-points-employed formula that can provide the values of APE per cent less than 10 per cent and r^2 above 0.90 (Table 2). Despite having the values of r^2 below

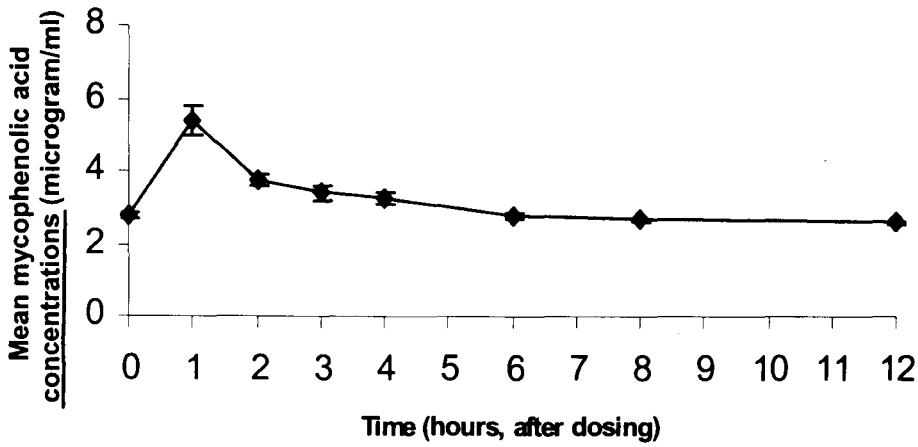

Fig. 1. The mean concentrations of MPA at different time points in 16 Thai kidney transplantation patients receiving 1 g/d of MMF.

0.90, equation 1, AUC = 12.17 C_8 + 5.02 (APE = 3.69%, r^2 = 0.72), and equation 2, AUC = 1.54 C_3 + 10.53 C_8 + 4.14 (APE = 2.58%, r^2 = 0.85) did have APE per cent below 10 per cent. Only C_8 and C_3 as well as C_8 were exploited in equation 1 and 2 respectively. Despite equation 3 and 4 providing more statistical results, 3 and 4 concentrations, respectively, had to be used in calculating abbreviated AUC (Table 2).

Various formulae of abbreviated AUC calculated by linear trapezoidal rule are displayed in Table 3. The least time-points-used formulae provided the best statistical correlation, although the values of r^2 were less than 0.90, were equation 5, AUC = 4.5 C_0 + C_1 + 1.5 C_2 + 5 C_4 (APE = 5.78%, r^2 = 0.78) and equation 4, AUC = 5 C_0 + C_1 + C_2 + 5 C_3 (APE = 6.21, r^2 = 0.76).

DISCUSSION

Pharmacokinetic monitoring of MPA by determining MPA levels and MPA AUC has been shown to correlate with the incidence of acute rejection and outcome in adults as well as children[7-9]. Because of the high occurrence of gastrointestinal adverse effects of MMF at the Western-recommended dose of 1.0 g twice or 2 g daily for adults[6], several Thai kidney transplantation recipients take MMF at the dose of 1 g/d. It is crucial to asses whether a lower dose of MMF could provide acceptable pharmacokinetic profile. In this regard, recent studies have suggested that the values of the trough concentrations ranging 1.0-2.5 μg/ml and those of AUC_{0-12} ranging 30-60 μg•h/ml could reduce the incidence of acute rejection (7,9). In the present study, the values of the trough concentrations (~2.75 μg/ml) and AUC_{0-12} (37.54 ± 0.80 μg•h/ml), thus, are in the optimal therapeutic levels.

In the present study, however, the concentrations of MPA at 8 h after dosing had the highest correlation with the complete AUC (AUC_{0-12}). The trough concentrations and C_{max} provided much lower statistical values (Table 1). This might be explained by the fact that MPA can undergo enterohepatic recirculation[6,13], leading to the reheightened blood MPA levels at the time after T_{max}.

Table 4 illustrates pharmacokinetic data of 1 g/d MMF between the present study and previous studies in the literature[10,11]. It is obvious that usage of 1 g/d MMF in Oriental kidney transplantation recipients could provide comparable pharmacokinetic data with those in Western countries. The discrepancies in some pharmacokinetic parameters might be caused by differences in race, body size, and methods in measuring MPA.

Table 2. Model equations derived from multiple stepwise linear regression analysis.

Equations	Model equations	APE %		r^2
		Mean ± SE	Range	
1	12.17C8 + 5.02	3.69 ± 0.61	0.07-8.66	0.72
2	1.54C3 + 10.53C8 + 4.14	2.58 ± 0.50	0.07-7.42	0.85
3	0.6C1 + 1.9C3 + 8.68C8 + 4.65	2.05 ± 0.32	0.52-5.23	0.92
4	0.72C1 + 2.01C3 + 3.72C6 + 5.01C8 + 3.09	1.23 ± 0.24	0.05-3.50	0.97

Table 3. Model equations calculated by linear trapezoidal rule.

Equations	Model equations	APE %		r^2
		Mean ± SE	Range	
1	5.5C0 + C1 + 5.5C2	11.51 ± 1.90	4.23-35.51	0.47
2	4.5C0 + 2C1 + 5.5C4	9.71 ± 1.23	1.56-19.25	0.74
3	5C0 + 2C2 + 5C4	6.50 ± 1.18	0.13-16.49	0.48
4	5C0 + C1 + C2 + 5C3	6.21 ± 1.46	0.03-20.67	0.76
5	4.5C0 + C1 + 1.5C2 + 5C4	5.78 ± 1.14	0.13-16.29	0.78
6	3.5C0 + C1 + 2.5C2 + 5C6	5.16 ± 0.95	0.25-12.48	0.64
7	2.5C0 + C1 + 3.5C2 + 5C8	6.20 ± 0.98	1.16-16.66	0.64
8	4.5C0 + C1 + C2 + C3 + 4.5C4	5.73 ± 1.29	0.16-16.78	0.73

Table 4. Comparison of pharmacokinetic data of 1 g/d MMF between previous studies in the literature and the present study.

Authors	n	T_{max} (h)	C_{max} (μg/ml)	C_{min} (μg/ml)	AUC (μg•h/ml)
Brunet et al (10)	10	0.93 ± 0.62	16.22 ± 12.49	1.76 ± 0.70	42.87 ± 17.8
Mourad et al (11)					
Patients without MPA-related side effects	30		C_{30} = 7.66 ± 8.95 C_{60} = 5.83 ± 2.6	1.75 ± 0.82	36.04 ± 10.82
Patients with MPA-related side effects	21		C_{30} = 10.47 ± 6.27 C_{60} = 9.67 ± 5.42	2.63 ± 1.58	48.38 ± 18.5
The present study	19	1.32 ± 0.82	5.70 ± 1.18	2.75 ± 0.29	37.4 ± 3.4

Despite providing more reliable pharmacokinetic data[7-11], calculation of complete AUC requires several blood samplings leading to time consuming, expensive, and unsuitable for routine practice. Determination of abbreviated AUC using few blood samplings at different time points could be a better solution. Although there were some reports of abbreviated AUC of MPA[14,15], the formulae in calculating abbreviated AUC was obtained by multiple linear regression analysis which could provide limited benefit. This is because such formulae cannot be generally applicable to different sets of pharmacokinetic data or when new data are added. To circumvent such limitation, in the current study, the abbreviated AUC was calculated by linear trapezoidal rule which is simpler to determine and can be applicable for different data. The least time-points-used formulae were $AUC = 4.5\ C_0 + C_1 + 1.5\ C_2 + 5\ C_4$ and $AUC = 5\ C_0 + C_1 + C_2 + 5\ C_3$.

In conclusion, MMF at the dose of 1 g/day could provide optimal pharmacokinetic profile. C_8, instead of trough concentrations or C_{max}, had the highest statistical correlation with the complete AUC. The best formula of abbreviated AUC derived from stepwise multiple linear regression analysis is $AUC = 0.6\ C_1 + 1.9\ C_3 + 8.68\ C_8 + 4.65$ while those obtained from linear trapezoidal rule are $AUC = 4.5\ C_0 + C_1 + 1.5\ C_2 + 5\ C_4$ and $AUC = 5\ C_0 + C_1 + C_2 + 5\ C_3$.

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เภสัชจลนศาสตร์ของมัยโคฟีโนลิคแอซิด ในผู้ป่วยปลูกถ่ายไตไทยที่ได้รับการรักษาด้วยยามัยโคฟีโนเลต โมเฟติลขนาดต่ำ (1 กรัมต่อวัน)

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ทำการศึกษาทางเภสัชจลนศาสตร์ของกรดมัยโคฟีโนลิคในผู้ป่วยปลูกถ่ายไต 16 ราย ที่รับประทานยามัยโคฟีโนเลต โมเฟติล นำค่าระดับกรดมัยโคฟีโนลิคในเลือดที่ 0, 1, 2, 3, 4, 6, 8 และ 12 ชั่วโมงหลังได้รับยา มาหาค่าพื้นที่ใต้กราฟระหว่างระดับกรดมัยโคฟีโนลิคในเลือดและเวลา โดยวิธีมาตรฐานด้วยการใช้กฎไลเนียร์ แทรปีซอยดอล พบว่ามีค่าพื้นที่ใต้กราฟเท่ากับ 37.54 ± 0.80 ไมโครกรัม•ชม/มล ระดับกรดมัยโคฟีโนลิคในเลือดที่ 8 ชั่วโมงหลังได้รับยามีความสัมพันธ์ทางสถิติสูงสุดกับค่าพื้นที่ใต้กราฟ ในการศึกษานี้ยังใช้วิธีทางสถิติและคณิตศาสตร์ในการนำระดับกรดมัยโคฟีโนลิคในเลือดบางจุดเวลามาใช้สร้างสมการในการคำนวณค่าพื้นที่ใต้กราฟ พบว่ามีความสัมพันธ์ทางสถิติที่ดีกับพื้นที่ใต้กราฟที่ได้จากการคำนวณโดยวิธีมาตรฐาน

คำสำคัญ : การศึกษาทางเภสัชจลนศาสตร์, กรดมัยโคฟีโนลิค, มัยโคฟีโนเลต โมเฟติล

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