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Effects of food and antacid on the pharmacokinetics of single doses of mycophenolate mofetil in rheumatoid arthritis patients

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1 Mycophenolate mofetil (MMF) is a prodrug of mycophenolic acid (MPA) and is being developed for the prevention of rejection following solid organ transplantation. This crossover study investigated the effect of food and antacid (Maalox® TC) on the plasma pharmacokinetics of MPA and its inactive glucuronide metabolite MPAG after giving single 2 g MMF doses orally to rheumatoid arthritis patients.

2 With food, the AUC of MPA in plasma was equivalent to that following an overnight fast. MPA t_{max} was slightly delayed and C_{max} was lowered about 25%, consistent with delay in gastric emptying in the fed state. MPAG C_{max} and AUC were higher in the fed relative to the fasting state, suggesting more complex processes involving changes in glucuronidation may also be occurring with food.

3 With antacid, AUC of MPA was lowered about 15% compared with fasting and C_{max} was decreased 37%. Plasma MPAG parameters were similarly reduced. These parallel changes in MPA and MPAG are consistent with reduced absorption.

4 The changes in MPA with both food and antacid are small in comparison with the interpatient variability and are not likely to have clinically major effects; the changes in MPAG are of mechanistic interest.

Keywords mycophenolate mofetil pharmacokinetics interactions food antacid

Introduction

Mycophenolate mofetil (MMF), the morpholinoethyl ester of mycophenolic acid (MPA), is a new immunosuppressive drug being developed for the prevention of allogeneic graft rejection following solid organ transplantation. MMF acts as a prodrug of MPA and improves the oral bioavailability of the latter [1]. Submicromolar concentrations of MPA inhibit lymphocyte transformation by T- and B-cell mitogens *in vitro* [2].

Following oral administration in man MMF is rapidly and essentially completely absorbed and then rapidly and completely de-esterified to form MPA. The latter undergoes conjugation to form the sole metabolite MPAG, a pharmacologically inactive, stable phenolic glucuronide. Both MPA and MPAG are present in plasma following oral administration of MMF, but MMF itself is not quantifiable systemically. Secondary peaks are seen in the plasma MPA profile, consistent with the occurrence of enterohepatic circulation (EHC). Excretion of administered drug substance is almost completely via the urine, and is almost all as MPAG [3].

Immunosuppressant use is chronic, so that it is important to determine the effect of drug administration with and without food. The fed state affects the pharmacokinetics of many orally administered drugs through a variety of mechanisms [4], and in some cases these effects may lead to clinical recommendations for dosing in relation to food. In the posttransplant setting, immunosuppressants are typically used with numerous concomitant medications, amongst which antacids are one of the commonest. The present study was designed

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to determine the influence of food and antacid on the systemic availability of MPA following single 2 g oral doses of MMF. The study was conducted in rheumatoid arthritis (RA) patients rather than renal transplant patients because the former group use fewer potentially confounding concomitant medications. Both MPA and the metabolite MPAG were measured in plasma.

Methods

Study population

RA patients were recruited from a previous efficacy study in which some of them had received MMF. All patients showed at least 4 of the 7 diagnostic criteria of the American Rheumatism Association (ARA) for RA. Men wishing to parent children or women of child bearing potential were excluded, as were patients with active medical conditions, severe kidney or liver dysfunction, or who had undergone previous major gastrointestinal surgery.

Use of nonsteroidal anti-inflammatory drugs (NSAIDs) and/or up to 10 mg day^{-1} of prednisone was allowed provided the dose had been stable for at least 2 months. Other concomitant medications were kept constant throughout the study. On the study day, any concomitant medications were administered after the 4 h blood draw. No alcohol was allowed for 72 h before each dosing and until after the final blood draw. Physical examination and routine laboratory tests were performed before and after the study. The study protocol was approved by an Institutional Review Board and all patients gave written informed consent prior to the study start.

Study conduct and plasma analysis

The study was of open-label, single-dose, three-period crossover design, conducted with sequential periods because of the potential dropout rate in this elderly and disabled patient group. Each patient received 2 g (8×250 mg capsules) of MMF (Syntex Research, Palo Alto), administered with 180 ml water on three separate occasions in the following sequence: fasting, after a standardized breakfast, and administered along with antacid. A 1 week washout period separated each treatment.

In each period patients were fasted overnight for at least 9 h. For the fasting period MMF was administered alone with the water. In the fed period, patients received a standardized high fat breakfast composed of 180 ml of orange juice, two scrambled eggs, three strips of bacon, one slice of toast with butter and grape jelly, and one cup of decaffeinated coffee with cream and sugar. This meal had a weight and volume of respectively 536.5 g and 340 ml, was composed of 46.5% fat, 38.9% carbohydrate, 14.8% protein and contained 602 calories. MMF was administered with the water 30 min after the completion of the breakfast. For the antacid period, 10 ml Maalox® TC (Rorer Pharmaceuticals, Fort Washington, PA) containing 1200 mg of aluminium hydroxide and 600 mg of magnesium hydroxide with a neutralising capacity of 56.6 mEq was taken at 08.00 h, 12.00 h, 16.00 h and 20.00 h on the day prior to dosing and at the same times on the day of dosing with MMF. Patients in the fasting and antacid periods continued fasting until 4 h after dosing with MMF.

Heparinized blood samples were collected by venepuncture at baseline, and 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 h after drug administration. Plasma was stored frozen at -20° C until analysis for MPA and MPAG by high performance liquid chromatography (h.p.l.c.) with ultraviolet (u.v.) detection [5]. The quantitation limit for both MPA and MPAG was 0.4 mg ml^{-1}. The interday coefficient of variation was less than 8% for MPA and less than 5% for MPAG.

Safety was monitored by routine clinical laboratory tests and by recording reported adverse events.

Pharmacokinetic and statistical methods

Plasma concentrations that were below the quantitation limit of 0.4 mg ml^{-1} were set to zero for calculation of mean plasma concentration and the computed parameters. Actual sampling times were used in all calculations. MPAG plasma concentrations were converted to 'MPA equivalents' by multiplying each MPAG drug concentration by 0.594 (the ratio of the molecular weight of MPA to the molecular weight of MPAG).

Maximum MPA and MPAG plasma concentration (C_{max}) and time to reach maximum plasma concentration (t_{max}) were obtained directly from the concentration-time data. The area under the plasma concentration-time curve up to 24 h AUC(0, 24 h) was computed using a linear trapezoidal rule. The duration of the sampling interval was too short to obtain a good estimate of terminal half-life and hence terminal half-life and total AUC are not reported.

Analysis of variance (ANOVA) appropriate to a replicate design was performed with the GLM procedure of the Statistical Analysis System (1985 edition. SAS Institute Inc., Cary, North Carolina). The ANOVA model incorporated terms for patient and treatment. Ninety percent classical confidence intervals (CI) were computed [6] as the ratio of each parameter for MPA and MPAG with the fasted result as the reference parameter. Statistical equivalence was determined by comparing these intervals to the equivalence interval of 80 to 120%.

Results

One patient withdrew from the study prior to dosing and another patient withdrew after the initial dose of MMF following an adverse event. They were not replaced, leaving 10 analysable patients. Mean (s.d.) age, weight, and height of the 10 patients (six females and four males) completing the study were 55.6 (10.5) years,

73.4 (13.2) kg, and 1.65 (0.07) m respectively. Six of the patients had previously received MMF, but in all cases dosing had ended at least 3 months prior to the present study. Nine and seven respectively of the 10 patients were taking concomitant prednisone and NSAIDs. Mean plasma MPA and MPAG concentrations are plotted on a logarithmic scale in Figures 1a and 1b respectively. Computed parameters are shown in Table 1.

Statistically significant differences in the mean plasma MPA concentrations were seen by ANOVA at 1 and 2 h, but not at any other sampling times. Median t_{max} was the same at 1 h in the fasting and antacid periods, but was 2 h after food. MPA C_{max} showed statistically significant differences by ANOVA, with a higher C_{max} in the fasting period than in the fed or antacid period. The mean (90% CI) C_{max} ratio for the fed to the fasted period was 75.4 (56.8–94.0)%, and to the antacid period was 62.3 (43.7–80.9)%. AUC(0, 24 h) was similar with and without food: the mean (90% CI) ratio for the fed to the fasted period was 97.0 (85.3–108.7)%. Mean AUC(0, 24 h) in the antacid period was lower than that in the fasting period: the mean (90% CI) ratio for the antacid to the fasted period was 83.2 (71.5–94.9)%. Thus for MPA, C_{max} in the fed state was reduced and not statistically equivalent to that in the fasted state, whereas AUC(0, 24 h) was similar and statistically equivalent. With antacid, both C_{max} and AUC(0, 24 h) were reduced and not statistically equivalent to those in the fasted state.

Table 1 Pharmacokinetic parameters of MPA and MPAG after a single 2 g oral dose of mycophenolate mofetil in 10 rheumatoid arthritis patients

Parameter	*Fasting*	*Fed*	*Antacid*
MPA			
t_{max} (h)	1.0 (0.5–2)	2.0 (0.5–3)	1.0 (0.5–2)
C_{max} (μg ml^{-1})	23.8 ± 11.6	18.0 ± 4.9	14.8 ± 6.7
AUC(0, 24 h) (μg ml^{-1} h)	79.9 ± 23.0	77.5 ± 20.9	66.5 ± 24.6
MPAG (as MPA equivalents)			
t_{max} (h)	2.5 (2–4)	3.0 (2–4)	3.0 (2–4)
C_{max} (μg ml^{-1})	52.7 ± 20.0	68.4 ± 12.7	38.8 ± 12.2
AUC(0, 24 h) (μg ml^{-1} h)	508 ± 168	580 ± 149	455 ± 169

Parameter values are median (range) for t_{max} and mean ± s.d. for C_{max} and AUC(0, 24 h). $P \leq 0.05$ for MPA C_{max}, MPAG C_{max} and AUC(0, 24 h) by ANOVA; $P \geq 0.05$ for all other parameters.

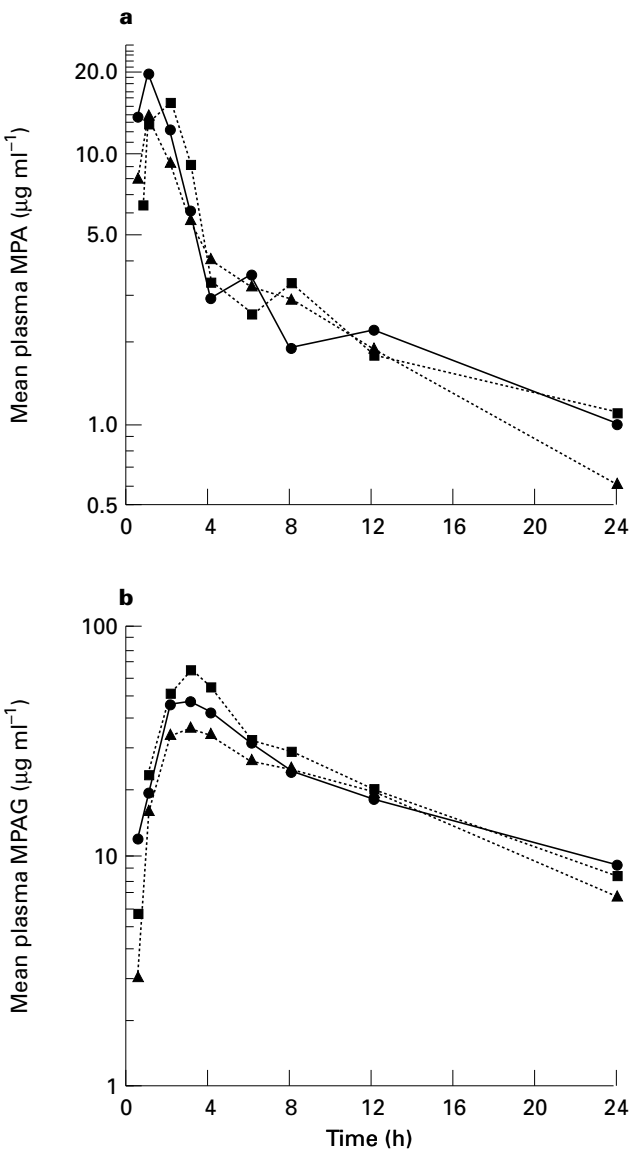

Figure 1 Mean plasma concentrations ($n = 10$) respectively of a) MPA and b) MPAG (in MPA equivalents) in the fasting (●), fed (■) and antacid-treated (▲) state following a single oral dose of 2 g of MMF.

Statistically significant differences by ANOVA in mean plasma MPAG concentrations were seen at 2, 3 and 4 h after dosing. Median t_{max} was close to 3 h following all three treatments. Statistically significant differences in MPAG C_{max} were seen between the treatments, with the fed period having the highest mean C_{max} followed by the fasting and then the antacid periods. The mean (90% CI) ratio of MPAG C_{max} for the fed to the fasted state was 129.8 (113–146.7)%, and for the antacid to the fasted period it was 73.7 (56.8–90.5)%. Differences in MPAG AUC(0, 24 h) were statistically significant by ANOVA. Compared with fasting, mean AUC(0, 24 h) was higher after food and lower after antacid treatment. The mean (90% CI) AUC(0, 24 h) ratio for the fed to the fasting state was 114.1 (102.9–125.4)%, and for the antacid to the fasting period was 89.5 (78.2–100.7)%. Thus for MPAG, both C_{max} and AUC(0, 24 h) in the fed state were increased and not statistically equivalent to those in the fasted state. With antacid, both C_{max} and AUC(0, 24 h) were reduced and not statistically equivalent to those in the fasted state.

One patient, a 71-year old female who had not previously received MMF, withdrew following the first dose administration with myalgia, arthralgia, malaise, chills and fever, and leucocytosis. Steroid dose was increased temporarily and these events resolved completely within 1 week. Plasma MPA and MPAG concentrations in this patient were similar to those from the other study patients. All other patients tolerated the MMF doses well. Six patients experienced at least one

adverse event, with nausea and diarrhoea being the commonest complaints. No clinically significant changes in laboratory tests or on physical examination were observed.

Discussion

Feeding decreased MPA C_{max} and increased t_{max}, but did not affect AUC(0, 24 h). Secondary plasma MPA peaks, occurring at about 6 h postdose when fasting, were delayed with food to around 8 h (Figure 1a). These changes suggest slowed gastric emptying is reducing the rate of drug input, but the MPAG results indicate other processes may also be involved. MPAG C_{max} increased with feeding about the same percent as MPA C_{max} decreased, with little change in t_{max}. The precursor-successor relationship of MPA and MPAG suggests food-induced enhancement of hepatic glucuronidation might explain this reciprocal C_{max} change. Increased biliary excretion could subsequently compensate for lowered MPA plasma concentration via increased EHC, and leave MPA AUC(0, 24 h) unchanged. Lorazepam undergoes hepatic and extrahepatic glucuronidation and EHC [7]. A high-carbohydrate, low-fat diet reduced plasma lorazepam AUC in healthy subjects [8], and decreased plasma AUC of lorazepam glucuronide. The opposite directions of these changes for MMF and lorazepam may arise from differences in the meals, or from more fundamental underlying pharmacokinetic properties of MPA and lorazepam.

Antacid containing aluminium and magnesium hydroxides reduced C_{max} and AUC(0, 24 h) for both MPA and MPAG. The MPA C_{max} decrease was comparable to that with food, and could similarly reflect slowed gastric emptying except t_{max} was not affected. Moreover, the AUC(0, 24 h) decrease arose from reductions in both the initial absorption and secondary peaks (Figure 1a). These parallel effects on MPA and MPAG parameters are most simply explained by reduced absorption in both the initial and EHC phases. From the MPA chemical structure chelation is a possible mechanism. Increase in gastric pH is an alternative, but this should not affect recirculatory absorption and hence AUC(0, 24 h). If pH increase were the mechanism, drugs which inhibit acid secretion should show effects similar to those of antacid.

Do the above changes have clinical consequences? Only the active immunosuppressant MPA need be considered for these purposes. Food or antacid decreased MPA pharmacokinetic parameters, so efficacy is the main concern. MMF is indicated for prevention of acute rejection in renal allograft transplantation. Immunosuppression *in vitro* is rapidly reversed by MPA removal, and shows a plateau of effect [2], suggesting that an important determinant of efficacy is maintaining plasma MPA concentration, for which MPA AUC could be a surrogate. Clinically, a significant relation has been observed between plasma MPA AUC and the probability of rejection [3]. Because C_{max} and AUC correlate, C_{max} also correlates with efficacy. However, from the *in vitro* observations C_{max} should matter only when mean plasma MPA concentrations are well below plateau effect concentrations. Thus, food is predicted to have little effect on MMF efficacy since it affects C_{max} but not AUC(0, 24 h), and consequently there is no compelling pharmacokinetic basis for MMF administration before or with food. In contrast, antacid co-administration could potentially reduce efficacy, since both C_{max} and AUC were reduced. In practice, over 80% of transplant patients receive concomitant antacids. Any practical consequence of the interaction is thus largely abnegated, since the efficacious dose was determined in clinical studies where an antacid/MMF interaction was already present in most patients.

In conclusion, co-administration of a high fat meal or antacid with MMF leads to statistically significant changes in the plasma pharmacokinetics of MPA and MPAG. These differences are small compared with the interpatient variability, and in therapeutic use are not likely to have clinically significant effects.

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