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Mycophenolic acid plasma concentrations in kidney allograft recipients with or without cyclosporin: a cross-sectional study

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Abstract

Background. Combining cyclosporin (CsA) and prednisone with mycophenolate mofetil (MMF) results in a significant reduction in the rate of biopsy-proven acute rejection after kidney transplantation. This is achieved with a standard daily MMF dosage of 2 or 3 g. Whether monitoring of the pharmacologically active metabolite mycophenolic acid (MPA) will lead to improved safety and efficacy is unclear.

Methods. We monitored MPA trough levels in 18 kidney transplant recipients treated with CsA, prednisone, and MMF (63 samples) and in 11 patients (31 samples) treated with prednisone and MMF only, in a cross-sectional study. All patients were at least 3 months after transplantation with stable graft function. All patients were treated with 2 g MMF for at least 3 months and 10 mg prednisone.

Results. The MPA trough levels in the CsA-treated patients were significantly lower ($P<0.0001$; Mann–Whitney) than those in patients on MMF and prednisone only (mean MPA levels 1.98 ± 0.12 *vs* 4.38 ± 0.40 mg/l respectively).

Conclusions. Although all patients were treated with an identical MMF dose, a significant difference was found in the MPA trough levels between CsA- *vs* non-CsA-treated patients. This suggests that CsA influences the MPA trough level. The level at which CsA affects the MPA trough levels is unclear.

Key words: mycophenolate mofetil; drug monitoring; kidney transplant recipients

Introduction

Three large, double-blind, randomized trials have shown that the addition of mycophenolate mofetil (MMF) to an immunosuppressive regimen consisting of cyclosporin (CsA) and prednisone results in a significant reduction in the rate of biopsy-proven acute rejection during the first 6 months after kidney transplantation [1–3]. The size of the reduction in incidence and severity of acute rejection episodes for patients treated with 2 or 3 g MMF was similar; however, the 3-g dose was somewhat less well tolerated [1–4]. Therefore, the current daily dose recommendation is 2 g [5].

Following oral administration MMF is rapidly and essentially completely absorbed and converted to mycophenolic acid (MPA), the active immunosuppressant [6–7]. The sole metabolite of MPA is the glucuronide conjugate MPAG, which is pharmacologically inactive [6–8]. Although clear conclusions have been drawn with regard to clinical efficacy of MMF [1,3], data confirming the usefulness of monitoring MPA concentrations or defining a therapeutic window in terms of plasma MPA concentrations are not available. So far, the simplicity of fixed dosing (2 g MMF), with the exception of dosing by body size at the extremes in adults and in children [9], is recommended for clinical practice [6]. Results of clinical trials investigating the potential role of therapeutic drug monitoring in MMF treated transplant recipients are not available so far.

Drug interactions with MMF include decreased absorption when coadministered with magnesium and aluminium hydroxide antacids [5]. Cholestyramine decreases bioavailability by interfering with the enterohepatic recirculation [10]. MPA is conjugated to the inactive MPAG [6,7]. CsA is extensively metabolized via the cytochrome P-450 system, an enzyme complex including enzymes that have a role in conjugation [10]. No interaction between CsA and MMF has been reported [10]. Tacrolimus and CsA are believed to be metabolized by a common pathway [11]. A recent paper showed higher MPA trough levels and increased AUC_{0-12} values in kidney recipients receiving tacrolimus + MMF compared to patients receiving CsA + MMF [12]. The authors suggested an inhibitory effect of tacrolimus on the conversion of MPA to MPAG to be the mechanism of interaction. However, the data we present in this paper show in fact that the CsA-treated patients have relatively low MPA levels.

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Subjects and methods

In a cross-sectional study we examined the effect of CsA on MPA trough levels. Included were 11 patients treated with MMF and prednisone, 1 year post-transplant, the 'non-CsA group'. All 11 patients had been on MMF treatment for at least 3 months and had stopped CsA treatment for at least 2 months.

From January 1997 all new kidney transplant recipients are treated with a triple-drug regimen consisting of CsA + MMF + prednisone during the first 6 months after transplantation. These patients form the 'CsA group'. All MPA samples from the 18 patients in this group were also drawn after treatment with CsA and MMF for at least 3 months. The median time from transplantation was 5 months (3–10) in the CsA group.

Fasted plasma MPA trough levels (EMIT–Mycophenolic Acid Assay, Behring Diagnositics Inc, San Jose, Ca, USA) were routinely measured from February 1997, always 12 h after the previous dose. This immunoassay has been reported to give good agreement with an HPLC assay [13]. For CsA whole-blood trough levels the EMIT immunoassay was also used. For both CsA and MPA we participate in the quality assessment scheme from Dr Holt, St George's Hospital, London [13].

Results

Figure 1 shows the clear difference in MPA trough levels between the two groups. In the CsA group MPA trough levels ranged from 0.49 to 4.98 mg/l (mean 1.98 ± 0.12, median 2.02), whereas the range in the non-CsA group was from 1.02 to 9.30 mg/l (mean 4.38 ± 0.40, median 3.75). The difference between the two groups is highly significant (two-sided P-value <0.0001; Mann–Whitney test). The median serum creatinine levels in the CsA-treated patients was 118 μmol/l (range 61–246, mean 124) and not different from the non-CsA-treated patients (median 110, range 72–213, mean 118, $P=0.72$). The average prednisone dose in the CsA-treated patients was comparable to the non-CsA-treated patients (10 mg). None of the patients in either group used any drug known to interact with MMF, nor was a pattern present with any drug being more prominent in either group.

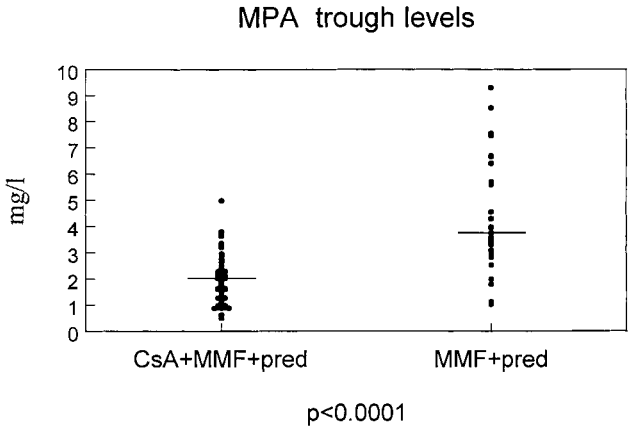

Fig. 1. Mycophenolic acid trough levels in 18 kidney transplant recipients treated with CsA + MMF + prednisone ($n=63$ samples) and in 11 kidney transplant recipients treated with MMF + prednisone only ($n=31$ samples). The difference is statistically significant ($P<0.0001$ Mann–Whitney test).

The median body weight and height of the CsA *vs* the non-CsA-treated group was 78 kg (62–92) *vs* 82 kg (61–100) and 176 cm (159–193) *vs* 174 cm (153–185) respectively. This was not a statistically significant difference for weight ($P=0.5$, Mann–Whitney) or height ($P=0.7$, Mann–Whitney). The intraindividual range for MPA trough levels per patient in the CsA *vs* the non-CsA treated group is shown in Table 1.

Discussion

For tacrolimus and CsA most clinicians agree that routine drug monitoring improves the safety and efficacy of these drugs in transplant recipients. Although in kidney transplant recipients a clear reduction in the incidence of acute rejections with MMF has been found [1,4], a further improvement of the outcome using therapeutic drug monitoring still has to be shown. This holds true for MPA monitoring in relation to acute rejection as well as to side-effects.

This paper shows the results of MPA monitoring in two groups of kidney transplant recipients. Although all patients were being treated with a total daily dose of 2 g MMF, a highly significant difference in MPA concentrations was found between the patients treated with CsA + MMF + prednisone and those treated with MMF + prednisone only. How CsA and MMF interact cannot be concluded from this study. Interaction at the level of absorption is unlikely, as bioavailability of MMF is reported to be almost 100% in healthy controls as well as in transplant recipients. However, within the

Table 1. Fluctuation of MPA trough levels (median + range) for individual patients in the CsA (CsA + MMF + prednisone) and non-CsA-treated (MMF + prednisone) groups

Patient	CsA-treated group ($n=18$)	Non-CsA-treated group ($n=11$)
1	1.05 (0.98–1.11)	3.43 (2.52–7.55)
2	2.39 (2.11–3.20)	4.30 (3.97–6.41)
3	2.43 (1.98–2.67)	4.11 (3.94–4.28)
4	1.09 (0.88–1.82)	1.02
5	2.02 (1.23–2.37)	1.8
6	1.05	1.79
7	2.1 (2.06–2.70)	5.63 (3.75–7.51)
8	0.57 (0.49–0.92)	5.71 (2.0–7.46)
9	2.31 (1.32–2.64)	3.34 (1.12–4.55)
10	3.74 (3.35–4.98)	8.53 (6.67–9.3)
11	2.77	3.6
12	1.48 (0.88–2.14)	
13	2.39 (1.56–2.96)	
14	2.28 (1.27–2.92)	
15	1.64 (1.12–1.75)	
16	1.22 (0.88–1.92)	
17	2.28 (2.02–2.93)	
18	2.97 (2.24–3.63)	

first weeks after transplantation absorption from the gut may be suboptimal in patients with a long history of uraemia. In this study all patients were at least 3 months post-transplantation, making it unlikely that differences in absorption explain the difference in MPA levels. In view of the similar serum creatinines in both groups, differences in renal function are also unlikely to be the cause.

Whether there is a certain therapeutic window of optimal MPA levels is unclear so far. A relation has been suggested for the concentration of the MPA level and the amount of immunosuppression, measured by the IMPDH activity which could be seen as an indirect measurement for synthesis of T and B lymphocytes [14]. There are unfortunately no clinical studies published yet which relate MPA levels to rejection rates, to provide tailor-made immunosuppression for the individual patient.

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References

1. European Mycophenolate Mofetil Cooperative Study Group. Placebo-controlled study of mycophenolate mofetil combined with cyclosporin and corticosteroids for prevention of acute rejection. *Lancet* 1995; 345: 1321
2. The Tricontinental Mycophenolate Mofetil Renal Transplantation Study Group. A blinded, randomized clinical trial of mycophenolate mofetil for the prevention of acute rejection in cadaveric renal transplantation. *Transplantation* 1996; 61: 1029
3. Sollinger HW, for the US Renal Transplant Mycophenolate Mofetil Study Group. Mycophenolate Mofetil for the prevention of acute rejection in cadaveric renal allograft recipients. *Transplantation* 1995; 60: 225
4. Halloran P, Mathew T, Tomlanovich S *et al*. Mycophenolate mofetil in renal allograft recipients. A pooled efficacy analysis of three randomized double-blind, clinical studies in prevention of rejection. *Transplantation* 1997; 63: 39
5. Lipsky JL. Mycophenolate mofetil. *Lancet* 1996; 348: 1357
6. Bullingham RES, Micholls A, Hale M. Pharmacokinetics of mycophenolate mofetil (RS61443): a short review. *Transplant Proc* 1996; 28: 925
7. Fulton B, Markham A. Mycophenolate mofetil. A review of its pharmacodynamic and pharmacokinetic properties and clinical efficacy in renal transplantation. *Drugs* 1996; 51: 278
8. Nowak I, Shaw LM. Effect of mycophenolic acid glucuronide on inosine monophosphate dehydrogenase activity. *Ther Drug Monit* 1997; 19: 358
9. Filler G, Ehrich J. Mycophenolate mofetil for rescue therapy in acute renal transplant rejection in children should always be monitored by measurement of trough concentration. *Nephrol Dial Transplant* 1997; 12: 374
10. Seifeldin R. Drug interactions in transplantation. *Clin Ther* 1995; 17: 1043
11. Christians U, Braun F, Sattler M *et al*. Interactions of FK506 and cyclosporine metabolism. *Transplant Proc* 1991; 23: 2794
12. Zucker K, Rosen A, Tsaroucha A *et al*. Augmentation of mycophenolate mofetil pharmacokinetics in renal transplant patients receiving Prograf and Cellcept in combination therapy. *Transplant Proc* 1997; 29: 334
13. Holt DW, Jones K, Lee T, Stadtler P, Johnston A. Quality assessment issues of new immunosuppressive drugs and experimental experience. *Ther Drug Monit* 1996; 18: 362
14. Langman LJ, LeGatt DG, Halloran PF, Yatscoff RW. Pharmacodynamic assessment of mycophenolic acid-induced immunosuppression in renal transplant recipients. *Transplantation* 1996; 62: 666

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