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Mycophenolate mofetil in patients with acute renal failure: evidence of metabolite (MPAG) accumulation and removal by dialysis

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Abstract Pharmacokinetics of mycophenolic acid (MPA) was analyzed in eight patients with posttransplant acute renal failure. Furthermore, the effect of hemodialysis upon blood levels of MPA and its major metabolite, MPA glucuronide (MPAG), was determined. The mean duration of the posttransplant renal failure was 18 days, but renal function resumed in all patients eventually. The patients were treated with 3 g/day of mycophenolate mofetil for 28 consecutive days combined with cyclosporine A, methylprednisolone, and ATG for induction therapy. In all patients, accumulation of MPAG but not of MPA was observed. MPA trough levels were in the range between 0.5 μg/ml at day 2 and 2.3 μg/ml at the end of the study period. However, this concentration difference did not reach statistical significance. Trough levels of MPAG accumulated, reaching levels as high as 358 μg/ml. However, with increasing recovery of renal function, MPAG levels fell to a median trough concentration of 141 μg/ml. MPAG, but not MPA, could partially be removed from the circulation by hemodialysis treatment.

Key words Immunosuppression · Drug accumulation · Renal failure · Hemodialysis

Introduction

Mycophenolic acid (MPA) is a powerful new immunosuppressive drug. MPA is a non-nucleotide inhibitor of the type 2 isoform of inosine monophosphate dehydrogenase (IMPDH), a key enzyme of guanosine nucleotide metabolism in activated lymphocytes [1–3]. Stimulation of T- and B-lymphocytes increases the de novo synthesis of guanosine nucleotides as a prerequisite for DNA synthesis. Most eukaryotic cells can use two major pathways of purine nucleotide synthesis, but lymphocytes are totally dependent upon IMPDH-catalyzed de novo synthesis. MPA is a potent inhibitor of IMPDH type 2, blocking the de novo synthesis of guanosine nucleotides by 40–80 %. In contrast to other cell types, lymphocytes lack the salvage pathway of purine synthesis. For this reason, actively dividing lymphocytes of T- and B-lineage are highly susceptible to MPA. Mycophenolate mofetil (MMF) is the ester prodrug of the active moiety, MPA. After oral administration, MMF is extensively absorbed and undergoes a presystemic metabolism to MPA, which is the active compound. The major metabolite of MPA is MPA glucuronide (MPAG). This metabolite is inactive and is mainly eliminated via urinary secretion and, to some extent, into the feces. The efficacy, safety, and tolerability of MMF as an immunosuppressant have been demonstrated in a variety of clinical studies [4]. However, the potential clinical impact and pharmacokinetics of repeated dosing of MMF in patients with renal insufficiency are not completely established. Single-dose administration of MMF to patients with severe chronic renal insufficiency yielded an increase of the area under the curve (AUC) compared to that of healthy individuals and the AUC of MPAG was increased up to sixfold. Therefore, we aimed to analyze the pharmacokinetics of MPA and its major metabolite,

MPAG, in patients receiving multiple dosing of MMF in the setting of posttransplant acute renal failure and hemodialysis treatment.

Patients and methods

After written informed consent, eight patients with acute renal failure of the cadaver renal allograft were studied. In all patients, renal function eventually resumed after a mean duration time of 18 days (6–39 days) posttransplantation. The immunosuppressive induction treatment consisted of ATG (Fresenius, Bad Homburg), 4 mg/kg body weight for 7 days; cyclosporine A (Sandimmun; Sandoz, Nürnberg) 6 mg/kg body weight/day; methylprednisolone (Urbason; Hoechst, Hoechst) 20 mg/day; MMF 1.5 g twice daily, kindly provided by Syntex, given orally for 28 consecutive days. Trough blood levels of MPA and MPAG were determined by means of high-pressure liquid chromatography (HPLC; Medeval, USA). In addition, 12 h profiles of plasma concentrations were performed at days 1, 7, 14, 21, and 28 of MMF treatment. In patients requiring hemodialysis, the blood levels of MPA and MPAG were also determined during dialysis treatment.

Results

MPA and MPAG levels were determined in eight patients with acute posttransplant renal failure (ARF). The duration of ARF was a mean time of 18 days (range 6–39 days). The patients were treated with 3 g MMF daily for 28 consecutive days according to our protocol. Median values of MPA trough levels were found in the range between 0.6 μg/ml ± 0.42 μg/ml at day 2 and 2.35 μg/ml ± 1.1 μg/ml at day 28 of the study period (Table 1). Concomitantly, MPAG accumulated, starting from a median value of trough levels between 59.5 ± 85.55 μg/ml at day 2 and reaching a plateau of 358 ± 117.35 μg/ml between day 10 and day 16. With increasing recovery of renal function, indicated by a constant fall of the serum creatinine and a glomerular filtration rate (GFR) exceeding 20 ml/min, the median trough levels of MPAG decreased to 141 ± 43.8 μg/ml, indicating renal excretion of MPAG (Table 2).

In patients undergoing hemodialysis therapy, plasma levels of MPA and MPAG were determined. After 1 h of hemodialysis, blood samples were drawn simultaneously from the afferent arterial (input coil) and the efferent venous (output coil) bloodstream. Under these conditions, MPA mean concentration in the input coil was 2.55 μg/ml and in the output coil 2.49 μg/ml, indicating that MPA was not substantially removed by hemodialysis. In contrast, the mean concentration of MPAG decreased from 118.7 μg/ml in the input coil to 101 μg/ml in the output coil. The amount of MPAG removed from the circulation through dialysis was dependent upon the blood concentration. Starting with mean blood concentrations of MPAG of 80 μg/ml in the input coil, the mean concentration found in the output coil was essentially the same. In subjects with a mean concentration of MPAG of 188 μg/ml in the input coil, the mean concentration of MPAG was decreased to 137 μg/ml in the output coil.

Table 1 Mycophenolic acid *(MPA)* trough levels from eight patients treated with 3 g mycophenolate mofetil (MMF) daily. All patients suffered from acute posttransplant renal failure. This increase of MPA levels during the study period of 28 days did not reach statistical significance

Day	Median MPA concentration (μg/ml)	SD	95 % confidence
2	0.6	0.42	0.309
4	1.05	0.96	0.665
6	2.1	3.46	2.401
8	1.95	1.20	0.834
10	1.85	1.84	1.272
12	1.35	1.71	1.186
14	2.5	2.42	2.125
16	1.6	0.80	0.591
18	1.65	1.37	1.097
20	2.1	1.97	1.458
23	3.25	2.47	2.425
28	2.35	1.10	0.760

Table 2 Mycophenolic acid glucuronide *(MPAG)* trough blood levels from eight patients treated with 3 g MMF daily. All patients suffered from acute posttransplant renal failure. The accumulation of MPAG resolved with recovery of renal function. MPAG concentrations are given as median values from eight patients

Day	Median MPAG concentration (μg/ml)	SD	95 % confidence
2	59.5	85.55	59.28
4	115	85.57	63.39
6	192	140.18	97.14
8	200	146.26	108.35
10	331	144.93	107.36
12	358	117.35	81.32
16	343	71.58	53.03
18	217	85.31	63.20
20	200.5	50.50	69.99
21	148	47.47	41.61
23	149	78.49	76.92
28	141.5	43.80	30.35

Discussion

The efficacy, safety, and tolerability of MMF as an immunosuppressant have been demonstrated in a variety of clinical studies [4]. However, the potential clinical impact and pharmacokinetics of repeated dosing of MMF in patients with renal insufficiency has not been completely established. Therefore, this small study was undertaken in order to gain more insight into the pharmacokinetics of MPA and its major metabolite, MPAG, in patients receiving multiple dosing of MMF in the setting

of posttransplant acute renal failure and hemodialysis treatment. After oral administration, the ester prodrug, MMF, is converted into the active immunosuppressant, MPA. More than 99 % of the MPA is bound to plasma proteins and is rapidly metabolised into the functionally inactive compound, MPAG. In eight patients treated with 1.5 g of MMF twice daily, the 12-h trough levels of MPA and MPAG were determined every other day by means of HPLC. After 4 days, the median concentrations of MPA from the eight patients were in the range of 2 μg/ml and there was no further increase reaching statistical significance. In contrast, trough levels of MPAG accumulated over time, but resolved with recovery of renal function. Protein binding of MPAG varies and the bound fraction reaches 82 %. However, with renal failure, the protein-bound fraction can decrease to 60 %. Only the free fraction of MPAG can be removed from the plasma by means of dialysis. These preliminary data reveal that dose adjustment of MMF according to the renal function or substitution after hemodialysis are not required, as deduced from this small single-centre study. However, with prolonged renal failure, patients should be monitored carefully for symptoms of drug toxicity and over-immunosuppression.

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