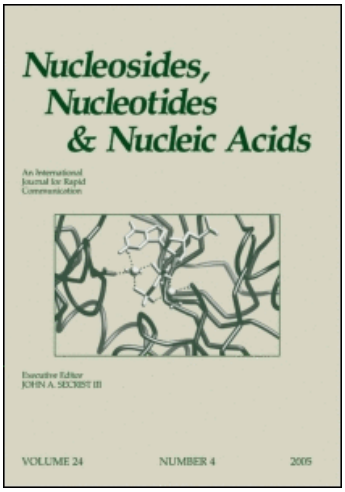

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GTP Concentrations are Elevated in Erythrocytes of Renal Transplant Recipients when Conventional Immunosuppression is Replaced by the Inosine Monophosphate Dehydrogenase Inhibitor Mycophenolic Acid Mofetil (MMF)

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ABSTRACT

We show that GTP concentrations rise in the erythrocytes of renal transplant recipients receiving the immunosuppressant MMF, and demonstrate that this effect is not caused by poor renal function after engraftment. We propose a model that is consistent with our observations.

Key Words: Mycophenolic acid; MMF; Immunosuppressant; GTP; Renal transplant.

INTRODUCTION

The immunosuppressant mycophenolate mofetil (MMF) is increasingly replacing azathioprine (AZA) in renal transplantation. MMF is a pro-drug of mycophenolic acid

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(MPA) which inhibits IMP dehydrogenase, thereby reducing GTP synthesis essential for lymphocyte proliferation. Paradoxically, high GTP concentrations have been noted in erythrocytes of heart transplant patients receiving MMF,[1] and in the erythrocytes of immunodeficient children treated with another IMPDH inhibitor, Ribavirin.[2]

Erythrocyte GTP concentrations are commonly elevated during renal failure, but normalise following successful kidney engraftment.[3] Consequently we investigated whether elevated GTP in renal transplant recipients might reflect poor renal function and/or impending graft failure.

METHODS

We measured nucleotides (erythrocytes) using anion-exchange HPLC, and RPLC for metabolites (plasma) in the blood samples from two groups of 25 patients, matched for age and time elapsed since transplant. Both groups were receiving prednisolone and cyclosporin A. One group received azathioprine (AZA) as part of the conventional immunosuppression, the other group received MMF either because of a history of chronic allograft nephropathy, or for acute cellular rejection shortly after engraftment.

RESULTS

The patients receiving MMF therapy had higher mean concentrations of creatinine (217.9 ± 97.1 μmol/l) and of GTP (125 ± 68.2 μmol/l) than did those receiving standard immunosuppression (creatinine, 131.5 ± 38.8 μmol/l; GTP, 40.4 ± 15.9 μmol/l). Data from individual patients show that GTP concentrations rose within a few weeks of beginning MMF, stabilising at a significantly higher mean value of 146.7 ± 62.9 μmol/l after four months. Closer examination of the data (Table 1) showed that

Table 1. The rise in GTP concentrations does not signal poor renal function.

A: 25 renal transplant patients placed on therapy including MMF		
Months MMF therapy	GTP (erythrocytes) μmol/l	Creatinine (plasma) μmol/l
0–3 months	50.4 ± 23.4	293 ± 71.4
4–8 months	136.5 ± 57.2	225 ± 106.9
More than 8 months	154.3 ± 68.4	177.6 ± 82.2
B: 25 renal transplant patients placed on therapy including AZA		
Months since transplant	GTP (erythrocytes) μmol/l	Creatinine (plasma) μmol/l
0–3 months	36.3 ± 11.8	99.0 ± 14.9
4–8 months	39.7 ± 29.0	131.8 ± 18.3
More than 8 months	41.6 ± 13.7	139.1 ± 42.8
Reference values:	46 ± 9 (adults)	65–101(male) 80–122(female)

plasma creatinine concentrations decreased during therapy with MMF, despite the increase in GTP concentrations in the erythrocytes. In the AZA group, GTP remained constant while creatinine increased slightly.

DISCUSSION

Our data confirm that GTP concentrations increase in erythrocytes of renal transplant recipients receiving MMF. The rise is a direct effect of exposure to MPA, and is not caused by poor function of the transplanted kidney, since GTP continues to rise while creatinine values fall (reflecting improved kidney function).

We propose the following mechanism for the apparent 'up-regulation' in the GTP concentrations and IMPDH activity in erythrocytes: MPA binds to the active site of IMPDH in developing red cells, and stabilises its structure[4] so that mature red cells retain IMPDH activity, thus continuing to make GTP. The time–course of the increase in GTP parallels the time (approx. 3 months) required to replace erythrocytes in circulation. Thus, a high GTP concentration in erythrocytes reflects compliance with MMF therapy, and does not imply rejection of the kidney transplant.

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