Case Report

Interaction between theophylline and tacrolimus in a renal transplant patient

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Introduction

Tacrolimus is a calcineurin inhibitor. It is a potent immunosuppressive drug which has been approved in several countries. It is currently indicated for both prophylaxis and treatment of allograft rejection. Metabolism of tacrolimus occurs primarily in the liver via the cytochrome P450-3A4 (CYP3A4) enzyme system. There are many potential drugs interacting with tacrolimus which should be used with caution, particularly in patients who are concurrently taking CYP3A4 inhibitors or inducers [1,2]. We report herein the first case of tacrolimus and theophylline interaction in a renal transplant recipient.

Case

In March 1998, a 33-year-old man with end-stage renal disease due to diabetic nephropathy received a cadaveric kidney allograft. He had no history of cardiac or pulmonary disease. Post-transplantation maintenance immunosuppressive therapy included tacrolimus (7 mg/d), azathioprine (75 mg/d) and prednisone (7.5 mg/d). The patient was also receiving insulin with no other drugs. The post-operative course was uneventful with no rejection episodes and no hypertension. At discharge, the serum creatinine was 110 μmol/l. White blood count (WBC), haemoglobin (Hb) and haematocrit (Hct) values were 3870/mm³, 12.3 g/dl and 43% respectively. The tacrolimus trough blood concentration (tacrolimus TBC) assayed using a microparticle enzyme immunoassay and IMx autoanalyser, was stable within normal ranges (normal range, 5–15 ng/ml).

In May 1998, the patient developed post-renal-transplant erythrocytosis. Hb and Hct values rose to 19.4 g/dl and 54% respectively. WBC remained within normal range at 8340/mm³. Isotopic measurement of the red cell mass confirmed absolute moderate polycythemia. Serum erythropoietin (Epo) level was increased at 37 mIU/ml (normal 10–25). The kidney, liver, and spleen sonograms were normal. Allograft and native renal artery Doppler ultrasound images did not reveal any stenosis. In order to reduce Epo production, the angiotensin-converting enzyme inhibitor (ACEi) enalapril was added to the treatment, but without success. During a period of 3 months, eight phlebotomy sessions (300–400 ml/session) were used to control Hb levels. In October 1998, in order to reduce the need for phlebotomies, theophylline (600 mg/day) was added to the ACEi. After 1 month, serum creatinine and tacrolimus TBC rose to 145 μmol/l and 16 ng/ml respectively. Therefore, the theophylline dose was reduced to 300 mg/day four times weekly, which led to a significant reduction in the number of necessary phlebotomy sessions. Only two further phlebotomies were required to keep Hb and Hct levels within acceptable ranges. One month later, serum creatinine and tacrolimus TBC increased further to 173 μmol/l and 48.5 ng/ml respectively (Figure 1). Although theophylline serum concentrations remained low (2 and 6.7 mg/l; normal range 10–15), this drug was discontinued and both renal function and tacrolimus TBC rapidly returned to normal values. ACEi was replaced without further success by losartan, a specific angiotensin-II (A-II) receptor antagonist (25 mg/d). Therefore, the patient was readmitted for reintroduction of theophylline at a lower dose. At this time, the pharmacokinetics of tacrolimus were assessed. The patient was kept on the same doses of maintenance anti-rejection treatment, insulin therapy and losartan. Theophylline (125 mg/d) was administered from day one to day 4. Tacrolimus pharmacokinetics were...
Various causes have been suggested to explain this phenomenon [4–7]. It is thought to be a self-limiting process that requires appropriate management, including supportive therapy (phlebotomy) and a pharmacological approach in order to block Epo secretion. Options in this regard have included ACEi, specific A-II receptor antagonists and theophylline [8–10]. A number of clinically relevant interactions between calcineurin inhibitors and co-administered drugs have been reported [1,2,11]. However, to the best of our knowledge, no case of calcineurin inhibitor–theophylline interaction has been previously reported.

It is well known that CYP3A4 is primarily responsible for tacrolimus liver biotransformation. Substances known to inhibit CYP3A4 may decrease tacrolimus metabolism and thereby increase its blood concentrations. Aminophylline is rapidly hydrolysed during its first pass, which leads to the formation of the active compound theophylline [12]. CYP1A2 is considered to be the most important enzyme involved in theophylline liver metabolism [13], while CYP3A4 has a minor role in theophylline metabolism. It is therefore surprising that the tacrolimus–theophylline interaction appears in this matter.

In vitro, theophylline concentration, at 10 times molar excess of tacrolimus, barely inhibits (by 5%) CYP3A4 tacrolimus metabolism [14]. In the present case, at the time of interaction and despite low-dose theophylline, the calculated theophylline–tacrolimus concentration molar ratio was about 750. If the above in vitro findings are taken into consideration, this interaction may be explained by the very high ratio of theophylline/tacrolimus molar concentrations, as in fact expected when these two drugs are used concomitantly.

Conclusions

Theophylline interacts with tacrolimus liver metabolism by inhibiting the CYP3A4. Although in the present case a low theophylline dose led to tacrolimus AUC increase, renal function remained stable. Therefore low-dose theophylline can be used in transplant patients with erythrocytosis, provided that tacrolimus concentrations are closely monitored.

References


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