Acetazolamide may provoke cyclosporine toxicity—a case report

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Abstract
We describe a 58-year-old female renal transplant recipient with standard cyclosporine-based immunosuppression who developed a potentially toxic cyclosporine concentration of 265 ng/ml after having started acetazolamide for severe glaucoma. The mechanism explaining the interaction between acetazolamide and cyclosporine remains unknown, but the concomitant use of these agents is not uncommon. The follow-up of cyclosporine concentrations is necessary, and the reduction of the cyclosporine dose is likely to be needed when patients taking cyclosporine are started with acetazolamide.

Keywords: acetazolamide; cyclosporine; drug interactions; renal transplantation

Introduction

The common use of cyclosporine as an immunosuppressive agent exposes the patients with organ transplants to multiple drug interactions. Additionally, some interactions are still poorly recognized. Only one animal study, one case report and one case series of three patients published to date describe the possible interaction between cyclosporine and acetazolamide [1–3]. Acetazolamide is a carbonic anhydrase inhibitor commonly used for the treatment of glaucoma and petit mal epilepsy. In glaucoma, it decreases the production of aqueous humour and hence lowers the intra-ocular pressure. We describe a renal transplant recipient with standard cyclosporine-based immunosuppression, who developed a potentially toxic cyclosporine concentration after having started acetazolamide for severe glaucoma.

Case report

A 58-year-old woman with nephropathy caused by type 2 diabetes received a cadaveric renal transplant in May 2003. The function of the transplant was unproblematic. She had standard triple immunosuppression with cyclosporine, mycophenolate mofetil and methylprednisolone. Early on, the dose of mycophenolate was reduced to 500 mg daily due to the elevation of liver enzyme activities. The cyclosporine dose had stabilized at 150 mg and 175 mg every other day, divided into two daily doses, with which the blood cyclosporine level was in the upper target range of 90–140 ng/ml as tested by the fluorescence polarization assay. Other medications included bisoprolol, felodipine, telmisartan, furosemide, simvastatin, gabapentin, subcutaneous glargine and aspart insulin, and topical timolol and iopidine for glaucoma. In May 2006, allopurinol was started for hyperuricaemia. In August 2006, her blood cyclosporine level was 142 ng/ml while serum creatinine was 110 μmol/l.

In August 2006, an ophthalmologist detected severe neovascular glaucoma, and acetazolamide 125 mg t.i.d. was started. A week later, the patient reported having nausea and heartburn. In September, gastroduodenitis and oesophagitis were detected by gastroscopy. Pantoprazole 40 mg daily was started. In November 2006, on a routine control, a high cyclosporine level of 265 ng/ml was detected with slightly elevated serum creatinine (113 μmol/l). Cyclosporine concentration was controlled immediately and a high level of 239 ng/ml was again detected. The dose of cyclosporine was reduced to 150 mg daily. A week later, her cyclosporine level was still 187 ng/ml and slight tremor of the hands was noted as a possible sign of cyclosporine toxicity. Three weeks later, cyclosporine level was 220 ng/ml. The dose of cyclosporine was then reduced to 125 mg daily. Subsequently, the blood cyclosporine level started to gradually decrease and stabilized at the level of 99 ng/ml.

Discussion

We reported a patient with a symptomatic, nearly a 2-fold increase in the blood cyclosporine level due to the interaction between acetazolamide and cyclosporine. The observed increase in the blood cyclosporine level was moderate compared with the few previous human reports on this interaction that have reported as high as a 6-fold...
Acetazolamide may provoke cyclosporine toxicity increase in the whole blood cyclosporine concentration after the co-administration of acetazolamide [2,3]. Apparently, most nephrologists and ophthalmologists treating transplant recipients are not aware of this potentially hazardous drug interaction.

Cyclosporine is mainly metabolized in the liver through the cytochrome P-450 microsomal enzyme 3A4 (CYP3A4), and it is a substrate and inhibitor of the transporter protein P-glycoprotein. Cyclosporine is especially prone to interactions with drugs affecting the CYP3A4 metabolic route or P-glycoprotein activity. However, to our knowledge, no studies reporting acetazolamide affecting the CYP enzymes or the P-glycoprotein pathway are available to date. Thus, the mechanism explaining the interaction between acetazolamide and cyclosporine remains unknown.

Regarding other medications of the present patient, the proton pump inhibitor, pantoprazole, shares the CYP3A4 isoenzyme with cyclosporine for the first metabolic step, and additionally, proton pump inhibitors have been shown to inhibit the P-glycoprotein in vitro [4], indicating the possibility of a drug interaction with cyclosporine. However, a controlled trial of six renal transplant recipients on cyclosporine-based immunosuppression reported no effect of pantoprazole on the cyclosporine concentrations [5]. Additionally, there are a few case reports describing that the co-administration of allopurinol and cyclosporine may result in an elevated cyclosporine level [6,7]. Following 3 months of allopurinol administration, prior to the introduction of acetazolamide, our patient had, however, a normal cyclosporine concentration detected. Thus, neither the co-administration of pantoprazole nor of allopurinol seems likely to have caused the observed increase in the cyclosporine concentration.

The present case describes a potentially important effect of acetazolamide on cyclosporine clearance. It seems that the magnitude of the effect of acetazolamide on blood cyclosporine concentration is highly variable. The concomitant use of cyclosporine and acetazolamide is not uncommon, and therefore clinicians should be aware of this interaction. An intensive follow-up of cyclosporine concentration is warranted when patients taking cyclosporine are started with acetazolamide and the reduction of cyclosporine dose is likely to be needed.

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