

Case Report

Ranolazine can markedly increase tacrolimus blood levels

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Abstract

We report the case of a renal transplant patient on tacrolimus who developed a fully reversible renal failure and a doubling in serum tacrolimus closely associated with initiation of ranolazine (Ranexa) treatment, a new anti-angina drug recently introduced in Europe.

Keywords: interaction; Ranexa; ranolazine; tacrolimus

Background

Many drugs can interfere with the metabolism of calcineurin inhibitors, which are the backbone of anti-rejection therapies. Here, we present the case of a renal transplant patient on tacrolimus who developed a fully reversible renal failure and a doubling in serum tacrolimus closely associated with initiation of ranolazine (Ranexa) treatment, a new anti-angina drug recently introduced in Europe.

Case report

The patient, a 54-year-old male, started haemodialysis (HD) in 1977 at age 21 because of chronic glomerulonephritis. During HD treatment, he received many blood transfusions, and since 1994, antibodies had been detected against hepatitis C virus. Liver enzymes had always been normal, and he had no sign of portal hypertension.

In 1996, he received a cadaveric kidney transplant. In the following years, his renal function was excellent with a serum creatinine of 1.2 mg/dL (CKD-EPI GFR: 68 mL/min) 14 years after the transplant. Initially, he was treated with triple therapy which included steroids, cyclosporine (Neoral) and azathioprine. In 2000, cyclosporine was substituted with tacrolimus (Prograf) because of severe gingival hyperplasia. Since November 2005, the dose of tacrolimus had been 3 mg twice a day with trough levels (Abbott IMX) ranging in the last 4 years from 4.5 to 7.4 ng/mL (Figure 1). He was also receiving ramipril, lercanidipine, aspirin, fluvastatin, omeprazole, calcitriol and folic acid supplements.

In January 2010, the patient started to complain of angina. After extensive cardiological evaluation, including coronary angiography, transdermal nitrates were added.

On 14 July 2010, because of recurrent episodes of angina, ranolazine (Ranexa) was added at the dosage of 375 mg twice a day. Angina markedly improved, but as shown in Figure 1, in the following weeks, serum creatinine levels rose from 1.2 to 2 mg/dL, while his tacrolimus levels doubled increasing from 5 to 10.9 ng/mL. On 19 August 2010, ranolazine was stopped with complete reversal of renal failure. Concurrently, tacrolimus levels dropped to 3.6 ng/mL (Figure 1). High-dose oral nitrates were prescribed for angina control.

Discussion

Ranolazine is a new anti-angina drug which has been shown to be effective in randomized controlled trials [1–3].

Its mechanism of action is not completely understood. One hypothesis for its action as an anti-angina drug is that by inhibiting sodium channels, the drug reduces the left ventricular diastolic tension [4]. Since patients with end-stage renal failure have a high cardiovascular risk, even when they received a kidney transplant, it is quite common for them to be treated with new cardiovascular drugs. Ranolazine accumulates in mild and moderate renal insufficiency [5]. When our patient was prescribed ranolazine, we looked up Lexi-Interact™ on the Internet and PubMed for possible interferences with tacrolimus. No such interaction was reported in the literature. However, since ranolazine is metabolized by the cytochrome P450 isoenzymes CYP 3A4 and CYP 2D6 [6], a pharmacokinetic interaction with tacrolimus is very likely. Therefore, monitoring of serum creatinine and tacrolimus levels was intensified. When a possible interaction leading to doubling of serum creatinine and tacrolimus levels was observed, the drug was stopped. The complete regression of renal failure along with the concurrent drop in tacrolimus levels suggests that ranolazine was implicated in tacrolimus accumulation and the ensuing deterioration of renal function. We believe that the reversible decline in renal function in our

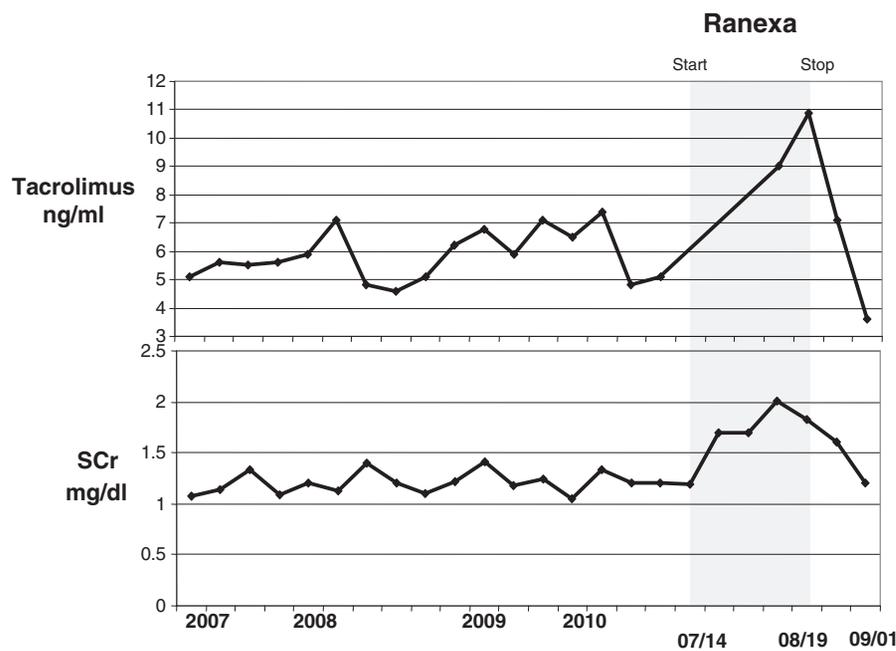


Fig. 1. Serum creatinine and tacrolimus trough levels. The grey area identifies the period on Ranexa treatment.

case was prompted by tacrolimus nephrotoxicity rather than by ranolazine. Ranolazine is considered to possess protective effects for the kidney [7] which makes it unlikely to be responsible for the deterioration in renal function we observed. Specific studies are warranted to study the interference of ranolazine with tacrolimus pharmacokinetics. Pending such studies, close monitoring of tacrolimus levels is recommended in transplant patients who initiate ranolazine treatment.

Conflict of interest statement. None declared.

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