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Increased Tacrolimus Levels After Administration of Ciprofloxacin to a Patient with Renal Transplant

Böbrek Nakli Olan Bir Hastada Siprofloksasin Kullanımı Sonrası Takrolimus Düzeyinde Artış

ABSTRACT

Tacrolimus is a calcineurin inhibitor that is used to prevent organ rejection following renal transplant. The tacrolimus dose is adjusted based on clinical response and blood concentrations because patient to patient variability exists in both pharmacokinetics and pharmacodynamics. Fluoroquinolones are frequently used for treatment due of their broad spectrum of activity; however, some are reported to increase the blood concentration of calcineurin inhibitors. In this study, we describe a patient who had undergone a renal transplant and experienced a clinically significant interaction between tacrolimus and ciprofloxacin. In this case, the patient required a very low dose of tacrolimus (1 mg/day) to achieve target blood levels. This was probably due to pharmacokinetic diversity related to the CYP3A enzymatic system and high blood levels after ciprofloxacin use. The blood levels of tacrolimus increased after the use of ciprofloxacin and returned to baseline once the drug was discontinued. Health care professionals should be aware of such drug interactions.

KEY WORDS: Ciprofloxacin, Cytochrome, Kidney transplant, Tacrolimus

ÖZ

Takrolimus böbrek nakli sonrası organ rejeksiyonunu öncelemede kullanılan bir kalsinörin inhibitörüdür. Takrolimus metabolizmasının kişiden kişiye hem farmakokinetik hem de farmakodinamik özelliklerinin farklılık göstermesi nedeniyle, doz ayarlaması kan düzeyi ve klinik takiplere göre ayarlanmaktadır. Florokinolonlar geniş spektrumlu etkilerinden dolayı enfeksiyon tedavilerinde sıklıkla kullanılmaktadır, ancak bazılarının ilaç etkileşimi nedeniyle kalsinörin düzeylerini yükselttiği bildirilmiştir. Bu olguda, böbrek nakli olan bir hastanın siprofloksasin kullanımı sonrasında gelişen ve takrolimus kan düzeyinde klinik olarak belirgin düzeyde artışa neden olan ilaç etkileşimi sunulmuştur. Muhtemelen takrolimusun CYP3A enzim sistemine bağımlı farmakokinetik değişkenliğinden dolayı, bu hastada, çok düşük dozda (1mg/gün) takrolimus kullanarak optimal kan düzeylerine ulaşılabilmekteydi ve siprofloksasin kullanımı sonrası takrolimus düzeyi belirgin olarak arttı. Siprofloksasin tedavisi kesilmesi sonrasında takrolimus kan düzeyi normal düzeylerine geriledi. Böbrek nakli ile uğraşan sağlık çalışanları bu tür ilaç etkileşimleri konusunda dikkatli olmalıdır.

ANAHTAR SÖZCÜKLER: Takrolimus, Siprofloksasin, Böbrek nakli, Sitokrom P-450

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INTRODUCTION

Tacrolimus is a calcineurin inhibitor that is used to prevent organ rejection following renal transplant. The appropriate dose schedule of tacrolimus is based on lean body weight in adults; however, this method is not suitable for everyone because patient to patient variability exists in both pharmacokinetics and pharmacodynamics.

Tacrolimus is metabolised by the hepatic cytochrome P450 (CYP450) 3A enzymes, and in particular by CYP3A4 and CYP3A5 (1, 2). A relationship between P450 (CYP450) 3A genetic polymorphisms and the pharmacokinetics of tacrolimus has been demonstrated (3). Some genetic polymorphisms can decrease the rate of metabolism of tacrolimus and subsequently increase the duration and intensity of drug action (4).

Ciprofloxacin may affect the metabolism of tacrolimus through the inhibition of CYP3A4 (5) and CYP3A5 (6,7). However, its clinical significance in adults has not been reported in the literature. Here, we describe a patient who had undergone a renal transplant and had experienced a clinically significant interaction between tacrolimus and ciprofloxacin.

CASE REPORT

A 65-year-old man (height 167.5 cm, weight 56.2 kg) with end-stage renal disease secondary to renovascular kidney disease received a renal allograft from a live donor in August 2015. Post-transplant immunosuppression was maintained with tacrolimus, mycophenolate mofetil, and prednisone.

Three days after transplant, the patient experienced pain on the right side of the abdomen (site of transplant) and guarding, along with a palpable mass and reduced haematocrit. A computed tomography scan was immediately performed; a perinephric hematoma was revealed. Due to the low haemoglobin levels, two units of packed cells were transfused, and anticoagulation treatment with low molecular weight heparin was stopped. Surgery was not advised because a Doppler examination revealed elevated resistive indices (0.62-0.65 ratio) in the three poles of the allograft kidney; there was no hydro-nephrosis due to the compressive effect of the hematoma. Three weeks after the transplant, a follow-up ultrasound showed partial resolution of the hematoma but delayed wound healing, and the discharge at the wound site was observed. Culture of the drainage fluid revealed carbapenem-sensitive E. coli.; intravenous antibiotic therapy (carbapenem, 1 gr qd) was started. The drainage volume gradually decreased and four weeks after transplantation, the patient's clinical condition significantly improved. Serum C-reactive protein decreased to 0.5 mg/dL, white blood count was 7500/mm^3, and creatinine was 0.76 mg/dL. The patient was discharged 45 days after transplant with oral ciprofloxacin to be continued for a further 10 days. Home medications included enoxaparine (1.2 mL/day), pantoprozole (40 mg/day), simvastatin (20 mg/day), prednisone (15 mg/day), mycophenolate sodium (1000 mg/day), and tacrolimus (1 mg/day) (target blood levels: 5-8 ng/mL).

The patient was readmitted to the hospital after completing a 10-day course of oral ciprofloxacin with nausea, headache, and tremor in the hands. Vital signs on admission were: blood pressure 145/71 mm Hg, heart rate 90/min, respiratory rate 13/min, and temperature 36.0°C. There were no clinically apparent features suggesting infection, and the laboratory findings were unremarkable (glucose: 97 mg/dL, haemoglobin: 10.3 gr/dL, albumin: 3.6 gr/dL, sodium: 136 meq/dL, potassium: 4.2 meq/dL, alanine aminotransferase: 14 mg/dL, aspartate aminotransferase: 17 mg/dL, creatinine kinase: 25 mg/dL and C-reactive protein: <5 nmol/L) except for elevated creatinine (1.26 mg/dL) and the tacrolimus (level increased from 8.1 ng/mL to 18.5 ng/mL) levels. The increase in tacrolimus levels was attributed to ciprofloxacin in the absence of another cause. The dose of tacrolimus was decreased to 0.5 mg/day. The blood levels of tacrolimus gradually decreased over several days and at the seventh day of readmission, tacrolimus dose was increased to the patient's preadmission dose of 1 mg/day. Therapeutic drug monitoring of tacrolimus was continued for a week and no change in blood level was observed. During this period, serum creatinine declined from baseline values of 0.7-0.8 mg/dL (Figure 1).

DISCUSSION

The pharmacokinetic profile of tacrolimus is well characterised (8) and the influence of CYP3A5 and CYP3A4 polymorphisms on the pharmacokinetics of tacrolimus is well established. The patient described in the current case report likely metabolises tacrolimus slower through the CYP3A

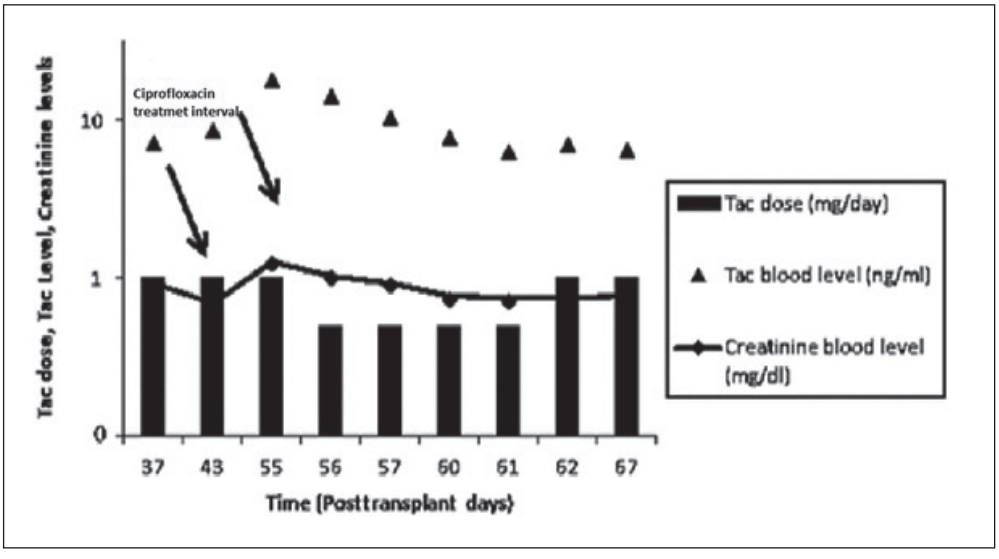

Figure 1: *Tacrolimus dose and trough levels of tacrolimus and creatinine.*

enzymes in the liver, because a very low dose of tacrolimus (1 mg/day) was required to achieve target blood levels. Tacrolimus is metabolised almost entirely by the CYP3A enzymes in the liver and intestinal wall. Expression of these enzymes can vary substantially between patients, resulting in significant differences in metabolism. Some allele carriers are known to require larger doses of tacrolimus to reach target blood concentrations (9-12). A previous study showed that carriers of the combined genotype of CYP3A4*1/*1-CYP3A5* 3/*3 require lower tacrolimus doses to achieve target concentration levels compared with patients with other alleles (4). There are also racial/ethnic disparities in carrier state (13).

The patient described in the present case achieved high blood levels after using ciprofloxacin, which uses the same cytochrome P450 system as tacrolimus, and may inhibit its metabolism. Fluoroquinolones are frequently used for treatment due to their broad activity spectrum; but some, including ciprofloxacin and norfloxacin, have been reported to increase cyclosporin blood concentrations because they are metabolised by the liver through the same cytochrome P450 enzymatic pathway (14-16). In addition, ciprofloxacin may affect the metabolism of tacrolimus and increase its blood level through inhibition of CYP3A4 (5) and CYP3A5 (6,7). Levofloxacin is known to partially inhibit the metabolism of both cyclosporin microemulsion and tacrolimus (17).

The patient was using pantoprazol and simvastatin, both of which can interact with tacrolimus, but these drugs had been prescribed for atherosclerosis and gastritis, so they were continued even after tacrolimus toxicity. Aside from ciprofloxacin, the patient was not on any medications known to interact with tacrolimus before tacrolimus toxicity. Blood levels of tacrolimus gradually decreased over several days after discontinuing ciprofloxacin, so the toxicity was attributed to ciprofloxacin usage.

Other multiple factors have been reported to influence the pharmacokinetics of tacrolimus, including graft type (e.g. kidney, liver, and heart), hepatic and renal function, time since transplant, patient's age and ethnic background, haematocrit and albumin concentrations, food intake, and diarrhoea (18). The patient's hepatic and renal function remained unchanged from baseline throughout the treatment course. Both haematocrit and albumin concentrations remained within normal limits and were consistent with baseline values. No episodes of diarrhoea were reported during the timeframe of the case report.

In conclusion, ciprofloxacin may lead to increased blood levels of tacrolimus, and to our knowledge, this case is the first report of a clinically significant interaction between tacrolimus and ciprofloxacin in an adult kidney transplant patient. Renal transplant patients must be closely monitored during the early period after renal transplantation, and the patient must be informed about drug interactions, side effects, and the benefits to early hospital admission.

CONCLUSION

Ciprofloxacin is widely used in transplant patients, but its clinical significance in adults has not been reported in the literature. To our knowledge, this is the first report to show increases in tacrolimus blood levels secondary to ciprofloxacin usage in a renal transplant recipient. Health care professionals monitoring tacrolimus blood concentrations should be aware of the variability in clinical presentation, especially in patients that may have slow tacrolimus metabolisms.

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