Note

Interaction between Tacrolimus and Lansoprazole, but not Rabeprazole in Living-Donor Liver Transplant Patients with Defects of CYP2C19 and CYP3A5

Keiko HOSOHATA1, Satohiro MASUDA1, Yasuhiro OGURA2, Fumitaka OIKE2, Yasutugu TAKADA2, Toshiya KATSURA1, Shinji UEMOTO2 and Ken-ichi INUI1

1Department of Pharmacy, Kyoto University Hospital,
2Department of Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Full text of this paper is available at http://www.jstage.jst.go.jp/browse/dmpk

Summary: We report different effects of administration of proton pump inhibitors on tacrolimus blood concentration in two living-donor liver transplant patients. In case 1, a 51-year-old man with liver cirrhosis due to hepatitis C virus underwent living-donor liver transplantation, and tacrolimus was orally administered. Omeprazole (40 mg/day) was introduced intravenously between postoperative days 5 and 6, and oral lansoprazole (30 mg/day) was introduced from day 6, leading to an increase in the concentration/dose ratio of tacrolimus from day 10. In case 2, a 41-year-old living-donor liver transplant woman received tacrolimus, and co-administered with omeprazole (40 mg/day) intravenously during 7 days immediately after surgery. During this period, trough concentration of tacrolimus was high, but the concentration/dose ratio of tacrolimus was gradually decreasing with time. Switched to rabeprazole (10 mg/day) orally on the postoperative 8th day, the concentration/dose ratio of tacrolimus remained low, indicating little drug-drug interaction between tacrolimus and rabeprazole. In both cases, the genotypes of CYP2C19 and CYP3A5 were defective both in the graft liver and in the native intestine. A drug-drug interaction between rabeprazole and tacrolimus was not observed in this case study presented, suggesting that this combination could be safely used in tacrolimus therapy after liver transplantation.

Keywords: CYP2C19; CYP3A5; living-donor liver transplantation; tacrolimus; lansoprazole; rabeprazole

Introduction

An immunosuppressant tacrolimus is widely used in organ transplantation. The systemic clearance of tacrolimus is mainly explained by cytochrome P450 (CYP) 3A4/5-mediated metabolism in the liver and small intestine. Proton pump inhibitors (PPIs), lansoprazole and rabeprazole, are empirically co-administered with tacrolimus in patients suffering from surgical stress-related gastric bleeding or gastrointestinal ulceration after organ transplantation. PPIs are primarily metabolized by CYP2C19 and CYP3As. Interaction between tacrolimus and PPIs is therefore assumed to occur especially in patients with CYP2C19 gene variants. However, no studies have investigated the effect of PPIs on tacrolimus pharmacokinetics in living-donor liver transplant (LDLT) patients.

We herein report the different effects of PPIs on tacrolimus pharmacokinetics in LDLT patients with CYP2C19 and CYP3A5 defect genotypes in both the graft liver and the native intestine.

Methods

Ethics: These studies were conducted in accordance with the Declaration of Helsinki and its amendments, and...
were approved by the Kyoto University Graduate School and Faculty of Medicine, Ethics Committee. Written informed consent was obtained from the recipients.

**Dosage regimen of tacrolimus, analysis of blood samples:** The basic immunosuppression regimen consisted of tacrolimus with low-dose steroids, methylprednisolone (Solu-Medrol®; Pfizer, New York, USA) and prednisolone (Predonine®, Shionogi, Osaka, Japan). The blood concentrations of tacrolimus (Prograf®; Fujisawa Pharmaceutical Co. Ltd, Osaka, Japan), under co-administration of omeprazole (Omepral®, AstraZeneca Co. Ltd, Osaka, Japan), lansoprazole (Takepron®, Takeda Pharmaceutical Co. Ltd, Osaka, Japan) and rabeprazole (Pariet®, Eisai Co. Ltd, Tokyo, Japan), were monitored using a semiautomated microparticle enzyme immunoassay (IMx®; Abbott Co, Ltd, Tokyo, Japan).

**Isolation of genomic DNA and genotyping:** CYP2C19 and CYP3A5 genotypings were performed using the polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) method with genomic DNA extracted from a liver biopsy specimen of the graft and peripheral blood from recipients by using a MagNAPure LC DNA Isolation kit I (Roche, Mannheim, Germany). The PCR products were digested with a restriction enzyme according to the condition of manufacturers’ instructions and separated on 3.5% agarose gel.

**Results**

**Case report 1:** Case 1 was a 51-year-old man weighing 84 kg who underwent a LDLT for hepatocellular carcinoma and liver cirrhosis due to hepatitis C virus. The graft-to-recipient body weight ratio (GRWR) was 0.99% and the blood type combination was identical (A+ to A+). Primary immunosuppression consisted of tacrolimus, prednisolone, and mycophenolate mofetil. Within 24 hours after surgery, administration of tacrolimus was started with an oral dose of 0.075 mg/kg twice daily (at 9 AM and 9 PM). The dosage of tacrolimus was adjusted to reach whole-blood trough

![Graph](image-url)

**Fig. 1.** Monitoring tacrolimus oral doses (A), trough concentrations (B, open circles) and C/D (B, concentration/dose, solid circles) ratio, and serum AST (aspartate aminotransferase, solid line) and T-Bil (total bilirubin, dashed line) levels (C) before and after the co-administration of lansoprazole with tacrolimus in patient 1. C/D, concentration/dose; AST, aspartate aminotransferase; T-Bil, total bilirubin; IV, intravenous administration.
Fig. 2. Monitoring tacrolimus oral doses (A), trough concentrations (B, open circles) and C/D (B, concentration/dose, solid circles) ratio, and serum AST (aspartate aminotransferase, solid line) and T-Bil (total bilirubin, dashed line) levels (C) before and after the co-administration of rabeprazole with tacrolimus in patient 2.

G/D, concentration/dose; AST, aspartate aminotransferase; T-Bil, total bilirubin; IV, intravenous administration.

concentrations ranging between 5 and 15 ng/mL during the first month. As prophylaxis for ulcer, omeprazole at 40 mg/day was administered intravenously for the period of days 5–6, switched to lansoprazole at 30 mg/day between days 6 and 19 (Fig. 1A), leading to an increase in the concentration/dose (C/D) ratio of tacrolimus. Graft liver function, as assessed based on the aspartate aminotransferase level and total bilirubin level, almost returned to normal during the first postoperative month (Fig. 1C). No other clinical events affecting the level of tacrolimus was reported. He had heterozygous variants at exons 4 and 5 of CYP 2C19 (*2/*3), which showed him to be a poor metabolizer. The donor was his 55-year-old brother with CYP2C19*2/*3. Furthermore, the genotype of CYP3A5 in both the graft liver (donor) and native intestine (recipient) was CYP3A5*3/*3 (CYP3A5 non-expressors).

Case report 2: Case 2 was a 41-year-old woman with liver cirrhosis of unknown etiology, who underwent a LDLT. The GRWR was 1.46% and the blood type combination was incompatible (B+ to A+). The recipient received triple-regimen-therapy including tacrolimus, corticosteroid, and mycophenolate mofetil. A standard corticosteroid tapering regimen was used, consisting of an intravenous bolus of methylprednisolone at 50 mg/day on day 1, 25 mg/day between days 4 and 6, and 15 mg/day on day 7, followed by oral prednisolone at 15 mg/day between days 8 and 28, and 5 mg/day on days 29 and 30. As prophylaxis for ulcer, omeprazole at 40 mg/day was intravenously administered during 7 days immediately after the surgery. During this period, the trough concentration of tacrolimus was high, but the C/D ratio of tacrolimus was gradually decreasing with time and/or grafted liver regeneration from postoperative day 5 (Figs. 2A, 2B). On the postoperative 8th day, there was a switch from omeprazole at 40 mg/day intravenously to rabeprazole at 10 mg/day orally, but the C/D ratio of tacrolimus remained low. There was little drug interaction between tacrolimus and rabeprazole (Figs. 2A, 2B). No other symptoms of liver impairment including jaundice or acute cellular rejection were observed. She had homogenous variants at exon 5 of CYP2C19 (CYP2C19*2/*2), which showed her to be a poor metabolizer. The donor was her 63-year-old mother with CYP2C19*2/*2. The geno-
Interaction between tacrolimus and proton pump inhibitors

Discussions

This is the first report that the effect of PPI on tacrolimus pharmacokinetics varied in patient 2. The C/D ratio of tacrolimus was high during 7 days immediately after surgery and after that, it was gradually decreased. The C/D ratio of tacrolimus remained low under co-administration of rabeprazole, indicating little effect of rabeprazole on the metabolism of tacrolimus.

The administration of oral lansoprazole or rabeprazole after intravenous omeprazole showed different effects on tacrolimus pharmacokinetics. One possible explanation for this difference is that the relative contribution of CYP2C19-mediated metabolism varies between the two PPIs. Another possibility is that this difference can be explained by an inhibition of P-glycoprotein-mediated intestinal efflux-transport of tacrolimus by lansoprazole, but not rabeprazole. P-glycoprotein is related to the inter-individual variation in the pharmacokinetics of tacrolimus as an absorptive barrier. Therefore, the intestinal expression level of P-glycoprotein can limit bioavailability of tacrolimus in patient 1.

To date, no interactions between lansoprazole and tacrolimus in LDLT patients have been demonstrated. Several reports stated that lansoprazole interfered with the metabolism of tacrolimus in renal transplant patients with CYP2C19 gene variants. These reports showed that the CYP3A4-mediated metabolism of tacrolimus may be competed with lansoprazole, but there were no examinations of the polymorphism in the CYP3A5 gene, which could not exclude the potential contribution of CYP3A5 to the interaction between tacrolimus and lansoprazole. In our report, the defective genotypes of CYP3A5 as well as CYP2C19 in both the graft liver and the native intestine could reveal the CYP3A4-mediated drug interaction between tacrolimus and lansoprazole more clearly. However, the contribution of CYP3A5 to the interaction between tacrolimus and lansoprazole or rabeprazole remains unclear. Because the genotypes of CYP3A5 significantly affected on the tacrolimus pharmacokinetics in LDLT patients, the interaction between tacrolimus and PPIs should be examined in future. In addition, further research is needed to confirm what extent rabeprazole is metabolized by CYP3A5 in vitro study.

In conclusion, we first found drug-drug interaction between tacrolimus and lansoprazole, but not rabeprazole, in living-donor liver transplant patients with genetic defects of CYP2C19 and CYP3A5, suggesting that rabeprazole could be safely used in tacrolimus therapy after the liver transplantation.

References

11) Masuda, S., Goto, M., Okuda, M., Ogura, Y., Oike, F., Kiuchi, T., Tanaka, K. and Inui, K.: Initial dosage adjustment for oral ad-


