
Note

**Distinct Effects of Omeprazole and Rabeprazole on the Tacrolimus Blood Concentration in a Kidney Transplant Recipient**

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**Summary:** Proton-pump inhibitors (PPIs, e.g. omeprazole and rabeprazole) are often administered to transplant patients as a treatment or prophylaxis for ulcers after surgery. Since tacrolimus and PPIs share the CYP3A4 system for metabolism, pharmacokinetic interactions are anticipated when they are administered simultaneously. We present a Japanese male patient who underwent a living-donor kidney transplantation having received tacrolimus, mycophenolate mofetil, and prednisolone for immunosuppression. The concentration/dose (C/D) ratio for tacrolimus was markedly higher during the period of treatment with omeprazole than ranitidine or rabeprazole. The results of liver functional tests were within the normal range during the use of these three antacid drugs. Since the higher C/D ratio for tacrolimus when omeprazole was being administered did not result from a decrease in the elimination of tacrolimus due to hepatic dysfunction, drug interaction between omeprazole and tacrolimus was strongly suspected. The present case indicates that rabeprazole can be used safely in place of omeprazole in kidney transplant recipients receiving tacrolimus.

**Key words:** drug interaction; tacrolimus; omeprazole; rabeprazole; CYP3A4; CYP2C19

**Introduction**

The contribution of tacrolimus to effective immunosuppression in the field of kidney transplantation is well-established.³ Tacrolimus is a macrolide antibiotic metabolized by the cytochrome P450 3A4 (CYP3A4) enzyme. Proton-pump inhibitors (PPIs, e.g. lansoprazole, omeprazole, pantoprazole, and rabeprazole) are often administered to transplant patients as a treatment or prophylaxis for ulcers. PPIs are metabolized by cytochrome P450 enzymes in humans, most prominently by CYP2C19 and CYP3A4.²³ Because tacrolimus and PPIs share the CYP3A4 system for metabolism, drug interactions are anticipated when they are administered simultaneously. However, it is still controversial whether interaction between tacrolimus and omeprazole (a typical PPI) is clinically relevant.⁴⁵ We present here a kidney transplant recipient in whom the effects of omeprazole and rabeprazole on the tacrolimus blood concentration were different.

**Methods**

**Patient’s profile:** A 32-year-old Japanese male underwent an ABO compatible living related kidney transplantation from his mother. Immunosuppression was achieved with tacrolimus, mycophenolate mofetil, and prednisolone after the transplantation.

**Determination of tacrolimus:** The blood concentration of tacrolimus was routinely measured using a semi-automated microparticle enzyme immunoassay (IMx, Abbott Japan, Tokyo, Japan). The IMx Tacrolimus II controls (Abbott Laboratory, North Chicago, Illinois) were used as quality control of the assay.

**Results**

**Effects of PPIs on tacrolimus blood concentration:** On postoperative day (POD) 17, the trough level of tacrolimus was 12.5 ng/mL for a daily oral dose of 17
The use of oral ranitidine (Ran, 150 mg/day) was switched to intravenous omeprazole (Ome, 40 mg/day) on POD 18. Omeprazole was switched to oral rabeprazole (Rab, 10 mg/day) on POD 21. Closed circle, tacrolimus blood concentration; Open square, tacrolimus dose; Closed triangle, tacrolimus concentration/dose ratio.
or absent. Since pharmacokinetic profiles of omeprazole and lansoprazole depend on the CYP2C19 genotype status, increased blood concentrations of these drugs can cause CYP3A4 overload, resulting in interactions in this pathway in patients with CYP2C19 gene mutations.

The frequency of CYP2C19 mutations is higher in Asians than in Caucasians. Therefore, Asian patients may have a higher risk of drug interaction between tacrolimus and these PPIs. Indeed, we recently reported that interaction between lansoprazole and tacrolimus was strongly suspected in a living-donor kidney transplant recipient and this interaction between lansoprazole and tacrolimus and these PPIs. Indeed, we recently reported that the effects of CYP2C19 polymorphisms are smaller on the pharmacokinetics of rabeprazole than on the pharmacokinetics of omeprazole or lansoprazole. However, Sugimoto et al. recently reported that differences in acid inhibition by rabeprazole were observed between the different CYP2C19 genotypes. Unfortunately, since informed consent could not be obtained from this patient, we were unable to access the genetic information. Therefore, it was not clear whether this patient had genetic polymorphisms on the CYP2C19 allele(s). On the other hand, while tacrolimus and PPIs interact with P-glycoprotein, the contribution of P-glycoprotein to the increased blood concentration of tacrolimus on the coadministration of omeprazole or lansoprazole is not clear. Clarification of the mechanism(s) behind the pharmacokinetic interaction between tacrolimus and PPIs is needed.

The present case indicates that rabeprazole can be used safely in place of omeprazole in kidney transplant recipients receiving tacrolimus. Since genetic information on CYP2C19 polymorphisms is not always clinically available for each patient, careful routine monitoring of tacrolimus trough levels is needed to optimize the dosage regimen in patients receiving tacrolimus and PPIs.

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References
