Title:

Hepatic drug interaction between tacrolimus and lansoprazole in a bone marrow transplant patient receiving voriconazole and harboring CYP2C19 and CYP3A5 heterozygous mutations

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ABSTRACT

Background: A drug interaction between oral tacrolimus (TAC) and lansoprazole (LAN) has been reported in patients with CYP2C19 homozygous mutations and the CYP3A5 *3/*3 genotype. A Pubmed search (date of implementation, March 16, 2011) using search terms drug interaction, tacrolimus, and lansoprazole, failed to identify the drug interactions in CYP3A5 extensive metabolizers , and parenterally administrated TAC.

Objective: To report a case of drug interaction between intravenous TAC and LAN in a patient being treated with voriconazole (VCZ) and harboring CYP2C19 and CYP3A5 heterozygous mutations.

Case Summary: An 18-year-old Japanese man weighing 53 kg with an anaplastic large cell lymphoma received continuous intravenous administration of TAC as post-transplantation prophylaxis against graft-versus-host disease (GVHD) after an allogeneic bone marrow transplantation (BMT). He began receiving intravenous LAN 60 mg/day and VCZ 400 mg/day initiated the day before BMT. His blood TAC concentrations were within the range of 9 -16 ng/ml from post BMT day 5 to 26. The engraftment of the donor's hematopoietic cells was observed on day 17. The LAN dose was reduced to 15 mg/day orally on day 26, and the blood TAC concentration subsequently decreased to 6.6 ng/ml, with GVHD related symptoms emerging on day 28. Consequently, the plasma VCZ concentration also decreased from 5.0 ng/ml to 2.5 ng/ml after reducing the LAN dose. VCZ was switched to liposomal amphotericin B on day 48. Thereafter, the blood TAC concentration decreased to 4.4 ng/ml on day

51. Ultimately, the patient died on day 77 because of the recurrence and progression of lymphoma. Other drugs taken were acyclovir, ursodeoxycholic acid, cefepime, meropenem, vancomycin, lenograstim and dopamine hydrochloride. The genotyping analyses using the pre-BMT and post-engraftment (day 33) samples indicated that both were CYP2C19 *1/*2 and CYP3A5*1/*3. The calculated Horn drug interaction probability scales between TAC and LAN is 6, indicating a probable interaction. TAC and VCZ concentrations were measured by an affinity column-mediated immunometric assay and high performance liquid chromatography, respectively. Mutant alleles were examined using the multiplex extension of unlabeled oligonucleotide primers with fluorescently labeled dideoxynucleotide triphosphates.

Conclusions: Blood TAC concentration decreased after reducing the LAN dose, which was likely caused by a reduction in plasma VCZ concentration, in a BMT patient with CYP2C19 and CYP3A5 heterozygous mutations.

INTRODUCTION

A drug interaction between oral tacrolimus (TAC) and lansoprazole (LAN) has been reported in patients with CYP2C19 hetero/homozygous mutations and the CYP3A5 *3/*3 genotype.[1,2,3] However, a Pubmed search (date of implementation, March 16, 2011) using search terms drug interaction, tacrolimus, and lansoprazole, failed to identify the drug interactions in CYP3A5 extensive metabolizers and,parenterally administrated TAC.

CASE DESCRIPTION

An 18-year-old Japanese man weighing 53 kg with an anaplastic large cell lymphoma received continuous intravenous TAC after an allogeneic bone marrow transplantation (BMT). Blood TAC concentrations were measured routinely by an affinity column-mediated immunometric assay. Intravenous LAN 60 mg/day and VCZ 400 mg/day were started after the day before BMT. The patient's blood TAC concentrations were within 9-16 ng/ml from post BMT day 5 to 26. The engraftment of the donor's hematopoietic cells was observed on day 17. The LAN dose was reduced to 15 mg/day orally on day 26, and the blood TAC concentration subsequently decreased to 6.6 ng/ml, with GVHD related symptoms emerging on day 28. (Figure). On the same day, the TAC dose was increased from 0.78 mg/day to 1.08 mg/day because of high fever and skin- graft-versus-host disease (GVHD) stage 3. On day 29, hydrocortisone was initiated at 200 mg/day to treat GVHD. On day 30, the TAC dose

was increased to 1.20 mg/day and because of a low blood TAC concentration (8.8 ng/ml), diarrhea and residual skin-GVHD stage 2. The plasma VCZ concentration was confirmed to have decreased from 5.0 μg/ml to 2.5 μg/ml after LAN dose reduction using stored samples by high performance liquid chromatography. When the blood TAC concentration increased to 10.8 ng/ml on day 32, GVHD symptoms abated nearly completely. On day 35, the blood TAC concentration fell to 8.8 ng/ml, and, consequently, the TAC dose was increased to 1.36 mg/day. VCZ was switched to liposomal amphotericin B on day 48; thereafter, the TAC concentration decreased to 4.4 ng/ml on day 51. Because of the recurrence of lymphoma, TAC was not increased to provide a graft-versus-leukemia effect. On day 77, the patient died due to disease progression. Other drugs taken were acyclovir, ursodeoxycholic acid, cefepime, meropenem, vancomycin, lenograstim and dopamine hydrochloride. The patient did not eat grapefruit and drink grapefruit juice while receiving the TAC infusion. Genotyping analyses using the pre-BMT (stored sample) and post-engraftment (day 33, fresh sample) samples indicated both harbored CYP2C19 *1/*2, CYP3A5*1/*3 and CYP2C9 *1/*1. This study was reviewed and approved by the ethics committee of Mie University, and written informed consent was obtained from the patient.

DISCUSSION

A drug interaction between orally administrated TAC and LAN was reported in liver transplant recipients with CYP2C19 *2/*3 and CYP3A5*3/*3 genotypes.[1] Another study revealed that the dose-adjusted area under the plasma concentration-time curve of TAC was highest in the CYP2C19 homozygous mutations with the CYP3A5*3/*3 genotype among various combinations of CYP2C19 and CYP3A5 genotypes.[2] However, drug interactions in CYP3A5 extensive metabolizers and parenterally administrated TAC have not been reported.

The increased severity of GVHD was judged to be related to reduced blood TAC concentrations during the management of this patient. Hepatic TAC metabolism due to CYP3A4/5 was thought to have increased after the LAN dose reduction, resulting in a lower blood TAC concentration because there were no changes in other medications including TAC dose, or liver and kidney function, before and after LAN dose reduction.

VCZ is well-distributed to organs, and the reported Ki value of VCZ for the inhibition of CYP3A is 1.04 μg/ml.[4] Since plasma protein binding rate of VCZ is reportedly ~58% [5], the free fraction of VCZ after LAN dose reduction was estimated to be 1.05 μg/ml (based on a total concentration 2.5 μg/ml), which is nearly equal to the Ki value for CYP3A. In addition, the blood TAC concentration fell after withdrawal of VCZ in our case. The drug interaction between TAC and VCZ was also reported in the liver transplant patients and allogeneic hematopoietic stem cell transplantation recipients. [6, 7] These facts suggest that the decline in plasma VCZ concentration distinctly influenced the decreased blood concentration of TAC after the LAN dose reduction.

The direct interaction between TAC and LAN was also considered in this case. The Horn drug interaction probability scale between TAC and LAN is 6, indicating a probable interaction (Table).[8] Although this case was not a genotypical CYP3A5 poor-metabolizer, inhibition of CYP3A5 by VCZ likely decreased the patient's capacity to metabolize TAC, recapitulating a CYP3A5 poor-metabolizer phenotype thus causing an interaction between TAC and LAN. This notion is supported by the recent report indicating hepatic CYP3A5 *3/*3 carriers showed 1.6-fold higher TAC concentration/dose ratio than CYP3A5 *1 carriers when LAN was concomitantly administered.[9]

CONCLUSIONS

Blood TAC concentration decreased after reducing the LAN dose , which was likely caused by a reduction in plasma VCZ concentration, in a BMT patient with CYP2C19 and CYP3A5 heterozygous mutations. Further studies using larger sample size are required to verify the VCZ-mediated drug interaction between TAC and LAN.

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FIGURE LEGENDS

Figure.

Blood concentrations of tacrolimus (open circles, left axis), plasma voriconazole concentrations (solid triangles, right axis) and GVHD symptoms after bone marrow transplantation.

LAN: lansoprazole, VCZ: voriconazole, L-AMB: liposomal amphotericin B, GVHD: graft-versus-host disease

Table The score of the Horn drug interaction probability scale for tacrolimus and lansoplazole in this study

Q.1	Are there previous credible reports of this interaction in humans? (Yes +1, No -1, Do not know 0)	+ 1
Q.2	Is the observed interaction consistent with the known interactive properties of precipitant drug? (Yes +1, No -1, Do not know 0)	+ 1
Q.3	Is the observed interaction consistent with the known interactive properties of object drug? (Yes +1, No -1, Do not know 0)	+ 1
Q.4	Is the event consistent with the known or reasonable time course of the interaction (onset and / or offset)? (Yes +1, No -1, Do not know 0)	+ 1
Q.5	Did the interaction remit upon dechallenge of the precipitant drug with no change in the object drug? (if no dechallenge, use Unknown and skip question 6) (Yes +1, No -2, Do not know 0)	0
Q.6	Did the interaction reappear when the precipitant drug was readministered in the presence of continued use of object drug? (Yes +2, No -1, Do not know 0)	0
Q.7	Are there reasonable alternative causes for the event? (Yes -1, No +1, Do not know 0)	-1
Q.8	Was the object drug detected in the blood or other fluids in concentrations consistent with the proposed interaction? (Yes +1, No 0, Do not know 0)	+ 1
Q.9	Was the drug interaction confirmed by any objective evidence consistent with the effects on the object drug (other than drug concentrations from question 8)? (Yes +1, No 0, Do not know 0)	+ 1
Q.10	Was the interaction greater when the precipitant drug dose was increased or less when the precipitant drug dose was decreased? (Yes +1, No -1)	+ 1
	Total score	6

Drug interaction scale: ≥ 9 = definite, 5-8 = probable, 1-4 = possible, 0 ≤ doubtful