Drug-herbal interaction between tacrolimus and rooibos tea in a recipient of allogeneic hematopoietic stem cell transplantation

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Tacrolimus has been widely used for the prophylaxis and treatment of graft-versus-host disease (GVHD) in allogeneic hematopoietic stem cell transplantation. Since tacrolimus is mainly metabolized by cytochrome P450 (CYP) enzymes, its drug interaction with a variety of agents has been clinically recognized. In addition, natural products such as food components and herbal products have also been reported to interact with tacrolimus. We here report the first case of a drug interaction between tacrolimus and rooibos tea documented after allogeneic hematopoietic stem cell transplantation, in which the interaction reduced the concentration of tacrolimus and resulted in the development of GVHD. Transplant physicians and pharmacists should be made aware of the drug-herbal interaction between rooibos tea and tacrolimus, which is probably applicable to other drugs metabolized by CYP enzymes, such as cyclosporine A. (Journal of Hematopoietic Cell Transplantation 2(4): 109-111, 2013.)

Tacrolimus, a calcineurin inhibitor, has been widely used for the prophylaxis and treatment of graft-versus-host disease (GVHD) in hematopoietic stem cell transplantation or graft rejection in solid organ transplantation.¹ Tacrolimus is metabolized by cytochrome P450 (CYP) enzymes, mainly CYP3A, in the liver and small intestine.¹ Therefore, its drug interaction with a variety of agents which are substrates and/or inhibitors and inducers of these enzymes has the potential to affect the pharmacokinetics of tacrolimus.²³ In addition to prescribed medicines, natural products such as food components and herbal products have also been reported to cause such interactions.⁴⁶ These interactions can result in serious clinical events such as GVHD, graft rejection, and induction of the side effects of tacrolimus. We here report the first case of a clinically significant drug interaction between tacrolimus and rooibos tea.

A 38-year-old woman with acute myeloid leukemia underwent bone marrow transplantation from an unrelated donor after being conditioned with total body irradiation and cytarabine.⁷ Tacrolimus and methotrexate were given for the prophylaxis of acute GVHD. On day 29, she developed acute GVHD involving the gastrointestinal tract which was successfully treated with prednisolone (1 mg/kg). Tacrolimus was switched from oral to intravenous on day 36. The initial oral dose was 3 times greater than the intravenous dose, but was decreased after initiating oral voriconazole (400 mg per body) for the prophylaxis of fungal infection. After day 42, tacrolimus was given orally at a fixed dose (0.6 mg per body weight given in two divided doses every 12 hours) and the trough blood concentration of tacrolimus ranged between 9.2 and 10.3 ng/ml. The blood concentration of tacrolimus was measured every 2 to 3 days. On day 55, she began the regular consumption of a commercially purchased brand of rooibos tea at a rate of more than 2 liters per day. No other drugs or specific food components were initiated during this period. On day 59, the trough blood concentration of tacrolimus was found to be decreased to 3.0 ng/ml and skin GVHD recurred. The administration of tacrolimus was immediately switched
to continuous intravenous infusion (0.6 to 0.8 mg per day), and the blood concentration of tacrolimus was promptly elevated. The dose of tacrolimus was adjusted to maintain its steady state blood concentration between 10 and 20 ng/ml. The clinical course and dynamics of the blood concentration of tacrolimus are shown in Figure 1. The skin GVHD completely disappeared within 14 days.

In this case, the blood concentration of tacrolimus decreased promptly (4 days) after taking rooibos tea regularly and in massive amounts, which resulted in the development of GVHD. It is difficult to conclusively determine the drug-herbal interaction based on a single-case observation. However, the blood concentration of tacrolimus had been steady before the patient started taking rooibos tea, and no other agents or food components were initiated during this period. Therefore, it was strongly suggested that rooibos tea significantly affected the blood concentration of tacrolimus. To the best of our knowledge, this is the first reported case to clinically demonstrate the drug-herbal interaction between tacrolimus and rooibos tea.

The consumption of herbal supplements has been dramatically increasing worldwide. The interaction between such self-administered herbal products and prescribed medicines raises concern because some of the interactions are clinically relevant. Rooibos tea is one of several popular herbal teas made from the dried leaves of *Aspalathus linearis*, and is expected to suppress allergic reactions, such as pollen allergies or asthma. In contrast to St. John’s Wort and other herbal teas, the drug-herbal interactions associated with rooibos tea have scarcely been examined. Indeed, to our knowledge, there has been only one such report, a study evaluating the effect of rooibos tea on the metabolism of midazolam, a sensitive probe for analysis of the activity of CYP 3A, in a rat model. In that report, continuous ingestion of rooibos tea significantly increased the activity of CYP3A enzyme in the intestine, and reduced the blood concentration of orally administered midazolam. Although such an effect has not been examined in humans, it could potentially have contributed to the decrease in tacrolimus concentration after the consumption of rooibos tea in the present case.
In our case, initiation of intravenous tacrolimus (0.6 to 0.8 mg per day) promptly achieved the target blood concentration of tacrolimus. This finding suggested that rooibos tea affected the activity of intestinal CYP but minimally affected that of hepatic CYP, which was consistent with the results in the rat model. Therefore, it is likely that rooibos tea has the potential to trigger drug-herbal interactions specifically in the context of oral drug administration.

Herbal products are complex mixtures of various compounds. Therefore, unlike in drug-drug interactions, it is possible that several components in a certain herbal product could contribute to the interaction with drugs cooperatively or competitively. However, not all the compounds in herbal teas have been fully recognized, and their effects have not been thoroughly investigated. Rooibos tea is rich in flavonoids such as aspalathin and quercetin. Among these agents, quercetin has been reported to induce the activity of CYP 3A, and thus it could be a major component of the drug-herbal interaction of rooibos tea. However, other possible mechanisms, such as the inhibition of absorption due to chelation or effects on transporters, should also be explored in future studies.

We conclude that physicians and pharmacists should be made aware of the drug-herbal interaction between rooibos tea and tacrolimus, which is probably applicable to other drugs metabolized by CYP enzymes, such as cyclosporine A. We recommend that rooibos tea be added to the list of foods and herbal products which are to be avoided when patients are on calcineurin inhibitors.

Authors’ contributions

NB and TM took care of the patient and wrote the paper; JK, SK, and TK took care of the patient; OI and ST took care of the patient and collected data; SO took care of the patient and approved the manuscript.

Conflict of interest

None to disclose.

References