Delayed Effect of Grapefruit Juice on Pharmacokinetics and Pharmacodynamics of Tacrolimus in a Living-Donor Liver Transplant Recipient

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Summary: Tacrolimus is a calcineurin inhibitor that has been widely used to prevent allograft rejection after transplantation. We report a case of a living-donor liver transplant recipient experiencing a considerable increase in the trough blood concentration of tacrolimus after concomitant ingestion of grapefruit juice (250 mL) 4 times for 3 days. The trough blood concentrations of tacrolimus were not changed during or immediate after the repeated intake of grapefruit juice. However, almost 1 week after the final ingestion, the blood concentration of tacrolimus markedly increased to as much as 47.4 ng/mL from 4.7 ng/mL before the ingestion, resulting in a profound reduction of calcineurin phosphatase activity in peripheral blood mononuclear cells. Furthermore, headache and nausea, but not nephrotoxicity or hyperglycemia, took place throughout the period of the elevated blood concentrations. Grapefruit juice may have a clinically significant effect on the pharmacokinetics and pharmacodynamics of tacrolimus. It is recommended to avoid the consumption of grapefruit juice in transplant recipients treated with tacrolimus.

Key words: grapefruit juice; tacrolimus; pharmacokinetics; pharmacodynamics; liver transplantation

Introduction

Clinically relevant interactions have been reported between grapefruit juice and a number of drugs including cyclosporine, a substrate of cytochrome P450 (CYP) 3A4.1,2) The interaction has been considered to occur through a mechanism-based inhibition of the enzyme activity as well as downregulation of CYP3A4 protein expression in the gut wall by active ingredients in grapefruit juice.3) Tacrolimus is a calcineurin inhibitor that has been a cornerstone immunosuppressant in transplantation, and is metabolized extensively by CYP3A4 in enterocytes.4) We experienced a delayed interaction between grapefruit juice and tacrolimus in a living-donor liver transplant recipient. The aim of this study was to assess the potential effect of grapefruit juice on the pharmacokinetics and pharmacodynamics of tacrolimus.

Case Report

A 28-year-old female, who underwent a living-donor liver transplantation for biliary atresia at Kyoto University Hospital in 1999, had received maintenance immunosuppressive therapy consisting of tacrolimus, mycophenolate mofetil, and corticosteroids. The recipient was readmitted to the hospital because of an increase in liver enzyme concentrations 4 years after transplantation (day 0), and steroid pulse therapy was performed to treat biopsy-proven acute rejection between days 1 and 7. Chronic allograft rejection was histopathologically diagnosed on day 67, and the target trough blood concentration of tacrolimus was set within the range of 10 to 15 ng/mL. However, oral administration failed to effectively achieve a trough blood concentration above 10 ng/mL. Therefore, the continuous intravenous administration of tacrolimus was used to control the blood concentration within the target range for 4 weeks (average 1.8 mg/day). For her discharge
from the hospital, the administration of tacrolimus was converted to an oral dose of 6 mg/day on day 103. However, the trough blood concentration dropped below 5 ng/mL despite a dose escalation to as much as 10 mg/day. Finally, it was decided to use grapefruit juice as an urgent treatment to increase the blood tacrolimus concentration on day 111. The recipient was instructed to consume 250 mL of grapefruit juice (Minute Maid®) with her usual dose of tacrolimus (10 mg/day), as long as no severe adverse event was observed. Because it had become difficult for her to drink grapefruit juice due to its bitter taste, the recipient stopped the ingestion and consumed the juice a total of 4 times for 3 consecutive days (evening of day 111, morning and evening of day 112, and morning of day 113). The clinical course in the recipient before and after the intake of grapefruit juice is shown in Fig. 1.

Methods

Ethics: The evaluation of calcineurin phosphatase activity in blood samples was performed in accordance with the Declaration of Helsinki and its amendments, and was approved by the Kyoto University Graduate School and Faculty of Medicine Ethics Committee. Written informed consent was obtained from the recipient.

Drug assay: Blood samples were collected at around 8 AM to determine the whole blood concentration of tacrolimus with a microparticle enzyme immunoassay method.

Calcineurin phosphatase assay: The measurement of calcineurin phosphatase activity in peripheral blood mononuclear cells was conducted according to a procedure described previously.5,6) Pharmacokinetic analysis: Pharmacokinetic parameters including clearance (CL), volume of distribution (Vd), and bioavailability (F) before the intake of grapefruit juice were estimated by the Bayesian method using blood samples during the intravenous and oral administration with a population pharmacokinetic model.7) Assuming that the CL had been in a steady state after the first month of transplant, we used postoperative day 30 as a covariate of CL in the pharmacokinetic model. The elimination half-life (T1/2) before the ingestion was calculated as 0.693/(CL/Vd). The T1/2 after the increase in the blood tacrolimus
concentration was determined by linear regression for data points from the terminal phase of elevated blood concentrations.

**Results and Discussion**

Before the ingestion, the CL was approximately 5 times greater than the population mean estimate, and the $T_{1/2}$ was estimated as 10 h (Table 1). In addition, the F was about 3 times as large as the population mean estimate (Table 1). These results suggest that the large systemic clearance, probably by high CYP3A expression and activity in the liver, may be partly responsible for the difficulty to achieve the target blood concentration of tacrolimus in the recipient, although the Bayesian method applied in this study has a limitation to accurately estimate the CL and F. Grapefruit juice did not alter the trough blood concentration of tacrolimus during or immediately after its ingestion. However, 1 week after the final consumption of grapefruit juice, the trough blood concentration was remarkably increased to 37.2 ng/mL without any alteration in the recipient’s biochemical profile, resulting in discontinuation of the oral administration. Thereafter, the blood concentration of tacrolimus gradually decreased showing variable change. The elimination half-life was increased approximately 10-fold after the elevations in the blood tacrolimus concentration compared with that before the ingestion ($T_{1/2} = 108$ vs. 10 h), indicating impaired hepatic metabolism of tacrolimus following the ingestion of grapefruit juice. Furthermore, it took almost 1 week for the blood tacrolimus concentration to fall below 10 ng/mL from the maximum of 47.4 ng/mL.

With the remarkable increase in the blood tacrolimus concentration caused by the intake of grapefruit juice, the calcineurin activity dropped profoundly to near 20 pmol/min/mg protein on day 121 from 83 pmol/min/mg protein on day 113. Thereafter, the enzyme activity gradually recovered and stabilized at around 40 pmol/min/mg protein on day 129, when the trough blood concentration of tacrolimus reached 7.2 ng/mL. Although no serious adverse events including nephrotoxicity and hyperglycemia occurred in the recipient, headache and nausea took place throughout the period of elevated blood concentrations. Her liver function improved with resolution of the chronic rejection, and the recipient was discharged from the hospital on day 133. During the follow-up period after the discharge, the trough blood concentration of tacrolimus was maintained between 5 and 10 ng/mL, and no clinically relevant increase in calcineurin activity was observed.

Clearly, the calcineurin activity was concentration-dependently inhibited by tacrolimus (Fig. 2). However, the enzyme activity was not completely suppressed at the maximum blood concentration of tacrolimus (47.4 ng/mL). We have recently shown that acute rejection is associated with increased calcineurin activity in living-donor liver transplant patients. As compared with the reference curve of population mean predictions reported in living-donor liver transplant patients, the recipient might have had low sensitivity to tacrolimus before the increase in the blood concentration caused by the intake of grapefruit juice (Fig. 2). Furthermore, the insufficient inhibition of calcineurin activity by tacrolimus might have been related to the chronic rejection episode in the recipient.

Our results are not consistent with the previous

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**Table 1. Pharmacokinetic parameters of tacrolimus in the recipient before the intake of grapefruit juice**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Population mean estimates$^a$</th>
<th>Individual estimates$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (L/h)</td>
<td>1.29</td>
<td>6.61</td>
</tr>
<tr>
<td>$T_{1/2}$ (h)</td>
<td>50</td>
<td>10</td>
</tr>
<tr>
<td>Vd (L)</td>
<td>93.6</td>
<td>98.4</td>
</tr>
<tr>
<td>F (%)</td>
<td>7.32</td>
<td>22.2</td>
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</tbody>
</table>

$^a$The population mean estimates were determined with the following pharmacokinetic model:

$$CL = (0.743 + 0.0157 \times POD) \times 0.792^{RF} \times 0.810^{HW} \times 600 \text{ when } POD = 30, HF = 0 \text{ (total bilirubin < 2.5 mg/dL), RF = 0 (serum creatinine < 1 mg/dL), and HW = 640; } \text{Vd} = 1.64^{HF} \times BW \text{ when } BW = 57, \text{ and } F = 0.0732.$$

$^b$The individual estimates were determined by the Bayesian method using blood samples during the intravenous and oral administration with the above pharmacokinetic model.

CL, clearance; $T_{1/2}$, elimination half-life; Vd, volume of distribution; F, bioavailability; POD, postoperative day; HF, hepatic function; RF, renal function; HW, grafted hepatic weight; BW, body weight.

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**Fig. 2. Relationship between blood tacrolimus concentration and calcineurin activity in the recipient**

Data were chronologically connected with dotted line. Each arrow indicates the elapse of time. Solid line is a reference curve of population mean predictions reported in living-donor liver transplant patients.
findings that grapefruit juice increased bioavailability of cyclosporine in the gut wall without affecting the systemic clearance immediately after oral administration with grapefruit juice. Moreover, they also provided in vitro evidence to suggest that the increase in the blood concentration of tacrolimus by pomelo may be attributable not to the inhibition of P-glycoprotein, an efflux transporter acting as an absorptive barrier, but rather to the mechanism-based inactivation of CYP3A4 in the small intestine. Although we could not fully explain the delay in the interaction between grapefruit juice and tacrolimus, it is speculated that grapefruit juice may gradually decrease intestinal CYP3A protein concentration in addition to the inhibition of the enzyme activity, and can accelerate intestinal absorption of tacrolimus with a time-lag. Furthermore, the elevation of tacrolimus concentration in portal vein might have resulted in saturation of the large hepatic extraction and subsequent remarkable increase in the blood concentration of tacrolimus in the recipient. Although it is conceivable that the interaction of grapefruit juice with tacrolimus more likely occurred in this case, the possibility can not be excluded that intraindividual variability and potential fluctuations in the tacrolimus pharmacokinetics might be underlying the present phenomena.

In summary, the observations in the recipient are of clinical importance and provide certain evidence of an elevated trough blood concentration of tacrolimus, resulting in a marked inhibition of calcineurin activity in peripheral blood mononuclear cells after grapefruit juice is ingested. Because the time of onset and duration of the interaction, and the magnitude of the effect were less predictable, careful dose adjustment should be necessary on the basis of the patient’s response and the trough blood concentration if transplant recipients are consuming grapefruit juice while receiving tacrolimus.

In conclusion, grapefruit juice may have a clinically significant effect on the pharmacokinetics and pharmacodynamics of tacrolimus. It is recommended to avoid the consumption of grapefruit juice in transplant recipients treated with tacrolimus.

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References