Tacrolimus Interaction with Clotrimazole
A Concise Case Report and Literature Review
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INTRODUCTION
Tacrolimus (FK506, Prograf) is a macrolide immunosuppressant that has become the mainstay of maintenance regimens in solid-organ transplantation. Both tacrolimus and cyclosporine undergo intestinal metabolism mediated predominantly by the cytochrome P450 3A4 (CYP 3A4) isoenzyme family, and they are substrates for P-glycoprotein (P-gp), a drug transport pump.

A number of clinically significant drug interactions occur between calcineurin inhibitors (CNIs) and commonly used agents, with the CYP 3A4 and P-gp systems playing a central role in CNI metabolism. Some of these widely used medications that inhibit these systems—such as erythromycin (e.g., E-mycin, Abbott), clarithromycin (Biaxin, Abbott), fluconazole (Diflucan, Pfizer), and the calcium-channel blockers verapamil (Calan, Pfizer; Verelan, Schwarz) and diltiazem (Cardizem, Biovail)—may potentiate CNI toxicity.1–5 Pharmacokinetic profiles of CNIs may have a significant role in drug interactions that occur with other agents frequently used in the post-transplant period.

Routine prophylaxis of oral thrush in post-transplant patients involves the administration of an azole antifungal agent, clotrimazole, in the form of buccal troches (Mycelex Troche, Ortho-McNeil). Similar to the other azole antifungal agents and the CNIs, clotrimazole undergoes metabolism by the CYP 3A4 system. However, given the unique delivery of clotrimazole via oral dissolution in the mouth, it had been widely presumed that systemic absorption was minimal. The first case report documenting an increase in tacrolimus serum concentrations was in a clotrimazole-treated liver transplant recipient, resulting in acute renal impairment.5

To date, there is a paucity of data characterizing the interaction between clotrimazole and CNIs; a review of the literature depicts two studies in which clotrimazole caused an increase in the bioavailability of tacrolimus that warranted a reduction in the tacrolimus dose to prevent toxicity. Although the exact mechanism of the interaction remains elusive, it is hypothesized that medications that either induce or inhibit CYP 3A4, P-gp, or both, alter the oral pharmacokinetics of CNIs.7

Lown et al. further concluded that besides CYP 3A4 activity, intestinal P-gp might play a significant role in the first-pass elimination of cyclosporine by being a rate-limiting step in absorption.8 Until further data are available, outcomes on drug interactions from studies conducted with cyclosporine will apply to tacrolimus and as a class effect.

This article describes a drug interaction that was observed in the transplantation clinic at North Shore University Hospital.

Case Study
The patient was a 23-year-old African-American woman with a history of end-stage renal disease secondary to membranous glomerulonephropathy who underwent live donor kidney transplantation. Immunosuppressive therapy consisted of tacrolimus 5 mg twice daily; mycophenolate mofetil (CellCept, Roche) 1,000 mg twice daily; and prednisone 30 mg daily, tapered over time to 5 mg daily.

Routine prophylaxis with clotrimazole troche (10-mg troches four times daily) was undertaken for the first postoperative month. Discontinuation of clotrimazole was associated with a decrease in tacrolimus trough levels from 13.7 to 5.4 ng/mL over a period of six days (Table 1).

After other potential causes of reduced tacrolimus levels were addressed, such as other pharmacological interactions and non-compliance, clotrimazole was restarted. An increased tacrolimus dose of 6 mg twice daily and the restarting of clotrimazole led to an increased level of tacrolimus 19.2 ng/mL on postoperative day 40. The dose of tacrolimus was then decreased to 4.5 mg twice daily, yielding a level of 13.4 ng/mL on postoperative day 44.

To achieve the target tacrolimus level of 11 to 12 ng/mL for the second month, the tacrolimus dose was further lowered to 4 mg twice daily. Clotrimazole was subsequently discontinued after the third post-transplant month, when the target tacrolimus level was between 4 and 7 ng/mL. The patient did not experience any adverse events from this drug interaction.

DISCUSSION
Discontinuing clotrimazole therapy was observed to have an effect of subtherapeutic tacrolimus serum concentrations in the early post-transplant period for this patient; subsequent actions included increasing the tacrolimus dose and restarting clotrimazole to prevent rejection. The exact mechanism that causes a rise in tacrolimus serum levels in clotrimazole-treated patients is unclear; however, a detailed background on drug metabolism aids in recognizing the dynamic interplay between metabolizing enzymes and efflux proteins.

Decreased bioavailability may be linked to impaired uptake or enhanced metabolism. It is thought that CYP 3A4 and P-gp complement each other because of their similar substrate specificity and their joint presence in small intestinal enterocytes, leading to coordination of an absorption barrier against drugs.9

The CYP 450 system has been well studied and accounts for most drug interactions pertaining to CNIs. Specifically, CYP 3A4 is responsible for phase 1 biotransformation reactions. P-gp, a membrane-bound drug efflux protein expressed on the intestinal epithelial cells, inhibits drug absorption.10

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**Table 1: Clinical Data from the Transplant Clinic Visit at North Shore University Hospital**

<table>
<thead>
<tr>
<th></th>
<th>Postoperative Day 31</th>
<th>Postoperative Day 37</th>
<th>Postoperative Day 38</th>
<th>Postoperative Day 40</th>
<th>Postoperative Day 44</th>
<th>Postoperative Day 49</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tacrolimus dose</td>
<td>4.5 mg twice daily</td>
<td>4.5 mg twice daily</td>
<td>6 mg twice daily</td>
<td>6 mg twice daily</td>
<td>4.5 mg twice daily</td>
<td>4 mg twice daily</td>
</tr>
<tr>
<td>Tacrolimus trough levels (ng/mL)*</td>
<td>13.7</td>
<td>5.4</td>
<td>4.2</td>
<td>19.2</td>
<td>13.4</td>
<td>11.3</td>
</tr>
<tr>
<td>Clotrimazole troche 10 mg four times daily</td>
<td>Discontinue</td>
<td>Restart</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*aTarget tacrolimus trough levels: first month: 12–15 ng/mL; second month: 10–12 ng/mL; third month: 8–10 ng/mL; after three months: 4–7 ng/mL.

absorption. Drug interactions formerly thought to be mediated only by the CYP 450 system may actually be related to the inhibition of P-gp. Furthermore, an increase in exposure and rapid metabolism by intestinal CYP 3A4 may occur as a result of repeated efflux–influx cycles of cyclosporine via P-gp. This would potentially decrease the rate of absorption and result in increased drug metabolism by CYP 3A4 relative to the drug as it crosses the intestine.

Two publications by Vasquez et al. have suggested that the interaction between tacrolimus and clotrimazole is presumably mediated by both CYP 3A4 and P-gp.

In a study of 35 tacrolimus-treated renal allograft recipients, mean tacrolimus trough levels were significantly higher in clotrimazole-treated patients on days 3, 5, and 7 (42 ± 14, 53 ± 7, and 33 ± 17 ng/mL, respectively) than in patients receiving nystatin (Mycostatin, Bristol-Myers Squibb) (15 ± 8, 15 ± 7, and 14 ± 6, respectively) (P < 0.05). Further, average tacrolimus doses were lower in the clotrimazole patients than in the nystatin group by day 7 (P < 0.05). These differences suggest an inhibitory cause, because drug effects on CYP 3A4 are not immediate. In addition, P-gp inhibition may play a role in the interaction that led to increased tacrolimus trough levels.

An open-label pharmacokinetic study, also by Vasquez et al., reported that six patients receiving stable doses of tacrolimus experienced a substantial increase in the rate and extent of tacrolimus absorption with concurrent administration of clotrimazole. Both the area-under-the-curve (AUC) and trough concentrations more than doubled with concomitant clotrimazole therapy (AUC0–12 467 vs. 188.7 ng • hours/mL, P = 0.002; and 27.7 vs. 11.6, P = 0.003, respectively). Two of the six patients receiving concomitant clotrimazole therapy complained of headache.

The Drug Interaction Probability Scale indicates a probable relationship to clotrimazole buccal troche, leading to a decrease in the clinic patient’s tacrolimus trough level upon routine discontinuation.

**CONCLUSION**

The case study and observations described in this article further substantiate the hypothesis that the presence of CYP 3A4 or P-gp in the intestine plays a role in the oral bioavailability of medications such as cyclosporine and tacrolimus. Concomitant administration of clotrimazole and tacrolimus in the transplantation clinic led to a decrease in tacrolimus trough levels upon routine discontinuation of clotrimazole. The dose of tacrolimus was subsequently adjusted, and clotrimazole was reinitiated to avoid subtherapeutic trough levels, which may potentiate rejection.

Clinicians should be cognizant of the interaction between CNIs and clotrimazole and should adhere to vigilant monitoring when discontinuing the antifungal agent. Additional pharmacokinetic studies are needed to fully describe this interaction.

**REFERENCES**