Pharmacokinetic Evaluation of the Drug Interaction between Intravenous Itraconazole and Intravenous Tacrolimus or Intravenous Cyclosporin A in Allogeneic Hematopoietic Stem Cell Transplant Recipients

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ABSTRACT

A single-institution, open-label prospective pharmacokinetic evaluation of the interaction between intravenous itraconazole and intravenous cyclosporin A and tacrolimus was conducted in allogeneic hematopoietic stem cell transplant recipients. The study was conducted in 2 phases, with patients acting as their own controls. In phase 1, steady-state concentrations and clearance of cyclosporin A and tacrolimus administered alone were evaluated. Phase 2 evaluated serum concentrations and clearance of cyclosporin A and tacrolimus administered alone were evaluated. Phase 2 evaluated serum concentrations and clearance of cyclosporin A and tacrolimus administered alone were evaluated. Phase 2 evaluated serum concentrations and clearance of cyclosporin A and tacrolimus under the influence of itraconazole therapy. Among 17 patients who completed both phases of the study, the mean increase in the serum tacrolimus concentration was 83% (P < .0001), and the mean increase in the serum cyclosporin A concentration was 80% (P = .0001). There was no correlation between serum itraconazole concentrations and the serum concentrations of tacrolimus or cyclosporin A. The drug interaction between itraconazole and calcineurin inhibitors is predictable and occurs within 48 hours of concomitant drug administration. The data suggest that dose reductions of tacrolimus and cyclosporin A in the range of 50% to 100% are necessary when itraconazole therapy is initiated and that subsequent close monitoring of serum concentrations is necessary to guide further dose modifications.

KEY WORDS

Itraconazole ● Cyclosporin A ● Tacrolimus ● Allogeneic hematopoietic stem cell transplantation ● Calcineurin inhibitor ● Drug interaction ● Pharmacokinetic

INTRODUCTION

Patients undergoing hematopoietic stem cell transplantation (HSCT) are at risk of developing bacterial, viral, and fungal infections as a consequence of immunosuppression and prolonged marrow suppression from cytotoxic chemotherapy in the preparative regimen. Similarly, posttransplantation immunosuppression to prevent the development of, as well as to treat, graft-versus-host disease increases the susceptibility to such infections.

Superficial and systemic fungal infections are important causes of morbidity and mortality in immunocompromised patients despite the aggressive use of antifungal agents. Administration of systemically available azole antifungal agents as part of the prophylactic strategy in this population has resulted in significant reductions in the number of systemic fungal infections [1-8], superficial fungal infections [2,7], fungal colonization [2], and the empiric use of amphotericin B [1,2,7]. The current Centers for Disease Control/Infectious Disease Society of America/American Society of Blood and Marrow Transplantation consensus guidelines for preventing opportunistic infections among HSCT recipients recommend routine use of flu-
conazole in HSCT recipients from day 0 until engraftment [9]. Fluconazole, although highly effective against *Candida albicans*, is ineffective against mold pathogens such as *Aspergillus* species that are being increasingly described in HSCT recipients [10]. Itraconazole, another triazole, has demonstrated a broader spectrum of activity against a wide variety of *Candida* and *Aspergillus* species [11-13].

The widespread use of itraconazole was limited in the past because of the lack of a formulation that provides reliable serum concentrations. Published data suggest that protection against *Aspergillus* species is best achieved with serum itraconazole concentrations >500 ng/mL [8,14]. The availability of both an oral solution (much improved bioavailability) and an intravenous (IV) formulation makes the attainment of target serum concentrations much more reliable. Recent data suggest a protective effect of itraconazole against invasive mold infections when used prophylactically in HSCT recipients [15,16] and in patients with hematologic malignancies [8]. Although it offers a broader spectrum of antifungal activity, itraconazole has several potential drug interactions in HSCT patients. Itraconazole is a potent inhibitor of the cytochrome P450 (CYP) 3A4 isoenzyme system, a common metabolic pathway for many medications. One of the most important interactions requiring consideration is that between itraconazole and the calcineurin inhibitors cyclosporin A and tacrolimus.

There are several published reports outlining a potential drug interaction between cyclosporin A and itraconazole in solid organ transplant recipients and HSCT recipients [17-24]. Increases in cyclosporin A serum concentrations ranged from 40% to 226% and often resulted in increases in serum creatinine. Similarly, several case reports/case series demonstrate a drug interaction between tacrolimus and itraconazole, with increases in serum tacrolimus concentrations up to 6.6-fold [19,25-31]. All of these reports involve the interaction between oral itraconazole and oral calcineurin inhibitors. An evaluation of the pharmacokinetic drug interaction between IV itraconazole and IV cyclosporin A/tacrolimus has not been reported. It can be hypothesized that the drug interaction would be similar despite differences in the route of administration, but this cannot be assumed. Earlier work characterizing the pharmacokinetic drug interaction between IV fluconazole and IV cyclosporin A/tacrolimus failed to demonstrate a clinically meaningful increase in serum cyclosporin A/tacrolimus concentrations [32], despite numerous case reports in the literature demonstrating a drug interaction when fluconazole and calcineurin inhibitors were administered orally [33-35]. We therefore conducted an open-label, prospective evaluation of the pharmacokinetic drug interaction between IV itraconazole and IV cyclosporin A and IV tacrolimus.

### METHODS

#### Study Design

A single-institution, open-label, prospective comparative pharmacokinetic study was performed from June 2000 to February 2002.

#### Study Population

Twenty-seven allogeneic (sibling and matched unrelated donor) HSCT recipients participated in a within-subject pharmacokinetic study to determine the effect of IV itraconazole on the pharmacokinetic profile of IV administered calcineurin inhibitors (cyclosporin A and tacrolimus). This study had the approval of the Institutional Review Board of the University of Florida, and voluntary, written, informed consent was obtained before any study procedures were undertaken. The US Department of Health and Human Services guidelines for human experimentation were followed in the conduct of this clinical research.

Men and women were enrolled in the study if they were eligible for an allogeneic (sibling or matched unrelated donor) HSCT protocol, were at least 18 years old, were receiving tacrolimus at the same dose for at least 60 hours before both pharmacokinetic evaluations or cyclosporin A at the same dose for at least 95 hours before both pharmacokinetic evaluations, were not being treated with medications that might affect hepatic CYP function, and had either tacrolimus blood concentrations of 5 to 15 ng/mL or cyclosporin A blood concentrations of 150 to 225 ng/mL before entry onto this study. To complete the study, patients had to have stable renal and hepatic function throughout both phases. Subject characteristics are summarized in Table 1. Patients were excluded from this study if they displayed unstable or impaired renal function, if they demonstrated evidence of an active fungal infection, if they were receiving other systemic prophylactic azole antifungal therapy within 7 days of study entry, or if they were receiving any drugs known to interact with the calcineurin inhibitors by induction or inhibition of the CYP3A4 isoenzyme system.

Upon determination of study eligibility, patients undergoing an allogeneic HSCT, either from a sibling or a matched unrelated donor, received either (1) tacrolimus administered as a continuous infusion (0.03 mg/kg ideal body weight per day) from the day before HSCT (day −1) until engraftment or (2) cyclosporin A 1.5 mg/kg (ideal body weight) IV as a 3-hour infusion every 12 hours from the day before HSCT until engraftment. Itraconazole injection at a dose of 200 mg IV every 12 hours for 2 days, followed by 200 mg IV daily, was initiated once steady state was achieved with either tacrolimus or cyclosporin A and the patients exhibited stable tacrolimus/cyclosporin A blood...
levels. All medications were administered IV through the transplantation course until granulocyte recovery (absolute neutrophil count >250/µL) or improvement of mucositis to World Health Organization grade I/II.

This study involved 2 separate phases, and each patient acted as his or her own control. In phase 1, once patients were at steady state and demonstrated stable tacrolimus/cyclosporin A dosing, daily serum tacrolimus/cyclosporin A concentrations were collected. The mean of 2 stable steady-state blood levels was used in the calculation of clearance. Upon completion of this phase, IV itraconazole therapy was initiated. Once steady state with itraconazole was achieved (approximately 2 days), daily blood samples were drawn to measure tacrolimus/cyclosporin A serum concentrations under the influence of itraconazole. The mean of 4 consecutive days of stable steady-state blood concentrations was used to calculate clearance. Itraconazole and hydroxyitraconazole levels were monitored daily after the attainment of steady state.

Serum creatinine was monitored daily, and liver function tests were monitored 3 times a week for the duration of the study. Concomitant medications that could potentially interact with tacrolimus or cyclosporin A were recorded.

**Drug Sampling**

On pharmacokinetic study days, whole-blood samples (5 mL) were obtained through the central line or via venipuncture and drawn into Vacutainer tubes (Becton Dickinson, Franklin Lakes, NJ) immediately before dosing. The cyclosporine whole-blood assay was used to quantitate the cyclosporin A concentration by using the fluorescence polarization immunoassay technology previously described. Once collected, samples were centrifuged in the laboratory at 9500 g for 5 minutes and assayed by using standard methodology. Tacrolimus serum concentrations were quantified by using the Imx Tacrolimus II assay (Abbott Diagnostics, Abbott Park, IL) with microparticle enzyme immunoassay technology. Trough blood samples for itraconazole were collected into a red-top tube, and the specimen was allowed to clot for 60 minutes. The serum was separated from the clot by centrifugation (3000 rpm for 10 minutes). The serum was removed by pipette into cryovials and frozen at −80°C. Samples were batched and sent frozen on dry ice to the Fungus Testing Laboratory in San Antonio, TX, for analysis.

**Itraconazole Assay**

Serum concentrations of itraconazole and hydroxyitraconazole were assayed with a previously described modified and validated reverse-phase high-performance liquid chromatography method [36].

**Pharmacokinetic Analysis**

Steady-state concentrations and clearance were compared between tacrolimus/cyclosporin A alone and tacrolimus or cyclosporin A with concomitant itraconazole.
Clearance was calculated with the following formula:

\[
\text{Dose (ng)/1440 (min) / Tacrolimus or cyclosporin A level (ng/mL) x IBW (kg) = mL/min/kg}
\]

**Statistical Analysis**

The change in tacrolimus or cyclosporin A concentrations and clearance with and without concomitant itraconazole was evaluated by using the paired difference t test after the Shapiro-Wilk test results demonstrated that the normality assumptions were satisfied. A change was considered to be statistically significant if the \(P\) value was <.05. A clinically meaningful change was predetermined to be 35% to 100%. The correlation between mean steady-state concentrations of itraconazole or hydroxyitraconazole with either tacrolimus or cyclosporin A was evaluated by using the Pearson correlation after the Shapiro-Wilk test results demonstrated that the normality assumptions were satisfied.

**RESULTS**

**Study Participants**

Twenty-seven patients were enrolled in this trial, and 17 successfully completed both phases of the study. Of the 10 patients who did not complete both phases, 2 were changed to alternate antifungal therapy (1 patient developed oral thrush before the initiation of itraconazole; 1 patient was switched to conventional amphotericin B for persistent fever), 3 were unable to achieve stable serum concentrations of cyclosporin A/tacrolimus within the allocated time, 1 patient developed renal dysfunction (due to sepsis from gram-positive bacteremia), 1 patient had elevated liver function tests at the completion of phase 1 before the initiation of itraconazole therapy, 1 patient developed vertigo during each itraconazole infusion and asked to be withdrawn, and 2 patients were protocol violations. Therefore, 17 patients were eligible for evaluation: 9 patients receiving tacrolimus and 8 patients receiving cyclosporin A.

**Itraconazole Serum Levels**

At the completion of the itraconazole loading dose (200 mg IV every 12 hours for 4 doses), the mean steady-state concentration was 0.541 \(\pm\) 0.326 ng/mL (median, 0.430 ng/mL; range, 0.136-1.214 ng/mL) for all 17 patients. At this time, 88.2% of patients achieved an itraconazole serum concentration of \(>250\) ng/mL, and 35.3% achieved an itraconazole serum concentration of \(\geq500\) ng/mL. Repeat itraconazole concentrations on the last day of the pharmacokinetic analysis resulted in 88.2% of patients achieving a serum itraconazole concentration \(>250\) ng/mL and 70.6% achieving a serum itraconazole concentration \(>500\) ng/mL. The mean serum itraconazole and hydroxyitraconazole concentrations achieved over time are shown in Table 2.

**Cyclosporin A/Tacrolimus Serum Levels**

The mean daily steady-state tacrolimus concentrations ranged from 7.6 to 12.75 ng/mL before the initiation of itraconazole and ranged from 16.65 to 22.52 ng/mL after the initiation of itraconazole therapy. The second set of serum concentration estimates was obtained starting 2 days after the initiation of IV itraconazole therapy. The mean of 4 days of serum concentration estimates was calculated. The mean steady-state cyclosporin A concentration without itraconazole was 101.5 \(\pm\) 216 ng/mL and increased to 226.25 to 298.5 ng/mL after the initiation of itraconazole therapy, as previously described. The daily distribution of the immunosuppressant levels is illustrated in box plots in Figures 1 and 2. The mean daily steady-state cyclosporin A concentration ranged from 101.5 to 216 ng/mL before the initiation of itraconazole and ranged from 226.25 to 298.5 ng/mL after the initiation of itraconazole therapy, as previously described. The daily distribution of the immunosuppressant levels is illustrated in box plots in Figures 1 and 2.
Correlation between Itraconazole Levels and Changes in Serum Concentrations of Calcineurin Inhibitors

The association between mean steady-state itraconazole with either tacrolimus or cyclosporin A concentrations, by using Pearson correlation coefficients, was not significant (tacrolimus: $R = 0.532$, $P = .14$; cyclosporine, $R = -0.189$, $P = .65$). Associations between the mean steady-state hydroxyitraconazole with either tacrolimus or cyclosporin A concentrations was also not significant (tacrolimus: $R = 0.518$, $P = .15$; cyclosporine, $R = 0.048$, $P = .91$).

Dose Modifications of Calcineurin Inhibitors

Among tacrolimus recipients, 1 patient (11.1%) required a 20% increase in the dose of tacrolimus, and 3 patients required no dosage modifications. Five patients (55.5%) required tacrolimus dose reductions. These reductions ranged from 20% to 76.5%. Among cyclosporin A recipients, 62.5% of patients required no dosage modifications, and 37.5% required cyclosporin A dose reductions that ranged from 24.4% to 41.1%.

Toxicity and Clinical Outcome

Two patients had a documented adverse event attributable to itraconazole therapy. One patient developed renal dysfunction as a consequence of sustained increased serum concentrations of tacrolimus, and 1 patient experienced a burning sensation during each infusion of itraconazole, although treatment was not stopped for this event. Four patients (23.5%) had itraconazole therapy changed to alternative antifungal therapy (2 patients changed to conventional amphotericin B, 1 patient changed to amphotericin B lipid complex, and 1 patient had conventional amphotericin B added to itraconazole therapy), although each patient completed both phases of the study before antifungal modification.

The median baseline serum creatinine level was 0.7 mg/dL (range, 0.5-1.3 mg/dL), which increased to a median peak serum creatinine level of 0.9 mg/dL (range, 0.4-1.5 mg/dL) during treatment with itraconazole and cyclosporin A/tacrolimus and remained at this value at the end of itraconazole therapy. The median peak bilirubin level during concomitant itraconazole and cyclosporin A/tacrolimus therapy was 0.9 mg/dL (range, 0.3-4.6 mg/dL), and this declined to 0.7 mg/dL at the end of itraconazole therapy (range, 0.2-5.1 mg/dL).

Among our study participants, the increases in serum concentrations of cyclosporin A and tacrolimus were relatively consistent. To explore whether or not phenytoin, given to patients receiving busulfan-containing preparative regimens, may have affected the interaction, we compared the results in recipients receiving phenytoin seizure prophylaxis ($n = 9$) with those in patients who were not receiving seizure prophylaxis ($n = 8$) within each group. Among patients in the tacrolimus group, there was no significant difference in the magnitude of the interaction between phenytoin and nonphenytoin recipients. Similarly, in the cyclosporin A group, there was no significant difference between the phenytoin and nonphenytoin group and the effect on increases in serum concentrations of cyclosporin A.

DISCUSSION

Azole antifungals differ not only in their spectrum of activity, but also in their metabolic pathways. These drugs are metabolized by the CYP isoenzyme system, the subfamily of CYP enzymes that seem to be responsible for the metabolism of the widest range of drugs and exogenous compounds in humans. Drugs that require metabolism by the same CYP enzymes compete for binding to and metabolism by CYP.
Therefore, in theory, any 2 drugs that are metabolized by identical CYP isoenzymes have a potential for interaction; however, the clinical significance of this interaction will rely on the drugs’ relative affinities for binding to these enzymes, concentrations achieved in the endoplasmic reticulum after therapeutic doses, dependence on CYP for elimination, and therapeutic ratios [37,38]. Fluconazole, theazole used extensively as prophylaxis against *Candida* species infections in HSCT recipients, inhibits and is metabolized by the CYP isoenzymes. Fluconazole is not a potent inhibitor of CYP3A4 isoenzymes at lower doses (<200 mg/d), but at higher doses it can inhibit CYP3A4. Itraconazole is also capable of inhibiting and being metabolized by CYP3A4 isoenzymes. Itraconazole is a far more potent inhibitor of the CYP3A4 isoenzymes and, as a consequence, may result in more drug interactions, as well as a greater magnitude when an interaction occurs.

Tacrolimus and cyclosporin A are primarily metabolized by CYP3A4 isoenzymes. The CYP3A4 isoenzymes are the most abundant isoforms of CYP, accounting for nearly 30% of the total CYP content in the human liver and as much as 70% in the gut wall. Therefore, there is a potential for major drug interactions between itraconazole, a potent inhibitor of CYP3A4, and cyclosporin A and tacrolimus. It has been postulated that tacrolimus and cyclosporin A are also metabolized in the intestine by CYP 3A4 isoenzymes. If this does occur, it might explain why a drug interaction is seen with other azoles and tacrolimus or cyclosporine when administered orally and not when administered IV. Earlier drug interaction research with fluconazole and tacrolimus/cyclosporin A yielded conflicting results (occurrence and magnitude) depending on the route of administration [32-35]. Numerous case reports demonstrated an interaction between oral fluconazole and oral tacrolimus/cyclosporin A. Osowski et al. [32] evaluated the drug interaction between IV fluconazole and IV tacrolimus/cyclosporin A in HSCT recipients. When administered IV, there was no statistically or clinically significant difference in the steady-state concentrations of tacrolimus and a statistically, but not clinically, significant increase (21%) in the serum cyclosporin A concentration.

These are considerable differences between theazole antifungals in their metabolic pathways, target CYP isoenzymes, and ability to inhibit CYP3A4 isoenzymes. This study was able to clearly characterize the pharmacokinetic drug interaction between IV itraconazole and IV tacrolimus/cyclosporin A. In this controlled pharmacokinetic study, we documented increases in mean steady-state serum concentrations of cyclosporin A and tacrolimus in all study subjects. The mean steady-state increase in the serum concentration of cyclosporin A and tacrolimus was 80% and 83%, respectively; however, there was considerable variability in the magnitude of the increase. Among patients who received cyclosporin A and itraconazole, the increase in serum cyclosporin A concentrations ranged from 24% to 149%. Similarly, tacrolimus recipients experienced increases in serum concentrations ranging from 49% to 117%. The onset of the increase in serum concentration occurred within 48 to 72 hours of the initiation of IV itraconazole. These data suggest that a reduction in cyclosporin A and tacrolimus in the range of 50% to 100% is needed and that this reduction would be advisable at the time of initiation of itraconazole. Because of the considerable variability in the magnitude of increase seen, no precise dose modification is likely to precisely achieve the desired blood concentration. One should weigh the relative risks of nephrotoxicity (from excessive calcineurin inhibitor exposure) and graft-versus-host disease (from low concentrations of calcineurin inhibitors) in judging the best dose reduction for a given patient.

Future studies could prospectively evaluate the effect of a prespecified dose reduction. There are several reports in the medical literature that describe an interaction between oral cyclosporin A and oral itraconazole and between oral tacrolimus and oral itraconazole. Most of the data for cyclosporin A arise from case reports in solid organ transplant candidates and are summarized in Table 3. The magnitude of the interaction seen with oral itraconazole, cyclosporin A, and 3-hydroxy-3-methylglutaryl-coenzyme A–reductase inhibitors were administered, rhabdomyolysis resulted [21,22]. The magnitude of the interaction seen with oral itraconazole and oral cyclosporin A is comparable to the magnitude of the interaction we have described with both agents administered IV.

Similarly, several case reports and case series characterize a drug interaction between oral tacrolimus and oral itraconazole, and these are summarized in Table 4. Serum concentrations of tacrolimus increased from 2- to 6.6-fold [25,27,28], thus necessitating dose reductions of 45% to 75% [18,25,26,29-31]. In 1 case report, the addition of 400 mg of oral itraconazole to a kidney transplant recipient receiving 7 mg of tacrolimus daily resulted in a 14-fold dose reduction, to a daily maintenance dose of 0.4 mg [28]. The magnitude of these reported interactions varies considerably, and the cause of this remains unknown because of the nature of the reports. Our data with IV tacrolimus and IV itraconazole are comparable to the results seen with oral administration.
Therefore, the pharmacokinetic drug interaction between IV itraconazole and IV tacrolimus/cyclosporin A differs considerably from the drug interaction between IV fluconazole and IV tacrolimus/cyclosporin A. A drug interaction that is clinically and statistically significant occurs between IV itraconazole and IV tacrolimus/cyclosporin A. The magnitude is similar to that reported with oral administration in numerous case reports, case series, and small pharmacokinetic analyses [17-31].

When designing this pharmacokinetic interaction study, we made an assumption, based on data from the manufacturer, that steady-state concentrations of itraconazole are achieved after the completion of the loading dose of IV itraconazole. We measured the concentrations of itraconazole and its metabolite hydroxyitraconazole from baseline through the completion of the pharmacokinetic analysis. Itraconazole and hydroxyitraconazole serum concentrations varied considerably from subject to subject. Upon analysis of the results, it is clear that adequate concentrations required to "prevent" an aspergillus infection were not achieved within that timeframe in most patients. The literature suggests that serum itraconazole concentrations of ≥500 ng/mL are required to prevent Aspergillus species infections [1,8,14,39]. At the completion of the loading dose, only 33% of patients had achieved this target concentration, and by the end of the pharmacokinetic analysis (at least 72 hours later), the proportion of patients who achieved this concentration increased to 71%. This suggests that steady-state concentrations were not achieved. Although the mean serum concentration of itraconazole at the conclusion of the loading dose was higher [40-41], this may be due to the fact that in this literature and our study, patients who achieved a serum concentration of ≥500 ng/mL after the loading dose were not included in the statistical analysis of the pharmacokinetic trial. Earlier clinical trials did not report that the current dose is insufficient to rapidly obtain a therapeutic concentration. Clinicians should not anticipate that most patients will be within the therapeutic range for 5 to 7 days after the completion of the loading dose, and this suggests that the current dose is insufficient in this patient population. Further analysis of the pharmacokinetic trial is needed to determine whether there was any effect of serum itraconazole and hydroxyitraconazole concentrations on the magnitude of the drug interaction with tacrolimus.

### Table 3. Literature Reports Characterizing a Drug Interaction between Itraconazole and Cyclosporine

<table>
<thead>
<tr>
<th>Study</th>
<th>No./Transplant Type</th>
<th>Data Type</th>
<th>Dose and Route of Cyclosporine Administered (before Interaction)</th>
<th>Dose of Itraconazole and Route of Administration</th>
<th>Results</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kwan et al. [17]</td>
<td>1/kidney</td>
<td>Case report</td>
<td>90 mg PO BID</td>
<td>100 mg PO BID × 6 weeks</td>
<td>↑ [CyA] 226%</td>
<td>↑ SCr 37%</td>
</tr>
<tr>
<td>Kramer et al. [18]</td>
<td>7/heart-lung (4); heart (2); lung (1)</td>
<td>Case series</td>
<td>Not stated</td>
<td>Not stated</td>
<td>↓ CyA dose by 33-84% (mean, 56%); ↓ SCr 25%, ↑ CRCl 35%</td>
<td>No other toxicities</td>
</tr>
<tr>
<td>Trenk et al. [20]</td>
<td>1/heart</td>
<td>Case report</td>
<td>110 mg PO TID</td>
<td>200 mg PO QD × 6 weeks</td>
<td>↑ [CyA] 40%</td>
<td>No change in SCr</td>
</tr>
<tr>
<td>Kramer et al. [19]</td>
<td>10 (7 × CyA; 3 × tacrolimus)/lung (9); heart-lung (1)</td>
<td>Case series</td>
<td>Not stated</td>
<td>100 mg PO BID × 3 months</td>
<td>↓ CyA dose by 48.5%; ↓ CyA daily cost by 9.5%</td>
<td>Not stated</td>
</tr>
<tr>
<td>Vlahanos et al. [21]</td>
<td>1/heart</td>
<td>Case report</td>
<td>225 mg PO QD</td>
<td>100 mg PO BID</td>
<td>↑ [CyA] 53% after 1 wk</td>
<td>↑ SCr and renal failure</td>
</tr>
<tr>
<td>Maxa et al. [22]</td>
<td>1/heart</td>
<td>Case report</td>
<td>75 mg PO BID</td>
<td>200 mg PO QD</td>
<td>Not stated</td>
<td>Rhabdomyolysis</td>
</tr>
<tr>
<td>Wimberley et al. [23]</td>
<td>24/lung</td>
<td>PK study</td>
<td>Varied</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Rhabdomyolysis</td>
</tr>
<tr>
<td>Florea et al. [24]</td>
<td>8/renal</td>
<td>PK study</td>
<td>PO; not stated</td>
<td>200 mg PO QD</td>
<td>↓ CyA dose by 48%</td>
<td>↑ CyA-induced nephrotoxicity</td>
</tr>
</tbody>
</table>

PO indicates orally; [CyA], cyclosporine concentration; SCr, serum creatinine; CRCl, creatinine clearance; ↑, increase; ↓, decrease; ↔, no change; LFTs, liver function tests; BID, twice a day; TID, 3 times a day; QD, once daily; PK, pharmacokinetic; CyA, Cyclosporin A.

*Patient also taking concomitant simvastatin.
Table 4. Literature Reports Characterizing a Drug Interaction between Itraconazole and Tacrolimus

<table>
<thead>
<tr>
<th>Authors</th>
<th>No./Transplant Type</th>
<th>Data Type</th>
<th>Dose and Route of Tacrolimus Administered (before Interaction)</th>
<th>Dose of Itraconazole and Route of Administration</th>
<th>Results</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kramer et al. [19]</td>
<td>10 (7 CyA; 4 FK)/lung (9), heart-lung (1)</td>
<td>Case series</td>
<td>Not stated</td>
<td>100 mg PO BID × 3 mo</td>
<td>FK dose 65%; Daily cost of FK by 48%</td>
<td>Not stated</td>
</tr>
<tr>
<td>Ideura et al. [25]</td>
<td>1/kidney</td>
<td>Case report</td>
<td>Not stated</td>
<td>100 mg PO QD</td>
<td>FK dose 75%; FK dose 0.035 mg/kg √FK dose 75% proven</td>
<td>Not stated</td>
</tr>
<tr>
<td>Outeda Macias et al. [26]</td>
<td>1/kidney</td>
<td>Case report</td>
<td>0.1 mg/kg/d PO</td>
<td>Dose not stated</td>
<td>[FK] 3-fold FK dose 45-75%*</td>
<td>Not stated</td>
</tr>
<tr>
<td>Furlan et al. [27]</td>
<td>1/lung (7); double-lung (7); heart-lung (9); heart (3)</td>
<td>Case series</td>
<td>8.4 mg/d (mean dose)</td>
<td>100 mg PO BID</td>
<td>No significant changes in SCr or LFTs</td>
<td>Not stated</td>
</tr>
<tr>
<td>Banerjee et al. [29]</td>
<td>1/kidney</td>
<td>Case report</td>
<td>4 mg QAM/3 mg QPM PO</td>
<td>400 mg PO QHS</td>
<td>Daily cost by 62%</td>
<td>Not stated</td>
</tr>
<tr>
<td>Cervelli and Russ [28]</td>
<td>1/lung (11)</td>
<td>Case series</td>
<td>Not stated</td>
<td>0.4 mg/d</td>
<td>FK requirements by 68%</td>
<td>Not stated</td>
</tr>
<tr>
<td>Capone et al. [30]</td>
<td>1/kidney</td>
<td>Case report</td>
<td>22/heart (2); heart-lung (9);</td>
<td>100 mg PO BID × 5 d</td>
<td>FK dose by 50%</td>
<td>Not stated</td>
</tr>
<tr>
<td>Mahnke et al. [31]</td>
<td>1/kidney</td>
<td>Case report</td>
<td>0.27 mg/kg/d PO</td>
<td>Not stated</td>
<td>FK requirements by 68%</td>
<td>Not stated</td>
</tr>
</tbody>
</table>

PO indicates oral; BID, twice daily; ↓, decrease; CyA, cyclosporin A; QD, once daily; QAM, every morning; QPM, every night; QHS, at bedtime; BUN, blood urea nitrogen; FK, tacrolimus; [FK], tacrolimus serum concentration; SCr, serum creatinine; →, leading to; LFTs, liver function tests.

*Age-dependent increases, where older patients had a greater magnitude of dose reduction.
†When itraconazole was discontinued, the mean dose increase of tacrolimus was 87%.
the interaction with cyclosporin A or tacrolimus (data not shown). No such correlation existed.

In conclusion, in a controlled pharmacokinetic study, we have demonstrated that there is a significant interaction between IV itraconazole and IV cyclosporin A, as well as between IV itraconazole and IV tacrolimus. This interaction is predictable, occurring within 48 hours of concomitant administration. Whereas the mean increases in the serum concentrations of cyclosporin A and tacrolimus are similar, there was considerable variability within each group in terms of the magnitude of the increase. The magnitude of the dose modification will be dependent on the initial serum concentration of the calcineurin inhibitor and the final target concentration. A recent publication evaluating the oral drug interaction between itraconazole and calcineurin inhibitors has demonstrated that an empirical dose reduction of the calcineurin inhibitor of 50% should occur when itraconazole is added (or the day before, if possible) [31]. Further dose reductions of 20% to 25% may be necessary 4 to 7 days after the addition of itraconazole. This will reduce the likelihood of wide fluctuations in tacrolimus and cyclosporin A concentrations and will reduce toxicity.

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