Pharmacokinetics of Posaconazole Suspension in Lung Transplant Patients with and without Cystic Fibrosis

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Invasive fungal infections (IFIs) are common among lung transplant recipients (LTRs). Posaconazole is an important antifungal agent for both prophylaxis and treatment of IFIs; however, detailed pharmacokinetic data are limited among LTRs, particularly those with cystic fibrosis (CF). Our objective was to conduct a pharmacokinetic study of posaconazole oral suspension among LTRs, with particular attention to patients with CF. We enrolled 20 LTRs, 7 with CF and 13 with other underlying lung diseases. Average daily doses in CF and non-CF patients were 829 and 862 mg, respectively. After ≥ 5 days of treatment, only 4 patients had average plasma concentrations of >0.7 $\mu\text{g/ml}$. Average steady-state plasma concentrations were 61% lower in CF patients (0.233 $\mu\text{g/ml}$) than in non-CF LTRs (0.594 $\mu\text{g/ml}$; $P = 0.03$). The average dose-normalized plasma area-under-the-curve (AUC) values were also lower in CF (0.007 h- $\mu\text{g/ml}$) than in non-CF LTRs (0.02 h- $\mu\text{g/ml}$; $P = 0.02$). The weight-normalized apparent oral clearance values were 2.51 and 0.74 liters/h/kg among CF and non-CF LTRs, respectively ($P = 0.005$). Despite significant interpatient variability, plasma trough concentrations were strongly correlated with posaconazole AUC across all LTRs ($r^2 = 0.95$, $P < 0.0001$). Taken together, our study highlights a critical need to incorporate new formulations of posaconazole into prophylaxis and treatment strategies for LTRs, particularly those with CF. Future pharmacokinetic studies of both tablet and intravenous formulations must consider LTR-specific factors and incorporate a therapeutic drug monitoring plan in this patient population.

Invasive fungal infections (IFIs) are common complications in solid organ transplant recipients, resulting in significant morbidity and mortality (1–3). IFIs are especially common among lung transplant recipients (LTRs), with a reported incidence ranging from 15 to 35% (4, 5). Accordingly, the use of antifungal agents for the treatment and prophylaxis of IFIs among LTRs is common. Posaconazole is an attractive antifungal agent for these indications due to its broad anti-mold activity and favorable toxicity profile compared to amphotericin B and voriconazole (6, 7). Posaconazole was initially approved as an oral suspension by the U.S. Food and Drug Administration in 2006, and subsequently as a sustained-release tablet and intravenous formulation in 2013 and 2014, respectively. Despite nearly a decade of clinical experience with posaconazole, there remains a paucity of pharmacokinetic and clinical data among LTRs (8, 9), particularly among patients with cystic fibrosis (CF), which is a major indication for lung transplantation.

Our experience with posaconazole oral suspension demonstrates that attaining therapeutic levels among LTRs is difficult (10). These data are corroborated by our laboratory experience. From October 2013 to August 2014, 66 clinical samples for therapeutic drug monitoring were received by Clinical Pharmacokinetics Laboratory at the University of Pittsburgh; 58% of samples yielded posaconazole concentrations of <0.7 $\mu\text{g/ml}$ (Fig. 1), a cutoff value shown to result in greater risk for IFIs (11). Achieving therapeutic concentrations of posaconazole is especially challenging for CF patients given population-specific factors such as poor oral absorption, a larger volume of distribution, and an increased clearance of certain drugs. Unfortunately, the pharmacokinetics of posaconazole oral suspension have been reported only in a limited number of pa-

tients with CF (8, 9). The administration of posaconazole as a sustained-release tablet results in improved pharmacokinetics among patients with hematological malignancy (12, 13); however, no data are available among LTRs. Our objective in the present study was to define the pharmacokinetics of posaconazole oral suspension among LTRs so that future studies of the tablet can be placed into an appropriate clinical context. We paid particular attention to include patients with CF, for whom there are limited data available.

MATERIALS AND METHODS

Subjects. Both men and women (≥ 18 years old) were included. Patients were eligible for study participation if they were initiated on posaconazole for prophylaxis or treatment of IFIs following lung transplantation between November 2011 and February 2014. Females of childbearing potential who were pregnant, breast-feeding, or intended to become pregnant or who were not using adequate contraceptive methods were excluded. The study was approved by the Institutional Review Board at the University of Pittsburgh. Written informed consent was obtained from all patients prior to initiation of any study-related activities.

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FIG 1 Distribution of posaconazole plasma trough concentrations during therapeutic monitoring.

Sample collection and posaconazole plasma concentration determination. Serial blood samples (3 ml) were collected in heparinized tubes from each patient just prior to (0 h) and at 2, 4, 6, 8, and 12 h after administration of posaconazole after a minimum of 5 days of therapy (i.e., steady state). After centrifugation, plasma samples were frozen at -80°C until analyzed. Posaconazole plasma concentrations were determined by a validated high-performance liquid chromatography with fluorescence de-

tection methodology. The standard calibration curves were linear over a concentration range of 0.02 to 3 $\mu\text{g}/\text{ml}$. The lower limit of concentration of the method was 0.02 $\mu\text{g}/\text{ml}$. A weighing factor of $1/Y$ was used to construct the equations for standard.

Posaconazole pharmacokinetic analyses. Pharmacokinetic analyses were performed using Phoenix WinNonlin 6.4. Posaconazole plasma concentrations were used to determine the pharmacokinetic parameters using a noncompartment model. The maximum plasma concentration at steady state ($C_{ss,\text{max}}$), the time to $C_{ss,\text{max}}$ (T_{max}), the minimum plasma concentration at steady state ($C_{ss,\text{min}}$), and the elimination rate constant k were obtained from each patient's plasma concentration-time profile. The C_{trough} was defined as concentration at time zero. The area under plasma concentration versus time curve (AUC) was determined from time zero to 12 h (or in some cases to 8 h due to frequency of dosing) using the trapezoidal method. Among patients with missing data, trough levels were projected using a k value calculated from at least 3 data points in the terminal phase. For subjects with <3 data points in the terminal phase, C_{12} or C_8 was assumed to be equal to C_0 given that all patients were at steady state. The average concentration at steady state ($C_{ss,\text{av}}$) was calculated as $\text{AUC}_{0-24}/24$. The oral clearance (CL/F) was calculated according to the following equation: $\text{CL}/F = \text{daily dose}/\text{AUC}_{0-24}$.

Statistic analyses. Statistic analyses were conducted using GraphPad Prism 6.0. Mann-Whitney nonparametric test was applied to compare the difference in pharmacokinetic parameters between LTRs with or without CF. A P value of <0.05 was considered statistically significant.

RESULTS

Patients demographics. A total of 20 patients, including 7 LTRs with and 13 without CF were enrolled (Table 1). The mean age and

TABLE 1 Patient demographic and clinical data summary

Characteristic	Patient group value			<i>P</i>
	CF (<i>n</i> = 7)	Non-CF (<i>n</i> = 13)	Total (<i>n</i> = 20)	
Demographic data				
Mean age in yrs (range)	36 (25–51)	61 (28–77)	52 (25–77)	0.0006
No. (%) of patients by age in yrs				0.04
≥ 18 to <65	7 (100)	7 (54)	14 (70)	
≥ 65	0	6 (46)	6 (30)	
No. (%) of patients by gender				0.07
Female	5 (71)	3 (23)	8 (40)	
Male	2 (29)	10 (76)	12 (60)	
No. (%) of patients by race				0.25
Caucasian	7 (100)	10 (76)	7 (85)	
Other ^a	0	3 (23)	3 (15)	
Clinical data				
Mean wt in kg (range)	56.7 (41.6–68)	78.2 (48.3–110)	70.6 (41.6–110)	0.01
Mean daily dose of posaconazole in mg ^b (range)	829 (400–1,200)	862 (400–1,200)		0.44
Feeding, no. (%) of patients ^c				0.14
Regular feeding	4 (57)	11 (85)	15 (75)	
Tube feeding	2 (29)	2 (15)	4 (20)	
No feeding	1 (14)	0 (0)	1 (5)	
Gastroesophageal reflux prophylaxis, no. (%) of patients				0.63
PPI	4 (57)	7 (54)	11 (55)	
H ₂ antagonist	3 (43)	6 (47)	9 (45)	

^a Two patients were Hispanic, and one patient was Asian.

^b At the time of sample collection, patients received the following dosing regimens: 200 mg four times daily (*n* = 1), 200 mg twice daily (*n* = 3), 200 mg three times a day (*n* = 2), 400 mg twice daily (*n* = 10), and 400 mg three times a day (*n* = 4).

^c Posaconazole administration with a high-fat meal was recommended for all patients.

FIG 2 Posaconazole plasma concentration-time profiles in 20 patients after a minimum of 5 days of therapy.

body weight were lower for CF patients than for non-CF patients. **Pharmacokinetic analyses.** The average daily dose in CF and non-CF patients were 829 and 862 mg, respectively ($P = 0.44$). Individual plasma concentration-time profiles of posaconazole were highly variable (Fig. 2). Significant interpatient variability was observed in both groups. Of 20 patients, a steady-state average concentration of 0.7 µg/ml was achieved in 14% (1/7) of CF patients and in 15% (3/13) of non-CF patients.

One patient from the non-CF cohort was excluded from the pharmacokinetic analysis due to administration of posaconazole within 6 h of sampling. The elimination rate constant k was applied to extrapolated C_{12} in 5 patients, and C_8 in 5 patients; plasma concentrations at 0 h were assumed to be identical to the concentrations at 12 h or 8 h at steady state in 6 patients. The $C_{ss,max}$, $C_{ss,min}$, and $C_{ss,av}$ values were lower among CF patients (Table 2). The corresponding values were associated with 56, 60, and 61% lower levels compared to non-CF patients, respectively. The dose-normalized AUC_{0-24} (0.007 h·µg/ml) for CF patients was 65% lower than the dose-normalized AUC_{0-24} (0.02 h·µg/ml) in non-CF patients ($P = 0.02$). Weight-normalized oral clearance, on the other hand, was higher in CF than in non-CF patients ($P = 0.005$). Across all patients, the C_{trough} levels were highly correlated with $AUC_{0-\tau}$ (Fig. 3, $n = 19$, $r^2 = 0.95$, $P < 0.0001$).

DISCUSSION

Taken together, our data highlight low plasma concentrations of posaconazole and significant interpatient variability after administration of the oral suspension of posaconazole. These findings were most pronounced among LTRs with CF, who are among the populations most likely to benefit from new formulations of the drug. Therefore, our results are essential in establishing comparator pharmacokinetic data for future studies of posaconazole among LTRs who receive sustained-release tablets, or other formulations. Moreover, at least some LTRs may continue to receive therapy with the oral suspension, or a newly approved intravenous formulation due to their inability to swallow whole tablets following transplantation.

Initial studies evaluating the pharmacokinetics of posaconazole sustained-release tablets have shown that 99% of patients achieve a C_{ss} of >0.5 µg/ml (12, 13); however, these data should be extrapolated to LTRs with caution. LTRs have several distinguishing characteristics that may influence the pharmacokinetics of posaconazole. These features include a need for acid-suppressing therapy and other medications associated with poor gastrointestinal tolerability, older age, and malnutrition (10). Until detailed pharmacokinetic studies of posaconazole tablets are conducted the full extent of these factors among LTRs will be unclear.

Achieving therapeutic posaconazole levels among LTRs with CF is a major challenge. We found significantly lower $C_{ss,av}$ and AUC_{0-24} /daily dose values in patients with CF versus LTRs with other underlying diseases. Suboptimal posaconazole exposures could be due to differential absorption, glucuronidation, and reabsorption of the drug. Since posaconazole is a lipophilic drug, decreased pancreatic enzyme secretion and altered bile acid turnover among CF patients may lead to reduced absorption (14). Increased activity of UGT1A4 and hepatic glucuronosyltransferase may also contribute to observed lower AUC of posaconazole (15, 16). Genetic variants of UGT1A4 may also explain the significant interpatient variability we noted in both CF and non-CF cohorts (17, 18). High concentrations of posaconazole have been reported in rat bile (14). A second peak plasma concentration was observed in several patients, suggesting reabsorption of posaconazole, subsequent to biliary secretion of posaconazole or the glucuronide conjugates of posaconazole (19). It is possible that not only initial absorption of posaconazole but also posaconazole reabsorption may be altered in CF patients, leading to lower exposure in CF patients.

We found no differences in apparent oral clearance of po-

TABLE 2 Pharmacokinetic parameters of posaconazole in CF and non-CF group

Parameter	Median (range)		<i>P</i> ^a
	CF cohort (<i>n</i> = 7)	Non-CF cohort (<i>n</i> = 12)	
<i>T</i> _{max} (h)	4.4 (0–7.8)	4 (0–11.8)	0.4
<i>C</i> _{ss,max} (µg/ml)	0.311 (0.021–0.968)	0.699 (0.227–2.983)	NA
<i>C</i> _{ss,min} (µg/ml)	0.189 (0–0.619)	0.474 (0.115–2.094)	NA
<i>C</i> _{ss,av} (µg/ml)	0.233 (0.01–0.772)	0.594 (0.154–2.455)	0.03
<i>AUC</i> _{0–24} /daily dose (h·µg/ml)	0.007 (0.0003–0.019)	0.02 (0.005–0.074)	0.02
Apparent oral clearance (liters/h)	143.16 (32.26–3278.69)	51.83 (13.58–216.33)	0.13
Wt-normalized apparent oral clearance (liters/h/kg)	2.51 (0.76–48.22)	0.74 (0.25–2.66)	0.005

^a NA, not applicable. Statistic analyses are not applicable to *C*_{ss,max} and *C*_{ss,min} values because the dosing intervals were variable among enrolled patients.

FIG 3 Correlation between C_{trough} and $AUC_{0-\tau}$ values.

posaconazole between patients with CF and without CF; however, weight-normalized apparent oral clearance was significantly higher among CF patients. These data are the first to demonstrate associations between weight and apparent clearance of posaconazole. Considering the lipophilic nature of posaconazole, it is plausible that patients with greater weight may have a larger volume of distribution. These data are hypothesis generating and should be investigated in greater detail in future studies.

Finally, our study supports the notion that posaconazole trough levels are a useful surrogate for AUC. Indeed, trough levels were well correlated with calculated AUC values in both CF and non-CF patients (Fig. 3). Although the recommendations for therapeutic drug monitoring of posaconazole have been derived almost entirely from patients with hematologic malignancies (20), it is important to demonstrate similar approaches are viable among LTRs. To this end, associations between posaconazole serum level and patient outcomes are now well described (10, 21), which reinforces a need for monitoring posaconazole administered as an oral suspension. The need for and importance of therapeutic monitoring when using new formulations of posaconazole are not completely understood at this time.

Some of the limitations of our study are as follows. The study was performed over a 12-h sampling period given the nature of dosing of this drug. Next, we were able to calculate apparent oral clearance, which does not necessarily represent the true systemic clearance of posaconazole and may have limited our ability to identify actual mechanism for the differences among CF and non-CF patients. Future studies using intravenous formulation are likely to provide more valuable mechanistic information. Nevertheless, we have conducted a detailed pharmacokinetic study among an understudied patient population that often requires posaconazole therapy. In doing so, we have shown that systemic exposure of posaconazole with the use of oral suspension was highly variable among LTRs and was significantly lower in CF patients. Our findings were most pronounced for LTRs with CF, who are the population in most need of new formulations of the drug. These data highlight an important need for future pharmacokinetic studies of new posaconazole formulations and corresponding recommendations for therapeutic drug monitoring in

LTRs. Along these lines, our study provides a basis to which forthcoming data can be compared and contrasted.

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