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Posaconazole Therapeutic Drug Monitoring in Pediatrics and Young Adults with Cancer

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Abstract

BACKGROUND—Limited information exists regarding the use of posaconazole for treating systemic fungal infections in children, adolescent, and young adult patients with cancer. At St.

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Jude Children's Research Hospital, the recommended posaconazole dose in patients less than 34 kg is 18–24 mg/kg daily given in 4 divided doses. For patients 13 years and older or those weighing 34 kg or more, the recommended dose is 800 mg daily given orally in four divided doses.

OBJECTIVE—This study was conducted to determine if the current posaconazole dosing guidelines achieved target posaconazole plasma concentrations of 0.7 µg/mL.

METHODS—We examined data from patients who received treatment-dose posaconazole with at least one posaconazole plasma concentration measurement.

RESULTS—Data from 33 patients who received posaconazole for the treatment of fungal infections were analyzed. The median age of patients was 11.5 years (range 0.5–23.2 years). Twenty-one patients out of 33 (63.6%) had posaconazole concentrations of 0.7 µg/mL (median 1.4 µg/mL; range 0.7–2.98 µg/mL) at the first measurement. The median posaconazole dosage referenced to total body weight in these patients was 20 mg/kg per day. Patients with concentrations < 0.7 µg/mL (median 0.4 µg/mL; range 0.025–0.69 µg/mL) received lower posaconazole dosages when referenced to body weight (median 12.9 mg/kg per day; $p = 0.02$). Of the 12 patients with concentrations < 0.7 µg/mL, seven (58.3%) were 13 years of age or older.

CONCLUSIONS—The current dosing approach for posaconazole yielded therapeutic plasma concentrations more frequently in patients < 13 than those > 13 years of age. This difference may be related to the practice of capping adolescent and young adult doses at the suggested maximum adult daily dose. Therefore, we recommend weight-based dosing in all pediatric, adolescent and young adult cancer patients with routine therapeutic drug monitoring in all patients to ensure adequate concentrations.

Keywords

posaconazole; pediatric; fungal infection; therapeutic drug monitoring

INTRODUCTION

Posaconazole is an extended-spectrum triazole antifungal approved for prophylaxis against invasive *Aspergillus* and *Candida* infections in high-risk immunocompromised adolescent and adult patients and for treatment of oropharyngeal candidiasis. In patients aged 13 years and older, the FDA-approved posaconazole dose for antifungal prophylaxis is 200 mg thrice daily.¹

Although not approved to treat invasive fungal infections, posaconazole is effective in treating adult patients with invasive (refractory or salvage) aspergillosis, zygomycosis, and candidiasis at a dose of 800 mg daily given in divided doses.^{2–4}

While optimal pediatric dosing has not been defined, posaconazole is occasionally used in this patient population. At St. Jude Children's Research Hospital, posaconazole is generally reserved for the treatment of suspected or proven systemic fungal infections such as invasive aspergillosis, zygomycosis, and candidiasis. To treat systemic fungal infections in children, the dose used at St. Jude Children's Research Hospital in patients weighing less than 34 kg is 18–24 mg/kg daily given orally in four divided doses. Usually, patients 13 years and older

or those weighing 34 kg or more are treated with 800 mg daily given orally in four divided doses. All patients are encouraged to take the medication with high-fat meals or acidic beverages.

The bioavailability and systemic exposure of posaconazole are affected by food and some medications. When posaconazole is administered with a nutritional supplement or high-fat meals, its bioavailability is significantly increased.⁵ Conversely, medications that increase gastric pH, such as proton pump inhibitors and H₂-blockers, have been shown to decrease posaconazole exposure.⁵

Numerous studies have found a correlation between plasma exposure and response. When posaconazole plasma concentrations were equal or greater than 0.7 µg/mL, the proportion of clinical responders increased for a cohort of 67 patients with invasive aspergillosis who received posaconazole for salvage treatment.² In another study, 9 patients received posaconazole for treatment of invasive fungal infections. Those patients that responded to treatment had higher posaconazole concentrations (median 0.955 µg/mL) than those patients who failed therapy (median 0.436 µg/mL).⁶

Posaconazole shows significant inpatient variability, mostly due to erratic absorption. In addition, posaconazole exhibits a concentration-effect relationship.⁷ For these reasons, some authors advocate monitoring to ensure that adequate drug levels are present.^{7–12} Even though a posaconazole target concentration has not been identified for treatment of invasive fungal infections,^{11,12} some authors recommend a provisional target of 0.7 µg/mL with escalation to 1.25 µg/mL if response is poor.¹¹ Based on the data available for patients 13 years of age and older, a posaconazole target concentration of equal to or greater than 0.7 µg/mL was chosen for this study.

The objective of this study was to determine whether the current dosing approach used at St. Jude Children's Research Hospital achieves posaconazole plasma concentrations greater than or equal to 0.7 µg/mL.

DEFINITIONS

Adolescents and young adults were defined as those patients whose age ranges from 12 to 24 years based on the WHO and the Youth Advisory Council Act (1989) definition. A patient's study period was defined as the time from the first posaconazole dose until a dosage change, posaconazole discontinuation, or the end of the observation period. Empiric treatment was defined as therapy given to treat a suspected or probable fungal infection. Treatment was defined as therapy given to treat a fungal infection that was proven by either positive culture or pathologic findings. Progression of infection was defined as evidence of progressive fungal disease based on a composite of clinical, radiologic, and/or mycologic criteria, while the patient received therapeutic doses of the drug. Safety and tolerability were also assessed for all patients included in the study.

METHODS

Retrospective clinical data were obtained for all patients who received posaconazole from January 1, 2007, to August 22, 2010. Only patients who received posaconazole for treatment of fungal infections and had at least one posaconazole plasma concentration measurement were included in the study. From 2007 through February 2010, concentrations were assessed by send-out to a reference clinical laboratory (University of Texas Health Science Center, Fungus Testing Laboratory, San Antonio, TX). Starting in March 2010, posaconazole concentrations were measured onsite in our clinical pharmacokinetic laboratory. Both laboratories use high-performance liquid chromatography with ultraviolet detection to measure posaconazole concentrations. Posaconazole plasma concentrations from five specimens were analyzed at our onsite laboratory and at the send-out laboratory. The average percent bias between measurements was 5.1% (range 2.7–24.6%). This 5% difference between methods is well within the total error expected for these assays (maximum total error allowed = 25%).

The first concentration obtained for each patient during the study period was used; having achieved steady state was not a prerequisite for inclusion of the data in the analysis. Posaconazole was considered to have achieved a steady-state plasma concentration after at least 7 days of dosing (1). For hospitalized patients, trough concentrations were obtained. When posaconazole concentrations were obtained in the outpatient clinics, patients were instructed not to ingest the morning posaconazole dose until the sample had been obtained. Adverse drug effects were characterized as described in National Cancer Institute Common Toxicity Criteria version 3.0 (Common terminology).¹³ The St. Jude institutional review board approved this study.

Data Collection

Information collected included patient demographics, primary diagnosis, posaconazole dosing, indication for therapy (prophylaxis, empiric or treatment), selected concomitant medications (H₂-blockers, metoclopramide, phenytoin, proton pump inhibitors, and rifabutin/rifampin), adverse effects (increase in liver function test, QTc prolongation, rash, nausea and vomiting), and posaconazole plasma concentration.

Data Analysis

Data were summarized, and the characteristics of patients with low plasma concentrations were compared with those of patients who achieved target concentrations (defined as posaconazole plasma concentration of ≥ 0.7 $\mu\text{g/mL}$). Because of the small sample size, the Mann-Whitney U Test and Fisher's Exact Test were used to analyze the data. A two-tailed p-value of less than 0.05 was considered statistically significant. Statistical computations were performed using Statistica version 10 (StatSoft®, Inc., Tulsa, OK).

RESULTS

Patient Characteristics

A total of 118 patients received at least one dose of posaconazole during the study period; 33 patients received posaconazole for the treatment of suspected (19/33; 57.5%) or proven infections (14/33; 42.4%) and had at least one posaconazole plasma concentration measurement (Table 1). The median age of patients in this analysis was 11.5 years (range 5 months to 23.2 years). Leukemia and lymphoma were the most common underlying conditions (81.8%). The majority (69.7%) of posaconazole concentrations were obtained at steady state (Table 2). The median posaconazole plasma concentration in these patients was 0.72 µg/mL (range 0.22–2.04 µg/mL). Three out of the 10 patients who had a posaconazole concentration measured before seven days of therapy had subtherapeutic levels.

Four study patients experienced infection progression as described below. Twelve of the study patients received concomitant medications with the potential to affect posaconazole plasma concentrations.

Twelve out of 33 patients had plasma concentrations below 0.7 µg/mL. These patients received significantly lower dosages of posaconazole referenced to body weight compared to patients with concentrations of 0.7 µg/mL or greater (median 12.9 mg/kg daily vs. 20 mg/kg daily, $p = 0.02$) (Table 3).

Twenty-one patients were younger than 13 years and twelve were 13 years or older (Table 4). When analyzing the data by age group, sixteen out of 21 (76.2%) of the patients less than 13 years of age achieved a target posaconazole concentration versus five out of 12 (41.6%) of patients 13 years of age or older (Fisher's $p = 0.06$). Comparison of the median plasma concentration in these two groups did not reveal a statistically significant difference. Patients less than 13 years of age received higher median posaconazole dosages referenced to body weight ($p = <0.001$) (Table 4).

Clinical Course

Nineteen patients received posaconazole as empiric therapy with only one patient experiencing a progression of infection. The remaining fourteen patients received therapy for a proven fungal infection. Three of the fourteen experienced a fungal progression.

Of the patients who experienced fungal infection progression, neither age, posaconazole plasma concentration, nor dosage was associated with progression (all p values > 0.05). One patient with infection progression was being treated for disseminated *Aspergillus* infection in both eyes and lungs. This patient had positive cultures from vitreous fluid and bronchoalveolar lavage. At the beginning of treatment with posaconazole, *Aspergillus* galactomannan antigen assay results were negative; however, after 1.5 months on posaconazole, *Aspergillus* antigen testing results became positive. The initial posaconazole concentration in this patient was 0.2 µg/mL. Although this patient achieved a concentration of 0.72 µg/mL after two months of therapy, a computed tomography scan showed that the infection had progressed, and the patient was switched to liposomal amphotericin B. The patient died of fungal infection. Another patient was receiving posaconazole, liposomal

amphotericin B, and micafungin for proven, disseminated *Candida albicans* and *C. famata* infections that started on the hard palate and spread to the left maxilla, nose, and left orbit. This patient died almost two months after starting treatment with antifungal combination therapy. This patient had two posaconazole plasma concentrations measured 12 and 20 days after starting posaconazole therapy; the measured concentrations were 1.63 µg/mL and 0.55 µg/mL, respectively. A third patient developed a fungal lesion on the left kidney 7 months after starting posaconazole therapy for the treatment of proven pulmonary zygomycete infection. However, after resection of the fungal kidney lesion, the patient was continued on posaconazole and was alive 11 months after the surgery. The initial posaconazole plasma concentration in this patient was 0.7 µg/mL. All subsequent posaconazole concentrations in this patient were above the target level. The fourth patient who was receiving posaconazole for suspected fungal infection was switched to voriconazole after a computed tomography scan demonstrated enlarging pulmonary nodules despite treatment with posaconazole for nearly a month. The posaconazole plasma concentration in this patient was 0.92 µg/mL.

Safety and Tolerability

Of the 33 patients included in this study, 7 (21%) experienced adverse effects. Two patients developed grade II liver toxicity during therapy and 5 developed grade III liver toxicity. A Naranjo score of 3 was obtained for each patient suggesting that posaconazole could possibly have caused the development of liver toxicity. However, all of these patients were receiving other medications that could have been responsible for the increase in liver function test (LFT). All adverse effects resolved while therapy continued.

The 2 patients with grade II liver toxicity experienced LFT elevation of 3 to 5 times the upper limit of normal, without further symptomatology. This toxicity was noted at five days and six days following initiation of therapy, respectively. The laboratory values returned to the normal range within 2–5 days while therapy continued.

Five patients with grade III liver toxicity experienced elevation of LFT greater than 5 times the upper limit of normal, without further symptomatology. This toxicity was noted after 10 days (2 cases), 15 days, 1.5 months, or 9 months of therapy, respectively. In each case, the laboratory values returned to the normal range between 3 and 20 days. This resolution occurred while therapy was continued.

Two patients had elevated LFT results prior to starting posaconazole; therefore, these patients were not considered to have experienced adverse effects from posaconazole. One of the patients with liver toxicity also had a grade III rash. However, the rash was not thought to be related to posaconazole, and posaconazole treatment was continued. The median dosage and median posaconazole plasma concentrations for patients who experienced adverse effects were not significantly different from that of patients who did not experience adverse effects. No other adverse events such as nausea, vomiting, rash or QTc prolongation were noted or recorded in the chart.

Concomitant Medications

Twelve patients received either an H₂-blocker or a proton pump inhibitor, both of which have been shown to decrease the absorption of posaconazole.³ None of the patients received metoclopramide, phenytoin, rifabutin or rifampin. There were no statistically significant differences in the median body weight-based dosages ($p = 0.42$) and posaconazole plasma concentrations ($p = 0.8$) in patients receiving concomitant medications versus patients not receiving concomitant medications.

DISCUSSION

We report on the relationship between the prescribed dosage of posaconazole used in pediatric and young adult oncology/hematology patients, patient age, and observed plasma concentrations. Because patients 13 years of age and older were dosed using the FDA-approved recommendations, they received a lower weight-based dosage of posaconazole and achieved lower plasma concentrations than patients younger than 13 years of age. Our assessment relies on the results of analyses conducted in the course of clinical care. "Trough" (pre-dose) concentrations were analyzed, and we limited our analysis to the first clinical concentration obtained; fourteen out of 33 (42.4%) patients had only one concentration determined during the course of treatment. Using the pre-dose concentration obtained is justified, since data demonstrate that there is minimal variability in posaconazole during the course of the day for most patients.¹⁴ We did include ten patients whose levels were obtained before a total of seven days of therapy had elapsed. These were included because the reported half-life of posaconazole ranges from 20 to 66 hours¹ and children routinely demonstrate shorter half-lives compared to adults, thus allowing for initial concentrations to be obtained earlier.

Few trials have described posaconazole therapeutic drug monitoring and dose relationships in children. Krishna et al. conducted a secondary analysis comparing plasma posaconazole concentration data from 12 children (mean age, 14 years; range, 8–17 years) with that from 194 adult patients in a multicenter, phase III, open-label study of posaconazole.¹⁵ With the exception of one pediatric patient, all patients received a maintenance dose of 800 mg daily posaconazole oral suspension in divided doses. The median dosage for the pediatric patients was 16.5 mg/kg daily. Plasma posaconazole levels were similar for pediatric and adult patients, with mean values of 0.776 µg/mL and 0.817 µg/mL, respectively. Additionally, Lehrnbecher et al. reported a median dosage of 21 mg/kg daily (range, 4.8–33.3 mg/kg daily) in 15 children (median age, 10 years) receiving posaconazole to treat fungal infections. Posaconazole concentrations were not reported in this study.¹⁶

In our study, the median age (11.5 years) was similar to the median age in the study conducted by Lehrnbecher and younger than that in the Krishna study. The median dosage in our study (17 mg/kg daily) was similar to the median dosage in the study conducted by Krishna but lower than that reported by Lehrnbecher. We found that lower dosages were related to lower plasma concentrations. Based on these plasma concentrations, patients 13 years of age and older appear to require more aggressive dosing than is currently recommended.

Although target concentrations for posaconazole have not been firmly established,^{9–12,17} several studies have demonstrated the relationship between clinical response and plasma concentration.^{2,6,18} In an open-label investigational study, Walsh et al. reported that patients with refractory invasive aspergillosis who had an average steady-state posaconazole concentration of 1.25 µg/mL had higher clinical response (75%) than those with an average steady-state concentration of 0.13 µg/mL (24%). Additionally, 53% of patients with an average steady-state concentration between 0.5 µg/mL and 0.7 µg/mL responded to treatment.² Another study evaluated the clinical efficacy of posaconazole among 86 patients who received posaconazole for prophylaxis and treatment of fungal infections. Of the eighty-six patients, seventy-two (84%) received posaconazole for prophylaxis and fourteen (16%) for the treatment of invasive fungal infections. Among the patients who received posaconazole for prophylaxis, 12 had breakthrough fungal infections. The median posaconazole concentration in these twelve patients was 0.289 µg/mL, which was significantly lower than those who did not develop breakthrough infections (median 0.485 µg/mL) ($p < 0.5$). Of the fourteen patients who received posaconazole for treatment of invasive fungal infection, nine were evaluated for treatment outcome. Four of these nine patients failed therapy. The median posaconazole concentration in these four patients was 0.436 µg/mL, which was significantly lower than those who responded to treatment (median 0.955 µg/mL) ($p = 0.19$).⁶ In addition, an exposure-response analysis of two randomized, active-controlled clinical studies revealed that a posaconazole plasma concentration of 0.7 µg/mL or greater is necessary to minimize the incidence of breakthrough infections.¹⁸

Using these data, we selected 0.7 µg/mL as our target concentration.^{2,6} While we were unable to demonstrate a relationship between clinical outcome and plasma concentrations, we did demonstrate a relationship between dose and those patients who achieved target-level posaconazole concentrations. Indeed, several factors have been shown to affect posaconazole pharmacokinetics, including gastric pH, dosing frequency, prandial state, timing of food consumption, gastric motility, underlying disease, and mucositis.^{5,19,20} Diarrhea has been identified as one factor correlated with reduced posaconazole absorption.²¹ In addition, several commonly used drugs, including omeprazole and ranitidine, can alter the pharmacokinetics. We were unable to demonstrate a relationship between posaconazole concentrations and use of medications known to modify posaconazole pharmacokinetics. Because of the known influences of dietary factors on posaconazole absorption, we attempted to explore the relationship between dietary behavior and plasma concentrations. Unfortunately, adequate dietary records were not available for the study. Finally, we did not examine the presence of diarrhea as a possible contributor to reduced concentrations.

Because posaconazole absorption is affected by several factors such as food, gastric pH, dosing frequency, mucosal health, and gastric motility,^{5,19} there is significant interpatient variability in the pharmacokinetic parameters.^{9,17} Therapeutic drug monitoring may have a crucial role in the care of patients receiving posaconazole, especially in those with suspected treatment failure, infections at sanctuary sites, infections due to drug-resistant organisms, mucositis, malabsorption, and in those unable to take posaconazole with high-fat food.^{8,9,22} Other studies have demonstrated that many adults, including neutropenic patients, treated with posaconazole fail to achieve desired plasma concentrations.^{12,23} Bryant et al. also

found that increasing the dose of the drug failed to result in an increase in concentrations in 4 of 6 neutropenic hematologic malignancy patients with low concentrations.²⁴ Our data and that of Krishna et al.¹⁵ draw attention to the question of whether using a higher weight-based dosage in adolescents may more frequently result in higher plasma concentrations.

In our study, posaconazole was well tolerated, with the most common adverse effect being a transient increase in LFT values that resolved while therapy continued. This result is concordant with those of other studies assessing the safety of posaconazole in pediatric patients.^{15,16} Lehnbecher et al. reported that 73% of their patients experienced some adverse events. The most commonly reported adverse events were fever, nausea and/or vomiting, abdominal pain, diarrhea, headache, skin eruptions, and elevated liver function test results. The frequent increases in laboratory hepatic parameters were attributed to the multiple concomitant medications that these patients received. Because therapeutic drug monitoring was not performed in this study, no associations can be made regarding the incidence of liver toxicity and posaconazole plasma concentrations.¹⁶ Similarly, in the study conducted by Krishna, the most common adverse events were nausea, vomiting, abdominal pain, and headache. In addition, two patients (16%) had elevated liver function test results. However, both of these elevations were deemed unlikely to be related to posaconazole treatment.¹⁶

There were several limitations of our study. Because this was a retrospective study, we were unable to assess adherence with posaconazole therapy. It is possible that adolescents were less compliant with drug therapy, thereby contributing to the lower concentrations noted in this age group. Furthermore, there was a lack of documentation of nutritional intake in the outpatient setting, making conclusions about the impact of diet difficult to ascertain. Patients with a subtherapeutic level may have had poor oral intake. Ten out of 33 patients had a posaconazole concentration measured before steady-state was achieved. Although only 3 patients had subtherapeutic concentrations, the concentrations may have been higher if posaconazole had been measured at steady-state. Lastly, we were unable to find a relationship between drug concentration and outcome. This may be related to the fact that we looked at the first posaconazole plasma concentration.

CONCLUSIONS

The current institutional dosing approach resulted in therapeutic posaconazole plasma concentrations more frequently in patients < 13 than in those > 13 years of age. This difference in concentrations was likely due to capping adolescent and young adult dosing at the suggested maximum adult dose. However, several other factors such as diet, concomitant medications, and adherence may have affected posaconazole concentration. In both age groups, therapeutic concentrations were not achieved in some patients. Larger studies are needed to determine appropriate dosing and therapeutic drug monitoring in pediatric patients. Until such data are available, we suggest routine therapeutic drug monitoring in all patients to confirm that adequate concentrations have been achieved. Furthermore, we recommend evaluation of the utility of dosing adolescent and young adult patients based on body size, potentially exceeding the usually recommended maximum adult dose.

ABBREVIATIONS

ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
CML	Chronic myeloid leukemia
Cp	plasma concentration
LFT	liver function test
SS	steady state

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TABLE 1

Patient Characteristics

Sex, n (%)	
Female	15 (45%)
Male	18 (55%)
Age, years	
Median	11.5
Range	0.5 – 23.2
Race, n (%)	
White	24 (73%)
Black	6 (18%)
Other	3 (9%)
Underlying Condition, n (%)	
ALL	10 (30.3%)
AML	11 (33.3%)
Relapsed ALL	3 (9%)
Relapsed AML	1 (3%)
Relapsed Hodgkin's lymphoma	1 (3%)
CML	1 (3%)
Aplastic anemia/glioblastoma multiforme	1 (3%)
Chronic granulomatous disease	2 (6%)
Chronic mucocutaneous candidiasis	1 (3%)
Severe combined immunodeficiency	1 (3%)
Astrocytoma	1 (3%)
Indication, n (%)	
Empiric Treatment	19 (57.5%)
Treatment of Documented Infection	14 (42.5%)

- ALL: acute lymphoblastic leukemia
- AML: acute myeloid leukemia
- CML: Chronic myeloid leukemia

TABLE 2

Description Based on Indication

	Treatment	Empiric	p-Value ^a
# of patients	14	19	-
Median age, years	11.7	11.0	0.46 (153.5)
Dosage, mg/kg/day			
Median	16.5	18.1	0.98 (134.0)
Range	10.2–32.8		6.5–26.67
Weight, kg			
Median	34.4	30	0.34 (159.5)
Range	11.0–78.6	7.0–123	
Cp, µg/mL			
Median	1.3	0.7	0.42 (155.5)
Range	0.2–2.1	0.03–2.98	
# of days from start of therapy to 1 st Cp			
Median	10.5	8	0.84(139.0)
Range	3–38	2–269	
# of patients with Cp measured at SS (%)	11 (78%)	12 (63%)	0.45 ^b
# of patients receiving high-risk medications (%)	5 (36%)	7 (37%)	1.0 ^b

^aP-values calculated using Mann-Whitney U test unless otherwise noted

^bP-value calculated using Fisher's exact test #: number

Cp: plasma concentration

SS: steady state

TABLE 3

Relationship between Age, Dosage, Weight & Posaconazole Concentrations

	Cp < 0.7 µg/mL	Cp 0.7 µg/mL	p-value ^a
# of patients	12	21	
# of patients receiving high risk medications (%)	4 (33)	8 (38)	1.0 ^b
Age, years			
Mean (± SD)	12.3 (±7.2)	8.4 (±6.0)	
Median	13.7	8.5	0.08 (173.0)
Cp, µg/mL			
Median	0.4	1.4	
Range	0.025–0.69	0.70–3.26	
# of days from start of therapy to 1st Cp			
Median	10	10	
Range	3–77	2–269	0.4 (146.5)
#(%) of patients with Cp measured at SS	9 (75)	14 (67)	
Dosage, mg/kg/day			
Median	12.9	20.0	0.02 (186.5)
Range	6.5–26.8	9–32.8	
Weight, Kg			
Median	57.2	30.0	0.14 (166.0)
Range	11–123	7–88	

^aP-values calculated using Mann-Whitney U test unless otherwise noted^bP-value calculated using Fisher's exact test

#: number

Cp: plasma concentration

SS: steady state

TABLE 4

Comparison of Age and Posaconazole Plasma Concentration (Cp)

	Age < 13 years	Age ≥ 13 years	p-value ^a
# of patients	21	12	
# with Cp ≥ 0.7, µg/mL	16	5	(0.06) ^b
Cp, µg/mL			
Median	0.8	0.6	0.3 (152.0)
Range	0.22 – 2.04	<0.125 – 2.98	
Dosage, mg/kg/day			
Median	22.0	11.9	<0.001 (223.0)
Range	9–32.8	6.5–20	

^aP-values calculated using Mann-Whitney U test unless otherwise noted^bP-value calculated using Fisher's exact test

#: number

Cp: plasma concentration