Supratherapeutic Posaconazole Concentration in a Pediatric Transplant Patient With Confirmed *Rhizopus* Infection

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There are a limited number of studies that guide dosing of posaconazole delayed-release (DR) tablets for the pediatric population. Current FDA-approved doses are only recommended for patients 13 years and older. For younger patients, providers are faced with the challenge of recommending posaconazole doses extrapolated from adult studies or choosing an alternative agent. We report on a case of a 10-year-old patient who experienced a supratherapeutic trough serum concentration and transaminitis after receiving the extrapolated adult dosage of posaconazole DR tablets (300 mg twice daily for the first day, followed by 300 mg daily) for 7 days. In the end, the patient required a smaller dose of 200 mg daily to achieve the desired trough target concentration for the treatment of a *Rhizopus* neck infection. Our findings highlight the need for additional studies to determine the optimal dosing of posaconazole DR tablets for children.

ABBREVIATIONS ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DR, delayed-release; FDA, US Food and Drug Administration

KEYWORDS invasive fungal infections; posaconazole; *Rhizopus*; supratherapeutic

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Introduction

Posaconazole is a broad-spectrum antifungal agent used to treat invasive fungal infections. In comparison to the oral suspension formulation, the delayed-release (DR) oral tablet is preferred because of improved bioavailability, fewer food interactions, and decreased interindividual variability associated with this tablet.^{1,2} However, a limitation of the DR tablet is the lack of pediatric data associated with its use. The dosing regimen of 300 mg twice daily for the first day, followed by 300 mg daily is FDA approved for adolescents ≥ 13 years of age, on the basis of extrapolated data from adults receiving the oral tablets and children receiving the oral suspension.³ For patients younger than 13 years of age, the most appropriate dosing strategy remains unclear. We describe a case using posaconazole DR tablets in a 10-year-old patient, which resulted in a supratherapeutic trough serum concentration and transaminitis after 7 days of treatment.

Case Report

A 10-year-old female patient (31 kg) with a history of small bowel transplant for short gut syndrome and diabetes was admitted with a fever (38.7°C) and severe erythema and swelling around a neck lesion. A biopsy was performed, with histopathologic findings of hyphal elements. Because of concern for a possible invasive fungal infection, combination therapy with liposomal amphotericin B and voriconazole was promptly initiated.

On day 11 of therapy, tissue cultures from the neck biopsy indicated the presence of *Rhizopus* species. The decision was made to discontinue voriconazole, to continue liposomal amphotericin B, and to add caspofungin for potential synergistic activity.⁴ The patient then underwent 2 extensive surgical debridements for source control, which successfully led to repeat negative biopsies. After 5 weeks (day 36) of therapy and multiple wound washouts, the patient was clinically stable and signs of progressive infection were absent; the decision was made to step down to an oral antifungal regimen. Caspofungin was discontinued, and posaconazole DR tablets were initiated at a dosage of 300 mg twice daily for the first day, followed by 300 mg daily. During this time, the patient was also taking 2.5 mg of oral tacrolimus twice daily. The dose of tacrolimus was preemptively reduced to 1.5 mg twice daily because of the CYP3A4 drug-drug interaction with posaconazole. The patient was also taking other medications that did not interact with posaconazole: vitamin D3, vitamin B6, ferrous sulfate, magnesium oxide, montelukast, cetirizine, albuterol, sodium citrate, aspirin, insulin glargine, amlodipine, ranitidine, lactulose, and rifaximin. Lactulose was being used to enhance gut motility, and rifaximin was prescribed to inhibit bacterial overgrowth in the patient's transplanted bowel.

At our institution, we typically target posaconazole trough serum concentrations between 1 and 2.5 mg/L for the treatment of mucormycosis.⁵ However, be-

Table. Clinical and Laboratory Parameters on Posaconazole (Initiated on Day 0)

Day	Posaconazole Dose	Posaconazole Concentration*	Tacrolimus Dose	Tacrolimus Concentration†	Laboratory Findings‡								
					ALT	AST	ALP	Total Bilirubin	Albumin	Ca	Mg	K	SCr
-1			2.5 mg every 12 hr	6.4	16	30	132	0.2	2.8	9.0	—	5.0	1.35
0	300 mg every 12 hr	—	1.5 mg every 12 hr	—	—	—	—	—	—	—	—	—	—
1	300 mg every 24 hr	—	1.5 mg every 12 hr	4.5	—	—	—	—	—	9.0	2.2	4.7	1.35
2	300 mg every 24 hr	—	1 mg every 12 hr	19	—	—	—	—	—	—	2.1	5	1.48
3	300 mg every 24 hr	—	Hold	13.5	—	—	—	—	—	8.5	2.1	4.7	1.51
4	300 mg every 24 hr	—	Hold	14	—	—	—	—	—	8.2	1.7	3.3	1.5
5	300 mg every 24 hr	—	Hold	18.2	—	—	—	—	—	8.5	2.3	3.1	1.99
6	300 mg every 24 hr	—	Hold	13.8	—	—	—	—	—	8.1	2.1	2.8	1.46
7	300 mg every 24 hr	5.5 (inpatient)	0.5 mg every 24 hr	12.1	—	—	—	—	—	8.6	2.1	3.3	1.13
8	300 mg every 24 hr	—	0.5 mg every 24 hr	7.6	—	—	—	—	—	8.4	1.9	3.3	1.1
9	300 mg every 24 hr	—	0.5 mg every 24 hr	8	—	—	—	—	—	8.7	1.7	3.9	0.99
10	300 mg every 24 hr	—	0.5 mg every 24 hr	5.6	—	—	—	—	—	0.99	1.7	3.9	0.99
11	300 mg every 24 hr	Notified of supra-therapeutic concentration	0.5 mg every 24 hr	5.6	—	—	—	—	—	8.7	1.7	3.8	0.93
12	200 mg every 24 hr	—	0.5 mg every 24 hr	8.2	119	72	187	0.2	2.6	8.4	1.7	5.1	0.98
13	200 mg every 24 hr	—	0.5 mg every 24 hr	8	97	37	220	0.3	3.1	8.7	—	4.4	0.83
14	200 mg every 24 hr	—	0.5 mg every 24 hr	8.2	111	86	169	0.3	2.8	8.7	1.8	4.2	0.69
15	200 mg every 24 hr	—	0.5 mg every 24 hr	4.7	98	61	158	0.2	2.5	8.3	—	3.7	0.69
16	200 mg every 24 hr	—	0.5 mg every 12 hr	5.7	80	55	182	0.5	2.4	8.3	1.6	3.9	0.71
17	200 mg every 24 hr	—	1 mg every 12 hr	10.1	67	30	198	0.5	2.8	9.4	1.7	4.3	0.65
18	200 mg every 24 hr	2.2 (inpatient)	0.5 mg every 12 hr	10.7	56	41	76	0.5	2.7	9	1.9	4.2	0.57
19	200 mg every 24 hr	—	0.5 mg every 12 hr	—	—	—	—	—	—	—	—	—	—
20	200 mg every 24 hr	—	0.5 mg every 12 hr	10.7	68	46	159	0.5	2.5	8.9	1.7	5.6	0.56
80	200 mg every 24 hr	2.5 (outpatient)	0.5 mg every 12 hr	11.3	22	39	133	0.2	2	8.2	1.9	4.8	0.6

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Ca, calcium; K, potassium; Mg, magnesium; SCr, serum creatinine; —, laboratory test not performed

* Posaconazole trough serum concentration goal 2–3.75 mg/L.

† Tacrolimus trough serum concentration goal 6–8 ng/mL.

‡ Age-related normal values: ALT (1–45 U/L); AST (1–35 U/L); ALP (38–126 U/L); total bilirubin (0.1–1.2 mg/dL); albumin (3.5–4.9 g/dL); Ca (8.5–10.5 mg/dL); Mg (1.5–2.5 mEq/L); K (3.5–5.2 mEq/L); SCr (0.5–1.1 mg/dL).

cause higher minimum inhibitory concentrations for posaconazole have been reported for *Rhizopus* spp., a target trough of >2 mg/L was chosen.^{6,7} A week after posaconazole was initiated, a trough concentration was measured using ultraperformance liquid chromatography–tandem mass spectrometry. Because the specimen was processed by an outside laboratory, it took 4 days for the result to return at 5.5 mg/L. The following day, we reduced the posaconazole dose to 200 mg daily and discontinued liposomal amphotericin B. We also requested daily monitoring of liver function tests.

The Table summarizes the timeline of posaconazole administration, drug serum concentrations, and relevant laboratory studies. Following the supratherapeutic trough concentration of 5.5 mg/L, liver function tests increased from baseline: alanine aminotransferase (ALT) 16 to 119 U/L, aspartate aminotransferase (AST) 30 to 72 U/L, and alkaline phosphatase (ALP) 132 to 187 U/L (See Table footnotes for normal reference ranges). We predict that these measurements were even higher on the actual day of the supratherapeutic trough concentration (day 7), although the patient never showed signs of acute liver injury. After a week of close monitoring and continuation of posaconazole at a reduced dose, the repeat trough returned therapeutic at 2.2 mg/L, and the patient's liver function tests improved. We did not identify any other adverse effects from posaconazole, such as QTc prolongation or electrolyte abnormalities (calcium, magnesium, potassium). A few days later, the patient was discharged home and given instructions to continue the same dosage until outpatient clinic follow-up occurred. Two months later, a repeat posaconazole trough remained therapeutic at 2.5 mg/L.

Discussion

We report our case of a 10-year-old patient with supratherapeutic posaconazole serum concentrations after receiving the extrapolated adult dosage of the DR tablets for 7 days. Despite guideline recommendations, the tablet formulation was chosen over the suspension to maximize drug bioavailability, especially because our patient had a history of small bowel transplant and was able to swallow pills. After achieving adequate source control through 2 surgical debridements, posaconazole was determined to be an appropriate step-down oral agent based on *in vitro* data⁸ demonstrating potent activity against *Rhizopus* species. We chose to prescribe an extrapolated adult dosing regimen of 300 mg twice daily for the first day, followed by 300 mg daily, based on the severity of infection, limited data mentioned below, and lack of information regarding the minimum inhibitory concentration for our particular *Rhizopus* species.

In 2013, posaconazole DR tablets were approved by the FDA for pediatric patients between the ages of 13 and 17 years. Approval was based on extrapolated data from adults receiving oral tablets and studies in pediatric patients receiving the oral suspension.³ One study⁹

conducted on 10 pediatric patients receiving the oral suspension for prophylaxis of invasive fungal infections showed similar mean steady-state posaconazole average concentrations among adolescents (13–17 years of age) and adults greater than 18 years of age. Another study by Krishna et al⁹ compared posaconazole concentrations from the oral suspension between children (ranging from 8 to 17 years of age) and adults; both groups received 800 mg/day, either 200 mg 4 times daily or 400 mg twice daily, and the patients had similar mean serum posaconazole concentrations (0.776 mg/L vs 0.817 mg/L). There was no difference in overall success rate or adverse events, suggesting that adults and children older than 8 years can be given the same dose. However, the study was limited by the disproportionate number of children (n = 12) compared with adults (n = 194) and included only one patient who was the same age as our patient. Furthermore, it is difficult to extrapolate these results to the DR tablets because the posaconazole suspension formulation is not interchangeable due to bioavailability differences.

In 2017, Döring et al¹⁰ conducted a study on posaconazole DR tablets for antifungal prophylaxis in patients with hematopoietic stem cell transplantation. A total of 32 patients were included, the ages for which were as follows: ≤6 years (n = 4), 7 to 12 years (n = 9), and 13 to 17 years (n = 19). Patients were administered a non-FDA-approved weight-based dosing regimen of 5 to 7 mg/kg twice a day as the initial loading dose, followed by 5 to 7 mg/kg daily. This translated to 100 mg (for weight of 15–21 kg), 150 mg (for weight of 22–30 kg), 200 mg (for weight of 31–35 kg), 250 mg (for weight of 36–40 kg), and 300 mg (for weight of >40 kg or >13 years of age). At the end of the study, no proven or possible fungal infections and no deaths were reported. When drug serum concentrations were compared, the posaconazole concentrations of patients younger than 6 years were not significantly different from those in the older age groups. Median concentrations were 0.874 mg/L at 7 days of therapy, 0.978 mg/L after 14 ± 1 days of therapy, and 1.541 mg/L after 28 ± 2 days of therapy. Most patients achieved prophylaxis targets of >0.7 mg/L and treatment targets of >1 to 1.25 mg/L for invasive fungal infection.^{9,11–18} Only 2 of 32 (6.3%) patients experienced drug-related events. One patient reported nausea, and the other patient experienced facial exanthema. Increases in ALT of >1.5 and >2.5 times the upper limits of normal were observed in 23 out of 32 patients (71.9%), and an increase in AST of >1.5 and >2.5 times the upper normal limit was observed in 21 of 32 patients (65.6%). Direct and total bilirubin concentrations were not affected. Our patient that we report on had increases in both ALT (>2.5 times the upper limit of normal [>112.5 U/L]) and AST (>1.5 times the upper limit of normal [AST >52.5 U/L]). Posaconazole has been associated with both transient aminotransferase elevations and acute drug-induced liver injury so it remains unclear whether our patient's transaminitis was

due to the latter or would have resolved independently on its own.^{9,15,19} However, we did observe improvements in transaminitis shortly after the posaconazole dose was reduced to 200 mg daily.

Currently, there are a very limited number of studies²⁰⁻²² investigating the relationship between posaconazole serum concentration and toxicity. In 2015, Martino et al²² reported a case of a 13-year-old female with suspected posaconazole toxicity after being inadvertently prescribed posaconazole DR tablets 400 mg twice daily. The trough serum concentration was 9.5 mg/L, and the patient suffered from nausea, fatigue, decreased appetite, musculoskeletal pain, hypokalemia, and anemia. Our patient's serum concentration was not as high, nor did she show similar signs of toxicity; however, we speculated that this could have occurred if the dose was continued at 300 mg daily. The study by Döring et al⁹ revealed that posaconazole concentrations can rise even after steady state is achieved. We chose to reduce the dose to 200 mg daily in the setting of transaminitis and to prevent even higher serum concentrations, especially because we considered 3.75 mg/L to be the upper limit for our trough target.²³

We considered various factors that could have contributed to the supratherapeutic trough concentration. It is known that posaconazole absorption can be affected by diet or nutritional status. Absorption can be enhanced with a fatty meal, particularly following administration of the oral suspension formulation.²⁴ However, this was not the case for our patient because she was known to be a selective eater and nutritionally deficient. Another consideration was our patient's hypoalbuminemia, because posaconazole is highly bound to serum albumin (>98%), which would result in more unbound drug freely available in the serum. Posaconazole absorption can also be enhanced with decreased gut motility, increased gastrointestinal surface area, or altered intestinal pH.^{25,26} Our patient had a history of small bowel transplant, so it is unclear how this could have affected her drug absorption. She was also taking lactulose, which enhances gut motility. In terms of drug interactions, ranitidine was discussed but dismissed after learning that the interaction occurs primarily with the suspension formulation and not the DR tablet formulation. Posaconazole suspension relies on low pH in the stomach to dissolve, whereas the DR tablets are released from their polymer in the small intestine.²⁵

Conclusion

We report on a case of a 10-year-old patient with a supratherapeutic posaconazole serum concentration and transaminitis after receiving the extrapolated adult dosage of posaconazole DR tablets for 7 days. In the end, this patient required a smaller dose of 200 mg daily to achieve the desired trough target concentrations for the treatment of a *Rhizopus* infection. This case report highlights the need for additional studies to investigate

dosing of posaconazole DR tablets in children.

Article Information

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