

Clinical Communications

Successful desensitization of voriconazole in an immunosuppressed pediatric patient

Tiffany Jean, MD, and Kenny Kwong, MD

Clinical Implications

- A voriconazole desensitization protocol was successfully designed for an immunosuppressed pediatric patient with limited options for empiric antifungal therapy.

TO THE EDITOR:

Voriconazole is an antifungal agent often used for empirical therapy in prolonged neutropenic fever. Type 1 hypersensitivity to voriconazole occurs in approximately 13% of the patients, which is detrimental for immunosuppressed patients susceptible to invasive fungal infections.¹ Successful desensitization to voriconazole has been reported in 1 adult; however, there are no desensitization protocols published for pediatric patients.² We successfully desensitized an immunosuppressed pediatric patient in the intensive care unit to voriconazole.

A 13-year-old boy with a diagnosis of pre-B-cell acute lymphoblastic leukemia was admitted to the pediatric intensive care unit for neutropenic fever, diarrhea, and diffuse abdominal pain. Two weeks before admission, the patient was treated for herpes simplex virus stomatitis with acyclovir. The patient had received a course of consolidation chemotherapy 4 weeks previously. Initial physical examination was remarkable for stomatitis and perirectal erythema. His abdomen was negative for tenderness, distention, or peritoneal signs. The patient was febrile to 101 F, with a heart rate of 95, blood pressure of 115/78 mm Hg, respiratory rate of 20, and O₂ saturation of 98% on room air. Laboratory values showed neutropenia, with absolute neutrophil count of 146; anemia, with hemoglobin level of 6.6; thrombocytopenia, with 3000 platelets; transaminitis, with aspartate aminotransferase 102 and alanine transaminase 62; and positive *C difficile* toxin. Abdominal computed tomography revealed significant wall thickening of ascending colon and cecum, concerning for neutropenic colitis. The patient was initially given vancomycin, flagyl, meropenem, cefepime, and oseltamivir for presumptive influenza while awaiting antigen confirmation. Prophylactic trimethoprim-sulfamethoxazole and acyclovir were continued.

Seven days after initial admission, the patient remained febrile to 102°F. Blood, urine, and fungal cultures remained negative. Empiric antifungal coverage against *Candida* was started, and 100 mg of micafungin was infused over 1 hour. This was the patient's first exposure to micafungin. Approximately 40 minutes later, the patient developed acute wheezing, facial swelling, and pruritic urticarial rash over his chest, back, and abdomen. His heart rate increased to 160 and blood pressure dropped to 106/45 mm Hg. The patient was given 0.3 mL of epinephrine (1:1000) intramuscularly, 5 mg of albuterol via nebulization, 50 mg of diphenhydramine intravenously, 60 mg of solumedrol intravenously, 150 mg of ranitidine intravenously, and 2 L of normal saline intravenous bolus. His respiratory distress and tachycardia improved. Facial swelling and urticarial rash resolved over the next few hours.

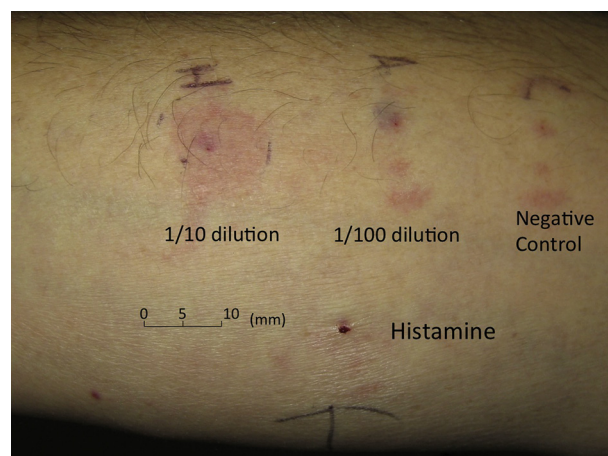


FIGURE 1. Voriconazole skin test. Voriconazole at 1/10 dilution elicited a 5-mm wheal and a 10-mm flare. Voriconazole at 1/100 dilution was negative.

TABLE I. Voriconazole intravenous desensitization protocol

Dose	Concentration (mg/mL)	Dose (mg)	Cumulative dose (mg)	Time (min)
1	0.1	0.02	0.02	15
2	0.1	0.05	0.07	30
3	0.1	0.1	0.17	45
4	1	0.25	0.42	60
5	1	0.5	0.92	75
6	1	1	1.92	90
7	5	2	3.92	105
8	5	4	7.92	120
9	5	8	15.92	135
10	5	16	31.92	150
11	5	32	63.92	165
12	5	64	127.92	180
13	5	128	255.92*	195
14	5	207	335†	210

*Maintenance dose is 4 mg/kg every 12 h, approximately 223 mg.

†Loading dose is 6 mg/kg, approximately 335 mg.

Twenty-eight hours later, voriconazole was initiated given that it was a different class of antifungal agent. The patient had never been exposed to voriconazole previously. Voriconazole was administered in the form of a graded challenge, beginning with 1/200th of the total dose. At 1 mg, the patient developed another anaphylactic reaction with facial urticaria and wheezing. Voriconazole was promptly discontinued, and intravenous solumedrol and nebulized albuterol were given with resolution of symptoms. Skin prick testing to voriconazole was performed, with a 5-mm wheal and a 10-mm flare elicited at 1/10 dilution of intravenous concentration (5 mg/mL) (Figure 1). Test results in 2 controls were negative at this dilution. Intravenous voriconazole was restarted after a desensitization regimen (Table I). Given the patient's anaphylaxis

from a small dose of 1 mg, a starting dilution of approximately 1:15,000 was used. First, 0.02 mg was given, and the dose was doubled every 15 minutes using 3 concentrations: 0.1, 1, and 5 mg/mL. Mild reactions involving cutaneous symptoms occurred twice at 4- and 16-mg doses. The patient received diphenhydramine, and the last dose that did not elicit a reaction was repeated. There were no systemic reactions. After 3 hours, the patient's cumulative dose reached the loading dose of 335 mg (6 mg/kg). A second loading dose and further maintenance doses of 223 mg (4 mg/kg) were tolerated for a total of 10 days without any allergic reactions.

This is the first report of successful desensitization of voriconazole in a pediatric immunocompromised patient. Urticaria has been reported to occur in 13% of the patients, and angioedema is documented in 1 case study.^{1,3} Although cutaneous hypersensitivity reactions are more common, anaphylaxis reactions are rare, with only 2 cases occurring during infusion.⁴ Micafungin anaphylaxis reactions are also rare, about 0.2%, and present only in those patients who take multiple medications for their underlying diseases.⁵ There is 1 other report of oral voriconazole desensitization for an adult patient with acute myeloid leukemia.² However, our protocol is created for intravenous voriconazole desensitization, and our pediatric patient had hypersensitivity reactions to 2 different classes of antifungals.

The patient had anaphylaxis to voriconazole and micafungin. Voriconazole was skin prick tested, which resulted in a 5-mm wheal and a 10-mm flare. Corticosteroids and antihistamines were given within the previous 28 hours and therefore skin testing reaction severity may be reduced. There are no control concentrations published. Two control subjects were used for the 1/10 dilution of the intravenous concentration (5 mg/mL). This was the first time the patient received micafungin and therefore it is unclear whether the reaction was due to a type 1 reaction because he was unlikely to be sensitized previously. It is possible that he received other antifungal agents in the same class as micafungin to which he had been sensitized. Alternatively, the reaction to micafungin may be non-IgE mediated. Skin testing to micafungin was not performed. Our rationale was that micafungin skin testing may cause anaphylaxis and the patient may be able to avoid that risk if the desensitization protocol with voriconazole succeeds. Graded challenge to voriconazole was performed because of the severity of the reaction with micafungin and concern for increased likelihood of allergic sensitization after initial allergic reaction to micafungin. The patient's reaction to the graded challenge confirmed the initial suspected hypersensitivity.⁶ His voriconazole reaction is most likely anaphylaxis given clinical symptoms and positive skin test result. Although the reaction may be part of the

biphasic reaction from micafungin, it is unlikely because voriconazole was given 28 hours after micafungin.

Our pediatric immunocompromised patient had severely limited options for treatment. Empiric fungal coverage for *Candida* and *Aspergillus* was required given the patient's high-risk acute lymphoblastic leukemia and prolonged neutropenic fever.⁷ The patient had anaphylaxis to both micafungin and voriconazole. Amphotericin was avoided because of renal toxicity.⁸ Therefore, voriconazole desensitization was the best option given voriconazole provided adequate coverage of *Candida* and *Aspergillus* without the severe adverse effects of amphotericin.⁹ Voriconazole was successfully desensitized using a 14-step protocol in 3.5 hours with 2 mild cutaneous reactions. This intravenous protocol can be adjusted on the basis of future patients' degree of hypersensitivity during desensitization.

Harbor UCLA Medical Center, Torrance, Calif

Conflict of interest: The authors declare that they have no relevant conflicts of interest.

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Corresponding author: Tiffany Jean, MD, Harbor UCLA Medical Center, 1000 W Carson St, Torrance, CA 90502. E-mail: tiffanytjean@gmail.com.

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