


Voriconazole-Induced Photosensitivity in Children: A Case Report and Literature Review

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Introduction

Voriconazole is a broad-spectrum triazole antifungal with a reliable oral bioavailability introduced in 2002. It is indicated for treatment of pulmonary aspergillosis, primary treatment of amphotericin B and fluconazole-resistant fungal infections such as *Fusarium* spp and *Scedosporium apiospermum* (asexual form of *Pseudoallescheria boydii*).^{1,2} Voriconazole is also used for empirical antifungal therapy of neutropenic fever in patients receiving nephrotoxins (cyclosporine, tacrolimus) and antifungal prophylaxis in high-risk patients undergoing bone marrow transplantation and patients with severe graft-versus-host disease.^{1,2} Common side effects include abnormal vision, elevation of liver enzymes, as well as skin rashes including allergic reactions and Stevens–Johnson syndrome.¹ Metabolic side effects include hypokalemia and hypomagnesemia. Photosensitivity is a rare complication of voriconazole therapy³; a limited number of cases have been reported in the pediatric population.^{4–12} We report a teenager with common variable immunodeficiency who developed voriconazole-induced severe photosensitivity reaction mimicking Stevens–Johnson syndrome requiring treatment in the burn unit with frequent dressing changes for 2 days.

Case Report

A 17-year-old Caucasian girl with history of common variable immunodeficiency presented with a 6-day history of nonpruritic, photo-distributed rash on face, arms, and legs associated with swelling of arms. The rash started after she was playing in the farm on a sunny day for a few hours. There was no history of fever. She had burning sensation in her eyes without drainage or blurring of her vision for a few hours prior to admission. She also had dryness with redness and early blistering lesions on her lips. She has no history of recent sick contacts.

She was diagnosed with common variable immunodeficiency at the age of 3 years following recurrent hospitalizations for ear infections and bacterial pneumonia.

She receives monthly intravenous immunoglobulin therapy. In the last 5 months, she developed recurrent episodes of cough and hemoptysis. Chest computed tomography (CT) scan showed tree in bud appearance and bronchoalveolar lavage fungal culture grew *Aspergillus fumigatus*. She was given oral voriconazole 200 mg twice daily for 4 weeks, which was then increased to 300 mg twice daily, 10 days prior to presentation, due to subtherapeutic serum voriconazole level. Her other medications at the time of admission were the following: Vynase (Lesdexamphetamine), 50 mg once a day, and Seroquel (Quetiapine), which was stopped 10 days prior to presentation in view of theoretical risk of QT prolongation due to drug interaction with voriconazole.

Her physical examination revealed a well-built, well-nourished teenager. She was alert but in moderate distress due to burning sensation of the arms and face. Her vital signs showed a temperature of 36.7°C, heart rate 65/min, respiratory rate 14/min, and blood pressure of 117/69 mm Hg. She had an erythematous rash on the face and both arms up to midarm level with swelling of both arms. The rash was also present on the neck and lower extremities. The skin was erythematous and shiny with tenderness to touch and pressure in all photo-distribution areas but was sparing the truncal area, buttocks, and the genital area. She also had cracked lips with mild bleeding without swelling or oral ulcers (Figure 1). The rest of the physical examination was normal.

Laboratory investigations at admission were as follows: white blood cells 3900/mm³ (neutrophils 74%, lymphocytes 16%, monocytes 8%, eosinophil 2%), hemoglobin 13.9 gm/dL, hematocrit 41.6%, platelets 196 000/mm³. Serum electrolytes were within normal

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Figure 1. Erythema of the face, with lower lip inflammation. Swelling and erythema of the dorsum of the hand. Swelling and erythema of the arm.

limits. Blood urea nitrogen 15 mg/dL, creatinine 0.7 mg/dL, bilirubin total 0.7 mg/dL, bilirubin direct <0.1 mg/dL, alanine aminotransferase 17 U/L, aspartate aminotransferase 28 U/L, alkaline phosphatase 93 U/L. Blood culture was negative. Voriconazole level by high-performance liquid chromatography was 2.5 µg/mL (therapeutic range being 2-6 µg/mL). Serum parvovirus B-19, *Mycoplasma*, and herpes simplex IgM levels were all negative.

She was admitted to the burn unit and was treated with intravenous fluid hydration and frequent Vaseline dressings to the affected areas for 2 days. This was followed by topical triamcinolone (0.1%) cream. Voriconazole was discontinued at the time of presentation. A skin biopsy showed mild vacuolar interface dermatitis with necrotic keratinocytes and superficial vessel involvement consistent with photosensitivity reactions. The rash gradually improved. The patient also reported improvement in tenderness and swelling of the extremities. Lip sores also improved in few days. She was instructed to minimize sun exposure and always use sun screens. The symptoms and skin findings resolved after 10 days. She completed a 6-week course of antifungal therapy for pulmonary aspergillosis with intravenous micafungin.

Discussion

Voriconazole-induced skin reactions can be varied and include cheilitis, hyperpigmentation, erythroderma, lentiginos, contact dermatitis, discoid lupus erythematosus, fixed drug eruption, and severe skin reactions such as Stevens–Johnson syndrome and toxic epidermal necrolysis.^{1,5,13} An

increasing number of skin reactions in relation to light exposure have also been reported including porphyria cutanea tarda, pseudoporphyria, photosensitization, and phototoxicity.^{14,15} In pediatric case reports of photosensitive reactions, the majority of patients presented with erythema of the photo-exposed areas of body like palms, soles, forearms, neck, and upper back. Cheilitis, dryness, and cracking of the lips have also been reported with voriconazole therapy.^{4,5} Other dermatological effects include macular pigmentation with chronic photodamage⁹ and desquamation of the lips, palms, and soles.⁵

Voriconazole-induced photosensitivity usually presents as sunburn on sun-exposed surfaces of the body. In adults, photosensitivity occurs in 1% to 2% of patients receiving voriconazole and usually presents after 12 weeks of therapy.¹³

In a review of voriconazole-induced phototoxicity (Table 1), 20 children have been reported with voriconazole-induced photosensitivity; 11 of 17 with identified gender were males. The mean and median ages were 11.4 years and 11 years, respectively. Among those, 5 had cystic fibrosis, 3 had allergic bronchopulmonary aspergillosis, and 12 had underlying immunodeficiency including chronic granulomatous disease or malignancy. Similar to adult reports, photosensitive reactions in children seem to be idiosyncratic and independent of duration or dose of voriconazole. These reactions were reported to occur as early as 2 weeks into voriconazole therapy to as late as 54 months.^{5,6} In our patient, photosensitivity occurred 5 weeks into therapy. Whether high doses of voriconazole are associated with increased risk of photosensitivity is unclear. In our patient, the reaction occurred 10 days after increasing the daily dose from

Table 1. Summary of Pediatric Cases of Voriconazole-Induced Photosensitivity (≤ 18 Years of Age).

Reference	Age and Gender	Diagnosis	Presentation	Skin Biopsy/Lab	Concurrent Medications	Outcome
Racette et al ⁴	15 years, female	Sinus infection and cranial invasion with <i>Curvularia lunata</i>	Erythema of legs, face; dryness and cracking of lips Photoaging of skin Lichen planus like eruption, lentiginos, and ephelides after 7 months	Urine porphyrins negative	None	Improved after stopping voriconazole
Rubenstein et al ⁵	11 years, male	CGD with aspergillosis	Erythema of face, neck, forearms, hands with flaccid bullae Cheilitis Chronic photodamage and lentigens 5 months later Desquamation of lips, palms, and soles with facial erythema, photosensitivity	Skin biopsy: perivascular dermatitis; epidermal necrosis Immunofluorescence: negative Serum porphyrins: negative NA	TMP/SMX, interferon gamma, caspofungin, MgO, montelukast, inhaled salmeterol: all for >1 year TMP/SMZ Cyclosporine, daclizumab, prednisone thalidomide topical tacrolimus, TMP/SMX	Continued voriconazole Counseling regarding sun protection Improved Resolved after stopping voriconazole and sun protection Photodynamic therapy for SCC
Cowen et al ⁶	9 years, male	ALL post-HCT, acute skin GVHD	Erythema of forearms, cheeks and lower extremities with ephelides and lentiginos x 3 years Chronic phototoxicity and photodamage Erythema, mild lentigo formation on side of neck, back of hand	Skin biopsy: actinic keratosis followed by superficial SCC in next biopsy 5 months later Skin biopsy: actinic keratosis followed by superficial SCC	NA Azathioprine, cyclosporine, daclizumab, sirolimus, prednisone, thalidomide TMP/SMX, interferon gamma x 4 months	Changed to itraconazole prophylaxis, rash resolved Changed to posaconazole, rash resolved after 3 weeks
Frisch et al ⁷	10 years, male	X linked CGD, prophyllaxis	Pruritic, multiple lentiginos on face, neck in photo-distributed pattern	NA	Prednisone 8 mg daily	
Patel et al ⁹	15 years, male	Sarcoma post-HCT, GVHD, pulmonary aspergillosis	Erythema of forehead, arms Malar rash on cheeks Erosions and bullae Pseudoporphyria cutanea tarda Pachy pigmentation, solar lentiginos in photo-distribution area (chronic photodamage)	NA		Changed to posaconazole, rash resolved after 2 weeks Changed to posaconazole, rash resolved after 3 weeks
Cheng et al ^{10a,b}	7 years, male	Cystic fibrosis with CNPA	Erythema/painful skin in photo-distribution areas	Photosensitivity was associated with a voriconazole level 4.6 mg/L (300 mg: 14.6 mg/kg/d)	Symbicort, inhaled tobramycin, vitamin A, pulmozyme	Changed to posaconazole, rash subsided after 6 days

(continued)

Table 1. (continued)

Reference	Age and Gender	Diagnosis	Presentation	Skin Biopsy/Lab	Concurrent Medications	Outcome
			Epidermal desquamation			
	16 years, male	Cystic fibrosis with CNPA	NA	Voriconazole trough 2.59 mg/L	Vitamin A	NA
	16 years, female	Cystic fibrosis with CNPA	Erythema of face after sun exposure despite using appropriate sunscreen	Photosensitivity was associated with a voriconazole level 8.04 mg/L (300 mg: 7.69 mg/kg/d)	Symbicort, inhaled tobramycin, and vitamin A	Decreased dose to 150 mg QD (3.85 mg/kg/d)
	18 years, female	Cystic fibrosis with CNPA	Macular pigmentation with solar lentigines in photo-distribution area	Photosensitivity was associated with a voriconazole level 2.38 mg/L	Vitamin A	NA
	18 years, female	Cystic fibrosis with CNPA	Rash after increased dose	Voriconazole trough 2.81 mg/L	Vitamin A	NA
	18 years, female	Cystic fibrosis with CNPA	Erythema with solar lentigines in photo distribution area	NA	Folic acid, KCl, vitamin D, acyclovir, cefuroxime	Voriconazole discontinued, improved
Vohringer et al ¹¹	8 years, male	AML chemotherapy, aspergillosis	Solar dermatitis followed by blistering facial lesions	NA	NA	Changed to posiconazole, improved
Frick et al ⁸	1 month, male	CGD, pulmonary aspergillosis	Erythema, vesicular lesions on face and sun-exposed areas	Normal voriconazole level	NA	Changed to posiconazole, improved
	16 years, female	Hyper-IgE syndrome, lung aspergilloma	Erythematous rash on face, extremities, and sun-exposed areas	Normal voriconazole level	NA	Changed to posiconazole, improved
	3 years, male	CGD, <i>Aspergillus nidulans</i> brain abscess	Severe erythema, lentiginous lesions affecting face	Normal voriconazole level	NA	Changed to posiconazole, improved
Hilliard et al ¹²	14 years	ABPA	Photosensitivity	NA	IVIg, inhaled steroids	NA
	11 years	ABPA (past)	Photosensitivity	NA	Prednisone, inhaled steroids	NA
	11 years	<i>Aspergillus</i> (sputum)	Photosensitivity	NA	None	NA
Present case	17 years, female	Common variable immunodeficiency	Photosensitivity, tender swollen arms and hands, cheilitis	Normal voriconazole level	Lesdexamphetamine Quetiapine	Changed to IV micafungin
			Biopsy: vascular dermatitis, necrotic keratinocytes			

Abbreviations: ITP, idiopathic thrombocytopenic purpura; CGD, chronic granulomatous disease; SCC, squamous cell carcinoma; TMP/SMX, trimethoprim/sulfamethoxazole; CNPA, chronic necrotizing pulmonary aspergillosis; QD, once daily; BID, twice daily; NA, not available; HCT, hematopoietic cell transplantation; GVHD, graft versus host disease; ALL, acute lymphocytic leukemia; ABPA, allergic bronchopulmonary aspergillosis.

¹¹Vitamin A was given as part of daily multivitamin regimen.

¹²Photosensitivity occurred in 5/6 study patients; all had visual disturbances.

400 mg to 600 mg. However, the voriconazole serum level was within the therapeutic range at the time of presentation. Similarly, others have reported photosensitive rashes after increasing the dose of voriconazole.^{9,10}

Among 20 pediatric cases of photosensitive reactions (Table 1), voriconazole was discontinued in 12 children. In 7 of the 12 children, antifungal therapy was changed to posaconazole in 6 cases and to itraconazole in 1 case.⁷⁻¹⁰ Voriconazole was continued in 3 cases: in 2 cases at the current dose and in 1 case at a lower dose.^{5,12} In a study by Walsh et al of 58 patients who received voriconazole, 8 had skin rash and 3 developed photosensitivity reaction that were long lasting (>30 days) but did not require discontinuation of the drug.¹⁶ Patients with photosensitivity reaction may continue to take voriconazole if needed. However, caution should be taken to avoid sun light exposure particularly if high doses are continued. Photosensitivity has rarely been reported with other azoles. Only 2 cases of photosensitivity due to ketoconazole¹⁷ and one from itraconazole have been previously reported.¹⁸ However, photosensitivity has not been documented due to fluconazole, to which voriconazole is structurally most closely related.

The timing of resolution of the photosensitive rash following discontinuation of voriconazole is variable. In our patient, the rash disappeared after 10 days and in other pediatric reports after 6 days to 3 weeks. In adults, facial erythema and cheilitis have been reported to disappear 4 months after stopping voriconazole.¹³

The cause of voriconazole-induced photosensitivity is unknown. Levels of all-*trans*-retinol (vitamin A) and 13-*cis*-retinol were elevated in adult patients with phototoxicity even months after the cessation of therapy. It has been postulated that voriconazole may inhibit the metabolism of all-*trans*-retinol and/or 13-*cis*-retinol, leading to increased plasma retinoid levels.¹³

Another proposed mechanism is that although voriconazole does not absorb in the UVA or UVB spectrum, its major metabolite, voriconazole N-oxide, absorbs UVB and UVA rays and may therefore act as the culprit chromophore for phototoxicity.¹⁹ In addition, various authors have reported occurrence of voriconazole photosensitivity in immunodeficient patients like Job syndrome and other B-cell and T-cell immunodeficiency disorders, including acquired immunodeficiency syndrome as well as chronic granulomatous disease.^{5,7,8,20} A defective host defense and recurrent antigenic stimulation leading to autoimmune phenomena and increased predisposition to photosensitivity due to voriconazole is another postulated mechanism. Retinol levels, specifically all-*trans*-retinol and 13-*cis*-retinol, were not measured in our patient.

Histopathological findings in patients with photosensitive reactions include superficial and perivascular dermatitis with epidermal necrosis and benign lentiginosities.⁵ Cowen et al reported 2 boys with chronic granulomatous

disease (9 and 11 years old) who developed actinic keratosis and squamous cell carcinoma after receiving prolonged voriconazole therapy (39 and 54 months, respectively).⁶ Miller et al reported 2 patients including a young adult with chronic granulomatous disease who had melanoma in situ lesions that developed at areas of chronic photodamage while receiving prolonged voriconazole therapy.²¹ The biopsy result in our case showed mild vacuolar interface dermatitis with necrotic keratinocytes with predominantly superficial vessel involvement, which made photosensitivity more likely diagnosis as the necrotic keratinocytes are usually situated in the upper epidermis whereas those of erythema multiforme and fixed drug eruption are usually seen in the lower part of the epidermis.

It is important for physicians to be aware of this uncommon occurrence of photosensitivity reactions in immunocompromised patients receiving voriconazole for invasive fungal infections. These reactions may occur at any time during the course of therapy and when voriconazole level is within the therapeutic range. It is also important to differentiate it from serious conditions such as Steven–Johnson syndrome. Skin biopsy may be helpful in unclear cases. It is not absolutely indicated to discontinue use of voriconazole but continued close monitoring and patient education is important. Posaconazole may be an effective alternative in patients with intolerable voriconazole side effects.⁹ Patients receiving voriconazole who may be exposed to sunlight should be advised to use sunscreen (sun protection factor 30) to prevent or minimize phototoxicity as well as avoid direct sun exposure and wear protective clothing. However, caution should be taken with long-term use in the setting of extreme photosensitivity as cases of progression to squamous cell carcinoma and melanoma have been reported.^{6,21} Further postmarketing surveillance on the incidence and impact of late-onset cutaneous side effects related to voriconazole is warranted.

Declaration of Conflicting Interests

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