Voriconazole phototoxicity in children: A retrospective review

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Background: Voriconazole, an antifungal agent, is associated with various cutaneous reactions, including phototoxicity, accelerated photoaging, and skin cancer. Incidence and risk factors for these reactions in children have not been well described.

Objective: We sought to determine the incidence of and factors associated with phototoxic reactions and nonmelanoma skin cancer in pediatric patients treated with voriconazole.

Methods: This was a retrospective analysis of 430 pediatric patients treated with voriconazole between 2003 and 2013 at Boston Children's Hospital.

Results: Incidence of phototoxicity was 20% in all children treated with voriconazole and 47% in children treated for 6 months or longer. Factors associated with phototoxicity included white race, cystic fibrosis, cumulative treatment time, and cumulative dose. Four patients (1%) had nonmelanoma skin cancer; all experienced a phototoxic reaction during voriconazole treatment. Of those with phototoxicity, 5% were discontinued on voriconazole, 6% were referred to dermatology, and 26% received counseling about sun protection from their primary physician.

Limitations: Our study is limited by its retrospective design and potential referral bias associated with a tertiary-care center.

Conclusions: Voriconazole-associated phototoxicity is relatively common in children and may lead to nonmelanoma skin cancer. However, those with phototoxic reactions are often continued on therapy, rarely referred to dermatology, and infrequently counseled on sun protection. (J Am Acad Dermatol 2015;72:314-20.)

Key words: nonmelanoma skin cancer; pediatrics; photosensitivity; phototoxicity; squamous cell cancer; voriconazole.

Voriconazole, a second-generation antifungal agent, is increasingly used because of its extended antifungal activity and improved bioavailability compared with other azole antifungals. It is *Food and Drug Administration* approved for use in children older than 2 years and has broad-spectrum activity against species of *Aspergillus*, *Candida*, *Scedosporium*, and *Fusarium*.[1] Voriconazole has been associated with various cutaneous reactions, including phototoxicity, pseudoporphyria, accelerated photoaging, and an increased incidence of squamous cell carcinoma (SCC) in immunocompromised patients.[2-4]

Phototoxic reactions in patients treated with voriconazole have been reported to occur in 17.3% of adults and 5% to 36.5% of children.[5-9] Prior studies

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in children have been small (<74 patients).[6] A stepwise progression has been demonstrated among patients who experienced erythema in photo-exposed areas in the first year of voriconazole treatment, followed by actinic keratoses in the second and third years of treatment, and subsequently SCC formation in the third and fourth years of treatment, suggesting that phototoxic reactions may result not only in acute discomfort but also significant long-term morbidity.[10]

Studies of lung transplant recipients have established long-term voriconazole use as an independent risk factor for SCC.[2,11-13] In a retrospective cohort study, exposure to voriconazole was associated with a 2.6-fold increased risk of SCC. Five years after transplantation, patients exposed to voriconazole had a 28% absolute risk increase in developing SCC.[11] In the pediatric literature, there are 7 reports of SCC in children treated with prolonged voriconazole therapy, ages 9 to 15 years. SCC were detected in these patients after 35 to 61 months of voriconazole treatment.[2,14,15] Although these cases are rare, these patients will have a lifetime of sequelae, including risk of invasive SCC and mortality.

Currently, there is limited literature regarding adverse cutaneous effects of voriconazole in children. The objective of this study was to assess the incidence of phototoxic reactions and nonmelanoma skin cancer (NMSC) in children treated with voriconazole and to explore potential predisposing risk factors.

CAPSULE SUMMARY

- Prolonged use of voriconazole is associated with phototoxicity and increased risk for squamous cell carcinoma in immunocompromised patients.
- Approximately 20% of children on voriconazole developed phototoxicity. Risk factors include white race and cumulative voriconazole dose.
- Children receiving voriconazole should receive counseling and monitoring to minimize cutaneous toxicity.

METHODS

This study was approved by the institutional review board at Boston Children's Hospital (project P00010524). Patients for whom voriconazole was prescribed or ordered through the electronic medical record at Boston Children's Hospital between 2003 and 2013 were identified. Clinical data were extracted, including age, gender, race, primary diagnosis, reason for voriconazole treatment, dose and duration of voriconazole, and concurrent photosensitizing medications. Data regarding dermatology visits and sun-protection counseling were also recorded. A phototoxic reaction was defined as documentation of erythema or blistering in sun-exposed areas, cheilitis, lip cracking, or lip dryness. Concurrent photosensitizing medications identified included tetracyclines, fluoroquinolones, sulfonamides, tricyclic antidepressants, hydrochlorothiazide, tretinoin, or methotrexate.

Statistical analysis was performed using software (SAS, PC Version 9.3X, SAS Institute Inc, Cary, NC). Median and range were reported for continuous variables, and frequencies were reported for categorical variables. To identify factors associated with a phototoxic reaction, Fisher exact test was used for categorical factors and a Wilcoxon rank sum test was used for continuous factors. Multivariate logistic regression analysis, using backwards selection, was used to identify factors that were independently and most strongly statistically significantly predictive of the occurrence of a phototoxic reaction. *P* values less than .05 were considered statistically significant.

RESULTS

Demographics and clinical characteristics

Voriconazole was used in the treatment of 430 pediatric patients (Table I). The mean age at voriconazole initiation was 11.86 years (SD 7.11 years). At the time of data collection, 297 patients (69%) were alive. The majority of patients were of white race (69%).

Among all patients treated with voriconazole, 267 had a primary diagnosis of blood malignancy (62%), 65 cystic fibrosis (15%), 33 immunodeficiency (8%), 31 bone-marrow failure (7%), and 31 had other diagnoses (8%). Transplantation was performed for 266 patients (53%), of which 183 were stem cell (81%), 28 lung (12%), and 15 other organ or combined (7%) transplants. The reason for voriconazole treatment was antifungal prophylaxis in 303 patients (70%), *Aspergillus* treatment in 91 patients (21%), *Candida* treatment in 6 patients (1%), and other fungal infection treatment in 30 patients (7%). In all, 330 patients (77%) had been treated with concomitant photosensitizing medications during their duration of voriconazole treatment and 120 patients (28%) had a history of radiation therapy.

Phototoxic reactions

A phototoxic reaction was described in 87 patients (20%). Among these, 57 had skin involvement (66%),