High frequency of voriconazole-related phototoxicity in cystic fibrosis patients

To the Editors:

Aspergillus fumigatus infection is common in cystic fibrosis (CF) patients and estimates of the rate of allergic bronchopulmonary aspergillosis range from 1–15%. Voriconazole, a new triazole antifungal, has been recognised as efficient and safe in the treatment of invasive aspergillosis [1–2]. Since it is available orally, voriconazole became the first alternative to itraconazole. We began giving voriconazole to CF patients in 2003, and we encountered an unexpectedly high frequency of moderate-to-severe skin reactions, which limited the administration of the drug.

We therefore reviewed all the medical files of children (aged <18 yrs; n=72) and adults (n=63) followed up in our tertiary CF reference centre between April 2003 and December 2008, in order to estimate the frequency of voriconazole-induced photosensitivity, as previously defined [3]. All the patients who were given voriconazole were selected. Demographic data, cystic fibrosis transmembrane conductance regulator (CFTR) mutations, clinical data, treatment, duration and voriconazole dosage, and related adverse effects (AEs) were collected. Qualitative and quantitative comparisons were analysed using the Chi-squared test and nonparametric Mann–Whitney test, respectively. Multivariate analyses were performed by using stepwise logistic regression.

A p-value <0.05 was considered statistically significant. Statistical analyses were performed using Statistica 8 (StatSoft, Maisons-Alfort, France).

31 (21.4%) out of the 135 CF patients were given voriconazole. Their characteristics are described in table 1. When genotypes were categorised into CFTR mutation classes, 36.5% and 58%, respectively, were heterozygous and homozygous for class II mutations, which alter the maturation of CFTR protein. Voriconazole-related AEs were reported in 19 (61%) patients. One patient suffered from a persistent dazzle. All others presented with photosensitivity reactions such as facial rash, moderate-to-severe sunburn or fine desquamation of exposed skin. Eight (44.5%) received voriconazole during the winter, and all were recommended to apply skin protection at the time of prescription. The onset time of photosensitivity was available in children and ranged from 22–349 days (median 146 days). 11 (61%) patients required interruption of treatment because of these reactions.

The frequency of AEs was not significantly different in children (63%) *versus* adults (50%) or in males (66%) *versus* females (50%). As expected, the daily dose (mg·kg⁻¹) given was higher in the paediatric population than in the adult one: median 9 (range 5.0–24.2) mg·kg⁻¹ *versus* 8 (5.2–9.3) mg·kg⁻¹ (p=0.034).

TABLE 1 Description of the whole population exposed to voriconazole and comparison regarding photosensitivity groups

	Total population	Photosensitivity	No photosensitivity	p-value
Subjects n	31	18	13	
Photosensitivity	18 (58.1)	18	0	
Age yrs	15.8 (4–35)	13.5 (4–26.1)	16.8 (6.75–35)	0.08
Age <18 yrs	19 (61.3)	12 (66.7)	7 (53.8)	0.28
Sex male/female n	15/16	8/10	8/5	0.60
Weight kg	44 (10.6–77)	41 (10.6–57)	50 (17.3–77)	0.03
CFTR mutation (ΔF508)				0.004
ΔF508/ΔF508	13 (41.9)	12 (66.7)	1 (7.7)	
ΔF508/other	16 (51.6)	5 (27.8)	11 (84.6)	
Other/other	2 (6.5)	1 (5.6)	1 (7.7)	
CFTR mutation (class II)				0.024
Class II/class II	18 (58.1)	14 (77.8)	4 (30.8)	
Class II/other	11 (35.5)	3 (16.7)	8 (61.5)	
Other/other	2 (6.5)	1 (5.6)	1 (7.7)	
Pancreatic insufficiency	27 (87.1)	17 (94.4)	10 (76.9)	0.36
Daily dose of voriconazole				
mg	400 (120–400)	400 (120–400)	400 (200–400)	
mg·kg ⁻¹	8 (5.0–24.2)	9 (1.3–28)	8 (2.5–64)	0.10
Time of drug exposure months	6.5 (1.3–64)	6.5 (1.3–28)	15 (2.5–64)	0.44
Treatment interruption in relation with skin reactions	11 (35.5)	11 (61.1)	0	

Data are presented as n (%) or median (range), unless otherwise stated CFTR: cystic fibrosis transmembrane conductance regulator.

Photosensitivity was strongly associated with $\Delta F508/\Delta F508$ genotype (OR 24, 95% CI 2.5–230.7; $p=0.004$) but was not with pancreatic insufficiency. The association remained when the analysis was extended to class II genotype (OR 6.3, 95% CI 1.6–52.6; $p=0.01$). The group with photosensitivity tended to be younger, and further analysis showed that seven out of the 12 concerned children were aged less than 9 yrs. Multivariate analysis showed that photosensitivity was only independently associated with $\Delta F508/\Delta F508$ genotype (OR 24.5, 95% CI 2.2–272.9; $p=0.009$). Seven patients were also given ciprofloxacin, and only one of them belonged to the photosensitivity group.

This survey observed a high frequency (58%) of photosensitivity among 31 CF patients treated with voriconazole. Voriconazole has been considered as a well-tolerated drug in large cohorts of patients with various immunity statuses. Skin eruptions [1] have been described in 0.5 to 5.3% of cases in various phase III trials [4], and recently up to 8.3% in an open study on chronic aspergillosis treatment [5]. On the other hand, voriconazole-related photosensitivity has rarely been reported in CF children or adult patients [2, 6–7]. This high rate of photosensitivity was not in line with the previous reported ratio of 14% in CF children [2], but closer to 40% in lung-transplanted CF adults [6]. A recent Canadian case report raised the question of voriconazole safety as five out of the six CF children treated with voriconazole presented photosensitivity. By comparison, WALSH *et al.* [8] reported 16% of cutaneous AEs in 69 non-CF children, and only three (4.3%) were identified as photosensitive. The patients from our CF centre were given prolonged voriconazole treatment, which might influence the AE rate. The mean duration of treatment was close to 1 year in our patients, which was comparable to that reported by BERGE *et al.* [6] (9.6–22 months) and CHENG *et al.* [7] (6–22 months), but longer than that reported by HILLIARD *et al.* [2] (<29 weeks). We nevertheless noticed that photosensitivity could occur at any time during the treatment; *i.e.* from a few weeks to 1 yr in our survey. The occurrence of voriconazole-related photosensitivity was related neither to the length of the treatment nor to the administered dose. Although not assessed in this survey, a relationship with high serum levels appeared unlikely as previously shown [6–8]. Lastly, ciprofloxacin, well known to induce photosensitivity, was excluded as an interfering risk factor.

The mechanism of voriconazole-related photosensitivity remains unknown. Voriconazole is metabolised by the human cytochrome P-450 and its isoenzymes, mainly CYP2C19 and to a lesser extent CYP2C9 and CYP3A4, but no relationship has yet been demonstrated between this pathway and photoreactions [1]. Thus, BERGE *et al.* [6] have recently proven that CYP2C19 genotypes influence voriconazole exposure without any impact on the occurrence of AEs [6]. Voriconazole-related skin reactions have been assimilated to retinoid-like sensitivity [3], as retinoid acid and metabolites induced photosensitivity and high serum levels were measured in three out of the five reported adults [5]. DENNING and GRIFFITHS [9] hypothesised that voriconazole might inhibit a step in the metabolic breakdown of all-trans retinol (vitamin A) through the cytochrome P-450 pathway that they shared. This led to the establishment of a possible link with the common vitamin A supplementation required in pancreatic insufficiency CF patients [7]. Although all the patients were indeed vitamin A supplemented, pancreatic insufficiency was not identified in our study as an associated factor for

photosensitivity, contrary to the strong relationship established with the $\Delta F508/\Delta F508$ genotype. This association has never been underlined, and it might be of interest that the genotype of the three patients with photosensitivity reported by HILLIARD *et al.* [2] was also $\Delta F508/\Delta F508$. Otherwise, ciprofloxacin-related photosensitivity has been stated as uncommonly appearing, with a high frequency in CF [10]. This suggests that CF disease itself might be a risk factor to facilitate the expression of drug-related photosensitivity, and would agree with a possible ability of voriconazole or one of its metabolites to elicit a phototoxic reaction, which is a common mechanism. $\Delta F508/\Delta F508$ mutation alters the maturation of the CFTR protein, which is an ATP-binding cassette transporter (ABC, subfamily C) and a cAMP-regulated Cl^- channel that mediates transepithelial Cl^- transport in various tissues. CFTR has been shown to limit reactive oxygen species (ROS) production. Interestingly, both ABC transporters [11] and ROS [12] have been implicated in phototoxicity mechanisms. This pathway could however not sustain the whole mechanism of voriconazole-induced photosensitivity that we observed. The genotype analysis of the patients with no skin reaction showed that all but two of them nevertheless carried two mutations deeply altering the CFTR protein either through its maturation or its production.

In conclusion, CF patients appeared highly photosensitive to voriconazole, independently of seasonality and despite the recommended skin protection that we provided. This should be taken into account by CF practitioners, as several case reports have warned on the association of prolonged voriconazole therapy with discoid lupus erythematosus-like lesions or secondary squamous cell carcinoma [8, 13]. Otherwise, the involvement of the $\Delta F508$ CFTR mutation might be helpful for further research in the understanding of these common adverse drug effects.

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