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Original Article

Voriconazole pharmacokinetics and photosensitivity in children with cystic fibrosis

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Abstract

Background: A high incidence of adverse skin reactions following long-term oral administration of voriconazole in children with cystic fibrosis and allergic bronchopulmonary aspergillosis (ABPA). The aim was to study the pharmacokinetics of voriconazole in these patients and to determine a possible association between drug levels and adverse effects.
Methods: Multiple venous blood samples were collected for HPLC determination of voriconazole concentrations and routine blood tests. Adverse events were recorded.
Results: No significant correlation was found between incidence of photosensitivity and voriconazole serum levels in 6 of 8 children with ABPA. 80% of patients had trough voriconazole concentrations<1000 ng/mL and were highly variable.
Conclusions: Long-term voriconazole therapy and greater sun exposure in Greece appear to play a major role in the occurrence of photosensitivity. Steady-state plasma drug concentrations were found to be highly variable and below the recommended therapeutic range in most patients, without any apparent negative influence on outcome.

Keywords: Voriconazole; Pharmacokinetics; Photosensitivity; Cystic fibrosis; Allergic bronchopulmonary aspergillosis

1. Introduction

Aspergillus spp and *Scedosporium* apiospermun are the most common filamentous fungi associated with clinical manifestations in patients with cystic fibrosis. Of these, *Aspergillus fumigatus* is by far the most isolated from respiratory specimens and can cause a wide range of diseases including allergic bronchopulmonary aspergillosis (ABPA), aspergilloma in pre-existing pulmonary cavities and invasive pulmonary aspergillosis in immunocompromised patients. The most frequent manifestation of *Aspergillus* spp is ABPA with a prevalence of approximately 1–15% in patients with cystic fibrosis [1].

The triazole antifungal drug, voriconazole (VRZ), has almost completely replaced amphotericin B for the treatment of aspergillosis [2]. For the management of ABPA, oral glucocorticoids remain primary therapy, but VRZ is now considered to be a significant adjunct to therapy, in particular in patients with serious complications from or refractory to corticosteroids. Only 2 prospective clinical trials have documented VRZ pharmocokinetics in children [3,4] and only 3 retrospective reviews have dealt with therapeutic/toxic outcomes of VRZ therapy in children specifically undergoing treatment for ABPA [5–7]. In the study of Hilliard et al. [5], 13 pediatric CF patients with ABPA participated, 3 experienced adverse effects (2 photosensitivity skin reactions and one hair loss), 3 a drop in IgE levels post treatment and steroid dosing was not decreased. In contrast, Glackin et al. [6] reported that only one out of 9 patients developed minor side effects (visual disturbance and photosensitivity), but a mean decrease in IgE levels post treatment as well as a decrease in steroid dosing. Neely et al. [7] reported liver function test abnormalities not

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significantly associated with VRZ concentrations and a pharmacodynamic association between VRZ trough concentrations >1000 ng/ml and survival.

Visual disturbances (photophobia or blurred vision), liver function test abnormalities and skin rashes/photosensitivity are the most common adverse events ascribed to VRZ, and relationships between VRZ mean or random concentrations and these side effects have been found [8,9], with the exception of adverse effects on the skin. Recently, several reports have associated long-term voriconazole therapy with skin reactions such as photosensitivity [10], the development of skin cancer [11,12] and severe phototoxicity [13]. The incidence of photosensitivity / rashes has been reported to be 14% [5],16%[3] and 17.3%[14]. In the Cystic Fibrosis centre of the Children's Hospital, "Aghia Sophia", Athens, the incidence of photosensitivity in 8 ABPA patients treated with VRZ for a period of >6 months was particularly high (75%) and prompted this study of the pharmacokinetics of VRZ in cystic fibrosis patients, primarily to determine if VRZ levels or other factors contributed to the occurrence of this side effect in these patients.

1.1. Aim of the study

In view of the observed high incidence of adverse skin reactions following long-term oral administration of voriconazole in children with cystic fibrosis and ABPA, our aim was to study the pharmacokinetics of VRZ in patients with cystic fibrosis and fungal infections, in particular those with ABPA, and to determine if drug levels achieved could possibly be associated with the occurrence of these or other adverse effects.

2. Patients and methods

2.1. Study design

A prospective, open-labeled, uncontrolled observational study. The study protocol was approved by the Scientific and Ethics Committees of the "Aghia Sophia" Children's Hospital, Athens. Written informed consent was obtained from parents/carers of each child.

2.2. Patients and methods

In all, 10 CF patients, five male and five female, with median age 14.8 years (range: 10–19) entered the study. Diagnosis of CF in all patients was based on typical clinical presentation together with at least two positive sweat chloride tests and two CF causing CFTR mutations. 8 of the patients had evidence of ABPA according to current diagnostic criteria [15] that included 5 or more of the following : a) acute or sub acute clinical deterioration in lung function (FEV1) not attributable to another etiology, b) total serum IgE>500 IU/ml, c) immediate cutaneous reactivity to *Aspergillus*, d) presence of serum IgE antibodies to *A. fumigatus*, e) precipitans/IgG antibodies to *A. fumigatus* , f) new or recent pulmonary infiltrates, mucus plugging or bronchiectasis that had not cleared with antibiotics and standard physiotherapy. Of the remaining 2 patients one had *Aspergillus* Bronchitis and one Scedosporium apiospermum exacerbation.

Patients were originally prescribed VRZ only if they did not meet any of the following exclusion criteria: use of concomitant medications known to be inhibitors, inducers or in any way interact with voriconazole, a history of hypersensitivity to azoles, liver disease defined as serum transaminase values more than twice the upper normal limit or serum bilirubin>50 mmol/L.

Each patient received 100 or 200 mg voriconazole twice a day depending on body weight. One blood sample was collected from each patient for genetic analysis. For voriconazole concentration measurements, venous blood was sampled, at steady state, just before drug administration and at 1, 2 and 4 h thereafter. The samples for VRZ analysis were centrifuged immediately at 3500 rpm for 5 min at approximately 4 °C, and the acquired plasma was stored at −70 °C until analysis.

At each trial visit, patients were asked whether they had experienced or were experiencing any adverse events with non-leading questions.

At the screening visit and fortnightly thereafter, blood was sampled for liver function tests and routine blood chemistry. For most hematological and biochemical tests pathological limits were set as defined by Lippert & Lehmen [16]. For enzymes the lower pathological limit was set at zero and the upper limit at twice the upper limit of normal.

2.3. Patient data collected and recorded

For each patient, the age, sex, weight, height, serum creatinine values, hepatic and renal function tests (aspartate aminotransferase (AST), alanine amino transferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (γGT) and serum creatinine (SrCr)), voriconazole dose and duration of administration, concomitant drug therapy were recorded.

2.4. Quantitative analysis of plasma samples

Voriconazole plasma concentrations were determined using a previously validated HPLC method [17]. The dynamic range of the assay was 200 to 10,000 ng/ml. The lower limit of quantification was 100 ng/ml. At 200 ng/ml the inter-day coefficient of variation (c.v.) was 7.46%, at 600 ng/ml, 4.3%, at 4000 ng/ml 1.85% and 10,000 ng/ml, 1.21%, while the intra-day c.v. at 200 ng/ml was 0.6%, at 600 ng/ml, 0.58%, at 4000 ng/ml, 0.53% and 10,000 ng/ml , 0.51%. A total of seven calibration standards were prepared per analytical run.

2.5. DNA extraction and genotyping

DNA was extracted from peripheral blood leukocytes using the Blood DNA kit (QiAgen, Germany) according to standard protocols. Polymorphisms of *CYP2C19*2* (rs4244285) and *CYP2C19*3* (rs4986893) were analysed using a real-time polymerase chain reaction (PCR) allelic discrimination assay with a Lightcycler LC 480 Instrument (Roche diagnostics, Germany).