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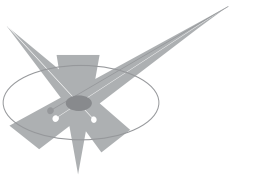

Original Paper

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Efficacy and safety of Voriconazole in immunocompromised patients – single centre experience

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background Data on epidemiology and survival after fungal infections in patients with cancer are primarily based on studies in adults, whereas few data are available on children.

Aim The objective of this study was to determine the safety and tolerability of the oral and i.v. formulations of voriconazole Vfend®, previously not reported in Poland.

Materials/Methods Twenty consecutive children and young adults aged 1 to 25 years, submitted for blood and marrow transplantation (BMT), were recruited during 10 months. When suspected or verified breakthrough systemic fungal infection occurred while kept on primary prophylactic fluconazole regimen, all patients received two loading doses of i.v. or oral voriconazole 6–9 mg/kg every 12 hrs, followed by a maintenance dose of 3 mg/kg every 12 hrs for five doses. If well tolerated, the voriconazole dosage was increased to 4 mg/kg every 12 hrs thereafter.

Results Fungal infection was possible in 15/20, organ involvement with pulmonary process in 13 pts; CNS changes in 2 pts. Fungal aetiology was *proven* in 3 children (pulmonary Aspergillosis in 2 and Candida krusei in 1 patient), and considered as *probable* in 2 patients, having lung (2) and CNS (1) involvement. Four patients died. Clinical and radiological improvement was obtained in 14 patients, while uncontrolled, progressive disease occurred in 1 patient. Transient visual disturbances occurred in one patient. Major caution is warranted due to drug interaction via the cytochrome P-450 system which may lead to unexpected toxicity of the coadministered drugs (e.g. Vinca alkaloids, cyclosporine, rifampicin, erythromycin, etc).

Conclusions Voriconazole is an advantageous new azole well tolerated in 20 patients. Outcome in BMT breakthrough infections was good.

Key words **HSCT • child • young adult • disseminated fungal infection • drug interaction • voriconazole**

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Background

Systemic (invasive) infections termed 'mycoses' are often fatal or life-threatening conditions in immunocompromised patients [1]. Some fungal infections only (for example, histoplasmosis, blastomycosis and coccidioidomycosis) can be serious in otherwise healthy people. Certain types of fungi (such as *Candida*) are normally present on body surfaces or in the intestines. Although normally harmless, these fungi sometimes cause local infections of the skin and nails, vagina, mouth or sinuses. They seldom cause serious harm, except in people with a weakened immune system or with foreign material (such as an intravenous catheter) in their body. These are for example individuals who have received an organ transplant, are being treated for cancer with immunosuppressive drugs, or who have AIDS.

Of the wide variety of spores that land on the skin or are inhaled into the lungs, most do not cause infection. The normally present bacterial flora in the digestive tract and vagina limit the overgrowth of certain fungi. When a person takes antibiotics, those helpful bacteria can be killed – allowing overgrowth of the fungi, resulting in symptoms which are usually mild. As the normal flora grows back, the balance is restored, and the problem usually resolved [2]. Data on epidemiology and survival after fungal infections in patients with cancer are primarily based on studies in adults, whereas few data are available on children where the overall and the infection-specific (fungemia or mycosis with deep tissue infection) mortalities are lower [3,4].

Aim

The objective of this study was to determine the safety and tolerability of the oral and i.v. formulations of voriconazole Vfend® in clinical prophylactic and therapeutic setting in blood and marrow transplanted (BMT) children and young adults. Its use has not yet been reported in Poland.

Materials and Methods

Twenty consecutive immunocompromised children and young adults aged 1 to 25 years with non-malignant and malignant diseases submitted for BMT were included in the study during 10 months' observation, 01.01.2006–30.09.2006 (Tables 1 and 2). All 20 patients enrolled were expected to develop neutropenia lasting for >10 days following the preparative regimen for BMT. EORTC criteria were used for classifying fungal infection as possible, proven or probable [5].

Study design

When a patient developed signs and symptoms of breakthrough systemic (suspected or verified) fungal infection while kept on fluconazole prophylaxis, the drug was stopped and the patient switched over to voriconazole and enrolled in the study. All patients received two loading doses of i.v. or oral voriconazole 6–9 mg/kg every 12 hrs, followed by a maintenance dose of 3 mg/kg every 12 hrs for five doses. If the 3-mg/kg dosage was well tolerated, the dosage was increased in that patient to 4 mg/kg every 12 hrs thereafter. The patients were permitted to continue in the study until day 7–50 if clinically indicated. No other antifungals were used in patients while on voriconazole therapy. The parents or legally authorized representative of underage patients as well as patients capable of understanding the study (aged 18 yrs and above) consented to the study before enrolment.

Results

Fungal infection was judged possible in 15/20 patients. Organ involvement with pulmonary process was present in 13 pts, CNS changes in 2 pts. Fungal aetiology was proven in 3 children having pulmonary process. Aspergillus aetiology was eventually ruled out in 2 pts and Candida krusei in 1 patient. Fungal infection was in addition considered as probable in 2 patients, having lung (2) and CNS (1) involvement.

Table 1. Summary of the patient material and BMT procedure.

Patients	20
Age	1–25 years
Sex: F: M	1: 19
Kind of transplant	18 MUD, 2 Haplo, 1 MSD

MUD–matched unrelated donor; Haplo – haploidentical; MSD – matched sibling donor.

Four patients eventually died of infection complicated with multi-organ failure. Clinical and radiological improvement was obtained in 14 patients, while uncontrolled, progressive disease occurred in 1 patient. One patient still has ongoing VCZ treatment.

Adverse effects

Transient visual disturbances occurred in one patient. As for caring for complicated clinical problems and giving advanced supportive treatment, a lot of difficult problems were present. It was the investigators' decision to determine whether the problem was induced by concomitant infections (bacterial septicaemia, viral reactivation) and/or subsequent polypragmasia using a lot of i.v. medications. Monitoring the patients by routine kidney and liver function test, there were no overt adverse events.

Safety assessments and criteria

Physical examinations and routine clinical laboratory tests were conducted at baseline and twice weekly, including the last day of administration of the study drug. As voriconazole is known to be associated with transient visual changes, patients having ocular problems were assessed for visual symptoms during therapy. If the patients were able and willing to cooperate, the following tests were performed by an ophthalmologist on clinical demand: near visual acuity in each eye, obtained using Snellen letters; and dilated fundoscopic examination with indirect ophthalmoscopy, paying particular attention to the optic nerves, retinal vessels, macula, retina and choroid vessels.

Discussion

This study is to our knowledge the first systematic investigation of the safety and tolerability of the parenteral and oral formulation of voriconazole following breakthrough fungal infection in immunocompromised paediatric patients kept on fluconazole prophylaxis in Poland. The patients enrolled in this study were immunocompromised children who were at risk for development of invasive fungal infections. The dosages administered in this trial were those that have been found to be effective in clinical trials in adults. The dosage range was selected to explore the same dosage that is used in adults. Safety was an overarching concern in designing this paediatric study, particularly given previous data in adults demonstrating nonlinear kinetics and potentially marked increases in plasma drug concentrations between the dosages of 3 and 4mg/kg. Voriconazole was well tolerated but was associated with transient visual disturbances in one patient.

Table 2. BMT performed for non-malignant and malignant diseases.

Conditions – diseases	Number of patients
Severe Aplastic Anaemia	1
Omenn Syndrome	1
Severe Combined Immune Deficiency	1
Non-Hodgkin's Lymphoma	1
Fanconi Anaemia	1
Chronic Granulomatous Disease	1
Acute Lymphoblastic Leukaemia	6
Acute Myeloid Leukaemia	1
Juvenile Myelo-Monocytic Leukaemia	1
Chronic Myeloid/Granulocytic Leukaemia	4
Myelodysplastic Syndrome	2

Voriconazole is a newer antifungal agent belonging to the triazole class, generally better tolerated, having a broad spectrum. Available for oral use with almost complete absorption, it is suitable for use in paediatric patients both as an oral preparation and for intravenous infusion. Having an extensive hepatic metabolism, approximately 80% of a single dose appears in the urine, but less than 5% is excreted in its unchanged form. Widely distributed in body tissues and fluids, it has an advantage penetrating into the brain and CSF. Unwanted effects include mild to moderate visual disturbances, skin rashes and transient abnormalities of liver enzymes [6,7]. The azoles are generally fungistatic (especially in Candida) and resistance to fluconazole is emerging in several fungal pathogens. All the azoles inhibit the P450

enzymes responsible for the synthesis of ergosterol, the main sterol in the fungal cell membrane. A major concern is that azole-drug interaction may lead to unexpected toxicity of the coadministered drug (e.g. Vinca alkaloids, cyclosporine, rifampicin, erythromycin, etc) relating to the ability of the azoles to increase plasma concentrations of other drugs by altering hepatic metabolism via the cytochrome P-450 system.

As azole antifungal agents have become important in the treatment of mucosal candidiasis in AIDS patients, reports of resistance have increased. In fact, azole resistance has now been found in patients not infected with HIV and, in some situations, in patients not previously exposed to antifungal agents [8,9].

In common with all azole antifungal agents, fluconazole may cause hepatotoxicity.

Serious superficial infections are relatively uncommon. During the last 3–4 decades there has been a steady increase in the incidence of serious systemic/invasive fungal infections. One factor has been the widespread use of broad-spectrum antibiotics, which eliminate or decrease the non-pathogenic bacterial populations that normally compete with fungi. Another has been the increase in the number of individuals with reduced immune responses due to AIDS or the action of immunosuppressant drugs or cancer chemotherapy agents; this has led to increased prevalence of opportunistic infections, i.e. infections with fungi which are either innocuous or readily overcome in immunocompetent individuals.

Data on epidemiology and survival after fungal infections in patients with cancer are primarily based on studies in adults, whereas few data are available on children. Risk factors are considered to be prolonged neutropenia, congenital granulocyte function deficits (chronic granulocytopenia) and defective T-cell immune response.

Conclusions

- Voriconazole is an advantageous new azole well tolerated in 20 patients.
- Transient visual disturbance occurred in one case only.
- Numerous drug interactions were documented, warranting drug interaction.
- Outcome in BMT breakthrough infections was good. Risk factors were prolonged neutropenia, GvHD, previous history of risk factors and drug interaction.

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