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Posaconazole with Combination Salvage Treatment in Pediatric Immunocompromised Patients

Bağışıklığı Baskılanmış Çocuk Hastalarda Posakonazol ile Kombinasyon Kurtarma Tedavisi

Murat Sütçü[1], Hacer Aktürk[1], Serap Karaman[2], Manolya Kara[1], Zeynep Karakaş[2], Nuran Salman[1], Sema Anak[2], Ayper Somer[1]

[1] *Department of Pediatric Infectious Diseases, Istanbul University School of Istanbul Medicine, Istanbul, Turkey*
[2] *Department of Pediatric Hematology and Oncology, Istanbul University School of Istanbul Medicine, Istanbul, Turkey*

Abstract

Objective: Posaconazole is a recently developed wide-spectrum antifungal medication for which insufficient data is available regarding its potential pediatric use as a salvage therapy for systemic fungal infections in Turkey. The present study makes a retrospective review of the use of posaconazole as a salvage therapy.

Material and Methods: The study included patients aged between 13 and 18 years who had undergone posaconazole salvage therapy for the treatment of invasive fungal infections (IFI) between 2010 and 2015. Demographical and clinical data was collected retrospectively from patient files. All patients were given the posaconazole active substance with the trade name Noxafil® in a 40 mg/mL oral suspension, divided into four doses of 800 mg/day.

Results: Posaconazole salvage therapy was used in a total of six patients with a median age of 14.5 years (range 13-16 years), of which two had a primary immunodeficiency, and four had hematological malignancies. Antifungal therapy was initiated for proven, probable and possible IFI in one, four and one patients, respectively, of which five patients had lung involvement and one had central nervous system (CNS) involvement. Posaconazole was given to all patients in combination with another antifungal medications in a weight-based median dose of 5 mg/kg. Blood concentrations of the drug were not measured. Of the total, two patients responded completely to therapy and were switched to posaconazole prophylaxis treatment; posaconazole was switched with another antifungal agent in one patient who experienced progressive infection, and three patients whose primary disease was not under control died while receiving therapy for active fungal infections.

Özet

Giriş: Posakonazol yakın zamanda geliştirilmiş geniş spektrumlu bir antifungal ilaçtır. Ülkemizde çocuk yaş grubunda sistemik mantar enfeksiyonlarının kurtarma tedavisinde kullanımı hakkında yeterli veri yoktur. Bu çalışmada, kurtarma tedavisi olarak posakonazol kullanımının geriye dönük olarak değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Çalışmaya 2010-2015 yılları arasında invaziv mantar enfeksiyonu (İME) kurtarma tedavilerinde posakonazol kullanılan 13-18 yaş arası olgular dahil edildi. Demografik ve klinik bilgiler hasta dosyalarından geriye dönük olarak tarandı. Tüm olgularda posakonazol etken maddeli Noxafil® 40 mg/mL oral süspansiyon, 800 mg/gün dört bölünmüş dozda kullanıldı.

Bulgular: Ortanca yaşı 14.5 yıl (aralık 13-16 yaş) olan toplam altı olguda posakonazol kurtarma tedavisi kullanıldı. İki olguda primer immünyetmezlik, dört olguda ise hematolojik malignite saptandı. Bir olguya kanıtlanmış, dört olguya mümkün ve bir olguya da olası İME nedeniyle antifungal tedavi başlanmıştı. Beş olguda akciğer tutulumu, bir olguda merkezi sinir sistemi (MSS) tutulumu vardı. Posakonazol bütün olgularda başka bir antifungal ilaç ile beraber verildi. Kilo bazlı ortanca doz 5 mg/kg/doz idi. İlaç kan düzeyi ölçülemedi. İki olguda tam yanıt alınarak posakonazol ile profilaksiye geçildi. Bir olguda enfeksiyonun ilerlemesi nedeniyle posakonazol başka bir anifungal ile değiştirildi. Primer hastalıkları kontrol altına alınamayan üç olgu aktif mantar enfeksiyonu ve tedavisi devam ederken kaybedildi.

Correspondence Address / Yazışma Adresi

Murat Sütçü
İstanbul Üniversitesi İstanbul Tıp Fakültesi,
Çocuk Enfeksiyon Hastalıkları Bilim Dalı,
İstanbul-Türkiye

E-mail: sutcu13@yahoo.com

Conclusion: A posaconazole oral suspension was used for the treatment of IFI in a complicated patient group, and a treatment success rate of 33 percent was recorded. It is possible that the target blood concentrations of the drug were not achieved, as the dosage used per kilogram body weight was relatively low and blood concentrations were not measured. As a result of problems associated with absorption and appropriate dosing of posaconazole in adolescents, it would appear to be a sensible approach to measure blood concentrations of posaconazole in order to ensure safe and effective therapy.

Keywords: Children, immunocompromised, posaconazole, salvage therapy

Sonuç: Posakonazol oral süspansiyon, komplike bir hasta grubunda İME kurtarma tedavisinde kullanılmış ve %33 oranında tedavi başarısı sağlanmıştır. Kilograma göre kullanılan dozlar görece düşük olduğundan ve ilaç kan düzeyi ölçülemediğinden hedef kan düzeylerine ulaşılamamış olabilir. Emilim ve özellikle ergen yaş grubundaki dozaj sorunları nedeniyle posakonazolün güvenle ve etkin olarak kullanılabilmesi için beraberinde ilaç düzeyi ölçümünün yapılabilmesi gerekmektedir.

Anahtar Kelimeler: Bağışıklığı baskılanmış, çocuk, posakonazol, kurtarma tedavisi

Introduction

Immunosuppression resulting from primary or secondary causes poses a high risk for the development of invasive fungal infections. Among these, the most commonly known and encountered form is that seen in patients undergoing chemotherapy due to hematological malignancies or those who have undergone a stem-cell transplant (SCT). Incidences of invasive fungal infections (IFI) have been reported in approximately 10 percent of patients with childhood acute myeloid leukemia (AML) or recurrent acute myeloid leukemia, and in patients receiving allogeneic SCT (1). This rate may vary depending on the chemotherapy protocol used and other risk factors in children undergoing treatment for acute lymphoblastic leukemia (ALL). Incidences of IFI are lower among pediatric patients who receive autologous SCT for non-Hodgkin's lymphoma (< %5) (1). On the other hand, another important risk group for IFI is patients with primary immunodeficiencies, who are being encountered more often as awareness of the condition increases, and due to improvements in diagnostic methods. In particular, chronic granulomatous disease, congenital neutropenias and type 1 leukocyte adhesion defects are among the primary immunodeficiencies that carry a significant risk of IFI (2).

Systemic fungal infections caused by yeast and/or fungus species may be encountered during the treatment and follow-up periods of all the above-mentioned conditions, although the most common species involved in these infections are *Candida* and *Aspergillus* (3,4). Diagnosing IFI is particularly challenging in pediatric practice, as there are usually no specific complaints or signs, and blood cultures rarely come back positive, particularly in the presence of aspergillosis infections, while other microbiological diagnostic methods fail to achieve 100 percent sensitivity (5). Blood cultures were found to be positive in less than half of the cases in which a tissue invasion of *Candida* infection occurred, based on an autopsy (6). Any delay in the initiation of antifungal treatments resulting from such diagnostic challenges may have unfavorable consequences. Antifungal prophylaxis is therefore recommended in the presence of diseases associated with IFI incidences of ≥10 percent, including AML, high-risk ALL, recurrent leukemia and allogeneic SCTs (7). On the other hand, there are no such clear recommendations for the use of antifungal prophylaxis in the presence of primary immunodeficiency syndromes, and every center follows their own protocols. Still, antifungal prophylaxis is strongly recommended, particularly in patients followed-up with a diagnosis of chronic granulomatous disease (2).

Posaconazole is a recently developed second-generation azole group of antifungal medications. Like all other azole groups of medication, it shows activity by inhibiting the functions of the enzyme (lanosterol 14 alpha-demethylase) required for ergosterol synthesis in the fungal cell membrane. It has shown to be effective against all species of fungi with ergosterol in their cytoplasmic membrane (yeasts, fungus, zygomycetes and dermatofits), and is becoming more common in pediatrics (8,9). Current guidelines stated that it can be used for primary prophylaxis in pediatric (age ≥ 13 years) cancer patients or in patients receiving SCT, and also for the treatment of proven or possible fungal infections, with varying degrees of evidence (1). In terms of primary immunodeficiencies, previous reports have described its use in chronic granulomatous disease (10,11). Although it is approved only for pediatric patients aged 13 years and above, it is still used off-label for salvage therapy in the treatment of younger patients (12). It is currently available as an oral suspension, as an extended-release tablet and, most recently, in an intravenous form. The monitoring of serum drug concentrations is recommended during treatment due to problems with drug absorption, and the generally recommended target concentrations are > 700 µg/L (1). The present study makes a retrospective review of the safety and efficacy of posaconazole when used as a salvage therapy for invasive fungal infections in pediatric patients with cancer or primary immunodeficiencies at a single center.

Materials and Methods

A retrospective review was made of the medical records of patients (aged 13-18 years) who had been given oral posaconazole 4 x 200 mg as a part of a salvage therapy for IFI between 2010 and 2015 in Department of Pediatric Infectious Diseases. Clinical and laboratory data was retrieved from patient files and hospital records, and demographical information on the patients, primary diagnoses, indications for antifungal treatment, radiological and microbiological findings, concomitant therapies, posaconazole dosage, side effects (liver function test increase, rash, nausea, vomiting, QTC prolongation on ECG) and data on treatment outcomes were recorded. All patients were given a posaconazole active ingredient via an oral suspension formulation of Noxafil® 40 mg/mL. Serum levels of posaconazole were not monitored in our clinics (due to technical limitations).

Definitions

Proven IFI (13): The reproduction of yeast or mold in the blood or sterile body fluids (aside from samples obtained from urine, bronchoalveolar lavage and cranial sinuses); or demonstrations of hypha or yeast forms via histopathological methods or direct microscopy.

Probable IFI (13): Presence of a disease/clinical condition that may predispose the host to fungal infections [neutropenia, allogeneic SCT, long-term corticosteroid use, receiving T-cell suppression therapy, primary immunodeficiency (such as chronic granulomatous disease, severe combined immunodeficiency)], presence of clinical findings consistent with fungal infection and supportive positive mycological findings (demonstration of mold in the sputum, bronchoalveolar lavage or sinus aspiration samples by cytology, direct microscopy or culture, or detection of galactomannan antibody in serum, bronchoalveolar lavage or cerebrospinal fluid, or detection of β-D-glucan in serum).

Possible IFI (13): Clinical signs consistent with fungal infections and predisposing host factors, in the absence of supportive positive mycological findings.

Complete clinical response or complete recovery: Complete resolution of clinical and radiological findings attributed to fungal infection and the ability to stop antifungal therapy.

Partial clinical response or partial recovery: Recovery of clinical signs attributed to fungal infection and a minimum 50 percent decrease in the size of radiological findings.

Progressive disease: Progression of clinical and/or radiological findings attributed to fungal infection requiring the treating physician to change the antifungal treatment dose and/or the agent used in treatment.

Results

Posaconazole was used for IFI salvage therapy in six patients aged between 13 and 16 years, with a median age of 14.5 years (Table 1). The primary underlying disease was primary immunodeficiency in two patients and hematologic malignancy in four, while five patients had lung involvement and one patient had central nervous system (CNS) involvement. Antifungal therapy was initiated for proven, probable and possible IMI in one, four and one patients, respectively. Lung tissue cultures were positive for the growth of *Aspergillus fumigatus* in one patient, and four patients were positive for galactomannan antibodies. The only patient (patient 4) without any positive supportive mycological findings was a 12-year-old boy who had been diagnosed with chronic granulomatous disease at age of 3.5 years. A thoracic computerized tomography, obtained following an increase in respiratory complaints from the patient, showed a consolidation and destruction of the neighboring bone-soft tissues along the tracheal vertebrae and periosteal elevation. An invasive diagnostic intervention could not be made due to absence of family consent, and the patient was thus considered as a case of possible IFI. The patient with central nervous system involvement (patient 6) experienced a seizure while undergoing phase 2 chemotherapy in the fifth month for standard risk ALL, and a later CNS imaging revealed nodular lesions of 1 cm in diameter consistent with fungal infection in the right frontal region. The patient was considered to have probable IFI, as he was also positive for galactomannan antibodies, and so treatment was initiated.

Of the total, five patients were already under primary fungal prophylaxis with fluconazole before the development of IFI, and all patients with hematological malignancies were neutropenic at the time of developing IFI. Before the initiation of posaconazole, all patients were given concomitant or consecutive therapies involving at least two different antifungal medications (median time: 13 months, range: 4-60 months). One patient with chronic granulomatous disease and invasive pulmonary aspergillosis (patient 5) underwent a surgical intervention before the initiation of posaconazole therapy. In all patients, posaconazole was added to and given in combination with at least one previously initiated antifungal medication (Table 1).

As a result of insufficient treatment response or disease progression, primary antifungal treatment regimen was changed in all cases except one. In the patient with CNS involvement (patient 6), the primary treatment was changed due to the onset of side effects. The patient had been started on voriconazole-caspofungin treatment, and lesion regression was noted, however voriconazole was stopped in the fourth

Table 1. Clinical characteristics of patients receiving posaconazole salvage therapy

	Age/ Gender	Primary disease	Mycological findings	Radiological findings	Other antifungal medication(s) combined with posaconazole	Outcome
Patient 1	14 / M	Recurrent ALL after SCT	Galactomannan-positive	Cavitary lesion in the left lung lower lobe and extensive consolidation in both lungs	Liposomal Amphotericin B + Caspofungin	Died
Patient 2	14 / M	Recurrent ALL after SCT	Galactomannan-positive	Extensive nodular infiltration in both lungs	Liposomal Amphotericin B + Caspofungin	Died
Patient 3	16 / F	Recurrent AML	Galactomannan-positive	Nodular infiltration in right lung middle lobe, halo sign, consolidation	Caspofungin	Died
Patient 4	15 / M	CGD	-	Bone-soft tissue involvement in the left lung lower lobe along the vertebrae and consolidated region with periosteal elevation	Liposomal Amphotericin B	Complete response, secondary prophylaxis with posaconazole for four months
Patient 5	16 / F	CGD	Aspergillus fumigatus growth in lung tissue culture	Fungus ball in left lung lower lobe, consolidated region with bone-soft tissue involvement neighboring the lesion in (left lung lower lobe) (?), consolidation in the left lung upper lobe	Liposomal Amphotericin B	While partial response was achieved with posaconazole, the treatment was switched to voriconazole due to growth of lung lesion and development of new lesion on 23rd month of treatment.
Patient 6	13 / F	ALL (standard risk)	Galactomannan-positive	Cranial MR showed a 1 cm diameter nodular lesion located in the right frontal region	Caspofungin	Partial response was achieved when posaconazole was initiated, posaconazole provided complete response and the patient is on complete response for eight months and receiving secondary prophylaxis with posaconazole for four months.

AC: Lung, ALL: Acute lymphoid leukemia, AML: Acute myeloid leukemia, M: Male, F: Female, SCT: Stem-cell transplant, CGD: Chronic granulomatous disease.

month of treatment as the patient developed auditory-visual hallucinations and posaconazole was initiated while continuing caspofungin. This new drug combination maintained the regression in the lesions, and a decision was made to continue treatment with posaconazole alone. As the lesion completely disappeared during follow-up, the patient was switched to secondary prohylaxis with posaconazole.

Posaconazole was used in doses of 4 x 200 mg in all patients. The mean daily dosage was 5 mg/kg (Range: 4 mg/kg/dose- 8 mg/kg/dose), and median exposure to posaconazole was 17 months (range: 2-60 months).

Of the total, two patients (recurrent ALL after stem-cell transplant) who were receiving antifungal therapy, including caspofungin, liposomal amphotericin-B and posaconazole, and one patient (recurrent AML) who was being treated with caspofungin and posaconazole therapy died due to fungal infections and an uncontrolled primary disease. Sufficient clinical and radiological response was achieved in two patients, and the other concomitantly used antifungal medications of these patients were stopped, with secondary prophylaxis treatment given with posaconazole alone. These patients are still receiving secondary prophylaxis with posaconazole. Posaconazole was stopped and voriconazole treatment was initiated in another patient who developed a progressive infection, being the 16-year-old patient with chronic granulomatosis and invasive pulmonary aspergillosis who had undergone a surgical operation. In the second year of posaconazole treatment, the medication of this patient was changed after a lung tomography revealed the development of a new lesion. The most commonly recorded side effect was transient nausea (4 patients), which was identified in five patients from liver enzyme levels at different time points during the course of posaconazole treatment. That said, no clear association with posaconazole treatment could be established, as these patients were receiving several concomitant antimicrobial and chemotherapeutic medications. No discontinuation of treatment was deemed necessary for that reason in any case.

Discussion

This report reports on the experiences of a university hospital with posaconazole use in pediatric patients requiring IFI therapy. While several international reports have been published on this topic, to the best of our knowledge, this is the first such data to be reported from Turkey. According to our data, posaconazole was used as IFI salvage therapy in six patients with an underlying severe immunodeficiency, and complete response was achieved in two patients, who were then switched to prophylaxis. Side effects emerged requiring the discontinuation of medical therapy, and three patients died despite receiving combined antifungal therapy, including posaconazole, as their primary disease could not be controlled and fungal infections did not respond to treatment. There have to date been several studies investigating the efficacy, safety and dose-plasma concentration relationship of the off-label use of posaconazole in pediatric IFI patients, including those younger than the age of 13 years. In a multi-center phase three trial, Krishna et al. compared data obtained from 12 children aged between 8 and 17 years with data collected from adult patients, and reported similar success rates and side effect profiles (14). Aside from one, all previous studies involved the use of 800 mg/day posaconazole in divided doses, and the median dose used in pediatric patients was 16.5 mg/kg/day. Successful outcomes were achieved with posaconazole treatment in nine (75%) of 12 cases in another study, while a further study evaluated the use of posaconazole in the treatment of suspected or proven fungal infections in 33 pediatric and adolescent cancer patients (median age: 11.5 years, range: 5 months–23 years) and reported progressive infections with this treatment in four patients (14). The median dose of posaconazole used in that study was reported as 17 mg/kg. It was stated that weight-based dose adjustments that are higher than the maximum recommended dose for adults could be made particularly in adolescents, and in this way, higher plasma concentrations can be reached (15). In another study evaluating the use of posaconazole as a salvage therapy for proven or probable IFI in 15 pediatric cancer patients aged between 3.6 and 17.5 years, complete and partial response was achieved in six and three patients, respectively, while two patients had stable disease and treatment failure was noted in four patients. In the present study, posaconazole was used alone for the treatment of six patients. While drug-plasma concentrations were not measured, the median used dose was reported to be 21 mg/kg/day (range: 4.8-33.3 mg/kg/day) (12). In the present study, posaconazole was also given in divided doses of 800 mg/day, although the weight-based median dose was lower than those reported in previous studies. No conclusions could be made relating to the potential reflections of the dose used on plasma drug concentrations, as they were not measured in this study. Various studies have demonstrated that a positive relationship exists between plasma concentration and clinical response (16-18). No predictable level of bioavailability was observed after the use of a posaconazole oral suspension, while a high degree of inter-patient variability was noted in bioavailability (19-21). There are several factors that may affect absorption of posaconazole, including foods consumed, fasting/satiety, stomach acidity, gastric motility, integrity of gastrointestinal mucosa, diarrhea and underlying diseases (8, 21-23). It is therefore recommended that plasma levels of the drug are monitored continuously during therapy (1). In the present study, treatment successes with posaconazole were lower overall than the rates reported in previous studies (33%). The weight-based doses used in this study were lower than those used in previous studies. As we were unable to measure plasma drug levels, the blood concentrations of posaconazole may not have reached recommended levels in our patients, and we may therefore have seen a relatively lower success rate.

Chronic granulomatous disease is one of the primary immunodeficiencies associated with the highest frequency of IFI, and was present in two of the patients in the present study (24). In the presence of hematological malignancies, the recovery of bone marrow and the improvement of neutropenia are crucial in recovery from fungal infections. That said, the permanent immune problems associated with primary immunodeficiency syndromes mean that the treatment of invasive fungal infections is generally much more challenging. The most important cause of mortality in patients with chronic granulomatous disease is invasive aspergillosis infection (25-27). There is a limited amount of data in literature on the use of posaconazole salvage therapy in primary immunodeficiencies. In a study by Segal et al. eight patients with chronic granulomatous disease and invasive pulmonary mold infection, in whom the primary treatment was unsuccessful, were given posaconazole salvage therapy, and complete response was achieved in all but one case (28). Complete response was achieved in both of the patients with chronic granulomatous disease in the present study, and treatment was terminated in these cases. Generally, studies have reported that posaconazole is well-tolerated and is rarely associated with serious side effects (12,15,28-31). On the other hand, high plasma concentrations have been associated with an increased frequency of side effects (32,33). Lehrnbecher et al. reported side effects in 73 percent of their patients, most of which were mild in intensity (12). The most commonly reported side effects were fever, nausea, vomiting, abdominal pain, diarrhea, rash and liver enzyme elevations (12). In another study, liver enzyme elevations were reported as the most frequent side effect, which

was resolved without requiring treatment discontinuation (15). In another study, Krishna et al. most frequently reported nausea, vomiting, abdominal pain and headache, and nausea was also common among the patients in the present study, while a case in which liver enzyme elevation was noted, there was no clear associating with posaconazole therapy (14).

In conclusion, the present study has investigated the use of posaconazole as an IFI salvage therapy in pediatric patients. The treatment was successful in almost one-third of the patients, and the drug was well-tolerated, overall. The inability to measure drug concentrations was one of the most significant obstacles to the safe use of posaconazole oral suspensions. The dose of medication required to reach effective plasma levels may vary from patient to patient, and this is particularly important in the pediatric patient group. The recently introduced extended-release form of posaconazole in our country and its intravenous forms, which are currently unavailable, may ensure a more effective treatment by providing better absorption and bioavailability. That said, the monitoring of plasma drug levels is necessary when using these formulations, and so technical facilities to allow the monitoring of such drugs should be made available, particularly in centers where complicated cases are commonly followed.

Ethics Committe Approval: This study was performed with the permission of Local Clinical Research Ethical Committee.

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