Posaconazole Use in Infants and Children
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Posaconazole provides a broad spectrum of antifungal activity, has a relatively mild adverse effect profile, and is available in both tablet and liquid dosage forms making it a useful option as both prophylaxis and treatment. The oral suspension was approved by the Food and Drug Administration in 2006 for prophylaxis of invasive Aspergillus and Candida infections in severely immunocompromised patients, such as those chemotherapy-induced neutropenia or hematopoietic stem cell transplant (HSCT) recipients with graft-versus-host disease (GVHD). It is also approved for the treatment of oropharyngeal candidiasis (OPC), including OPC refractory to treatment with fluconazole or itraconazole. In 2013, a delayed-release posaconazole tablet was introduced, and approval for both the tablet and oral suspension was extended to patients 13 to 17 years of age. An injection for IV administration was approved in 2014, but only for use in adults.

Mechanism of Action
Azole antifungals block the synthesis of ergosterol, an integral component of fungal cell membranes, through inhibition of the cytochrome P450-dependent lanosterol 14α-demethylase. Blocking this enzyme results in accumulation of the methylated sterol precursors and a depletion of ergosterol that weakens the structure and function of the fungal cell membrane. Posaconazole has been shown to be active against Aspergillus and Candida species, as well as some Cryptococcus, Fusarium, and Zygomycetes species.

Pharmacokinetics
Absorption of oral posaconazole is dependent on the formulation and the presence of food. In studies of healthy adults given a 300 mg delayed-release tablet, the mean maximum plasma concentration (C_max) was 0.94 mcg/mL (34 %CV) in the fasting group, with an area under the concentration-time curve (AUC) of 26,200 ng•hr/mL (28 %CV). In contrast, the group given a high-fat meal had greater absorption, with a C_max of 1.06 mcg/mL (25 %CV) and an AUC of 38,400 ng•hr/mL (18 %CV). In adults given a 200 mg dose of the oral suspension, the C_max and AUC were lower in both the fasting and fed states when compared to the delayed-release tablets, with values of 0.132 mcg/mL (50 %CV) and 4,179 ng•hr/mL (31 %CV) after fasting and 0.38 mcg/mL (43 %CV) and 10,753 ng•hr/mL (35 %CV) after a high-fat meal, respectively.

Similar differences were observed in a study comparing the two formulations in 63 children. The median trough concentrations in those given the delayed-release tablet were a median 3.2-fold higher than those given the oral suspension. Understanding the differences in plasma concentrations between the tablets and suspension, as well as the impact of administration with food, is an important part of avoiding errors in prescribing, dose preparation, and administration. All healthcare providers, as well as patients and families, should be aware that these products are not interchangeable.

Posaconazole is metabolized by UDP glucuronosyltransferase and is a substrate for p-glycoprotein efflux. It is excreted primarily as glucuronide metabolites, with an elimination half-life in adults of approximately 30 hours. While posaconazole does not undergo metabolism by cytochrome P450 enzymes, like other azole antifungals, it is a strong inhibitor of CYP3A4.

The pharmacokinetic profile of posaconazole in children has been assessed in a study of 14 patients (mean age 6.7 ± 2.8 years). The children were receiving a 100 mg dose of the oral suspension (approximately 120 mg/m² or 4.6 mg/kg) three times daily for antifungal prophylaxis. The mean C_max was 0.96 ± 0.63 mcg/mL, with an AUC and clearance also similar to adult values. The mean trough concentration of 0.86 ± 0.58 mcg/mL was above the goal for prophylaxis of 0.7 mcg/mL. While the optimal plasma concentrations of posaconazole for antifungal prophylaxis and treatment in children
have not yet been established, most pediatric studies have used the target trough concentrations established for adults: 0.7 mcg/mL for prophylaxis and 1.25 mcg/mL for treatment of invasive infections.\(^2\)

**Clinical Experience in Children**

In 2010, Lehrnbecher and colleagues published an initial assessment of the utility of posaconazole in children. In this multicenter retrospective study, 15 children were given posaconazole as treatment of invasive fungal infections.\(^3\) The patients (median 10 years, range 3-17 years) were treated with a median dose of 21 mg/kg/day (range 4.8-33.3 mg/kg/day) for a median length of therapy of 32 days (range 2-62 days). A complete or partial response was observed in 4 of 7 patients with zygomycosis, 3 of 4 patients with invasive mold infections, 1 of 2 patients with invasive aspergillosis, and 1 of 2 with disseminated candidiasis. Eleven of the patients had adverse effects (fever, nausea, vomiting, diarrhea, headache, and rash), but all completed therapy.

Döring and colleagues at the University Children’s Hospital Tuebingen have published a series of studies evaluating the effectiveness of posaconazole prophylaxis is children receiving chemotherapy or following allogeneic HSCT. Their first paper, published in 2012, was a single-center retrospective study of 60 children (median age 6 years) comparing an oral suspension dose of 4 mg/kg given three times daily (12 mg/kg/day) to a dose of 5 mg/kg given twice daily (10 mg/kg/day).\(^4\) There were no breakthrough invasive fungal infections in either group. Patients in the 12 mg/kg/day group had a median trough of 0.38 mcg/mL (range 0.061-1.24 mcg/mL), compared to only 0.13 mcg/mL (range 0.056-0.79 mcg/mL) in the 10 mg/kg/day group (p < 0.001). Adverse effects were generally mild, with the most common being nausea in 5% of patients. Twenty-two patients (37%) had elevations in liver function testing; however, levels normalized in 19 patients while still on therapy.

The following year, Bernado and colleagues at St Jude Children’s Research Hospital examined the records of 33 children (median age 11.5 years) treated with posaconazole oral suspension for invasive fungal infections.\(^5\) Children < 34 kg received 18-24 mg/kg/day given in four divided doses, while those 13 years of age or weighing ≥ 34 kg received 800 mg in four divided doses. Twenty-one patients (64%) had posaconazole concentrations ≥ 0.7 mcg/mL at one week. The median dose in these patients was 20 mg/kg/day. Patients with levels below goal received a significantly lower dose of 12.9 mg/kg/day (p = 0.02). The authors noted that 7 of the 12 patients with subtherapeutic levels were adolescents.

In subsequent studies, Döring and colleagues compared posaconazole 4 mg/kg three times daily (12 mg/kg/day) to other azole antifungals to determine efficacy and evaluate their relative safety profiles. They found comparable efficacy among posaconazole, itraconazole, and voriconazole in 150 children following allogeneic HSCT.\(^8\) Only five possible invasive fungal infections were identified, two in the itraconazole group and three in the voriconazole group. The percentage of patients with adverse effects were similar: 14% in the voriconazole group, 12% in the itraconazole group, and 8% in the posaconazole group. Elevations in AST and ALT were similar among the groups. Benefit was also shown in their later study comparing posaconazole, itraconazole, and fluconazole in 93 children receiving antifungal prophylaxis while neutropenic from chemotherapy.\(^3\) One case of proven aspergillosis was identified in each group, with possible infection in one patient receiving fluconazole and two receiving itraconazole. Adverse effects were uncommon, occurring in only five itraconazole patients, four fluconazole patients, and three posaconazole patients.

These investigators also conducted the first study comparing delayed-release posaconazole tablets and oral suspension in children receiving prophylaxis after HSCT.\(^9\) Sixty-three children (0.6-17 years) received either the suspension 4 mg/kg three times daily 10-20 minutes after a meal or tablets at a dose of 5-7 mg/kg twice daily on day 1, followed by 5-7 mg/kg once daily. No invasive fungal infections were observed over a median follow-up of 108 days post-transplantation. As anticipated, posaconazole tablets resulted in higher trough concentrations at all assessment points. The time until 50% or more of the trough levels were ≥ 0.5 mcg/mL was 3 days in the children taking tablets versus 14 days in those taking the suspension. Rates of adverse effects were 9.7% and 6.3% in the suspension and tablet groups, respectively. Elevations of AST and ALT values 1.5-2.5 times the upper limit of normal were observed in 67% and 72%. Hypokalemia occurred in 2% and 28%. The authors concluded that the both formulations were safe and effective for children after HSCT.

Four studies published in 2017 provided additional assessments of the relationship between posaconazole concentrations and efficacy in children.\(^10-12\) Döring’s group evaluated 172 plasma trough concentrations obtained from 33 children receiving posaconazole prophylaxis while neutropenic.\(^10\) All were treated with a dose of 4 mg/kg three times daily (12 mg/kg/day). The median level was 0.44 mcg/mL (range of 0.11-2.01 mcg/mL), significantly lower than the target of 0.7 mcg/mL; however, only one patient experienced an invasive fungal infection. The authors found no relationships between plasma concentrations and age or gender.

The largest study in children to date was published earlier this year by Vicenzi and colleagues in the *European Journal of*...
A total of 97 pediatric oncology patients were assessed during the first 6 weeks of therapy. Eighty-four children received prophylaxis (initial dose 12 mg/kg/day), while the remaining 13 received treatment with a dose of 15 mg/kg/day. The median trough in the prophylaxis group was 0.8 mcg/mL. Sixty-three percent had troughs ≥ 0.7 mcg/mL within a week after starting treatment. Only four patients (5%) experienced a breakthrough infection. The treatment group had a median trough concentration of 1.4 mcg/mL, with 77% achieving the target of 1 mcg/mL in the first week. While the majority of children achieved goal values, the authors noted the drug was often effective even in children with trough values below the target level.

Avoiding Pediatric Medication Errors
The importance of understanding the difference between posaconazole formulations was highlighted in a 2015 case report. A 13-year-old patient was receiving chemotherapy after surgical resection of a maxillary sinus tumor and developed a Coniothyrium fuckelii sinus infection. She was started on broad-spectrum antifungal therapy, then transitioned to posaconazole oral suspension 400 mg twice daily. She was inadvertently prescribed the delayed-release tablets at the same 400 mg twice daily dose for outpatient treatment. Within 2 weeks, she developed fatigue, decreased appetite, and musculoskeletal pain requiring hospitalization. On admission, she had hypokalemia (2.7 mEq/L) and anemia (8.3 g/dL). The error was identified and posaconazole was discontinued, with resolution of symptoms over the next week. The authors highlighted the risk for these errors and described changes made in their orders as a result.

Contraindications and Precautions
Posaconazole is contraindicated in patients with a known hypersensitivity to any azole antifungal, as well as in patients taking medications known to produce significant drug-drug interactions. Posaconazole has been associated with QTc prolongation and the development of torsade de points in post-marketing surveillance and should not be used with any medications known to prolong the QTc. Posaconazole has been reported in clinical trials and cases series in both adults and children to produce elevations in liver function tests, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, or other symptoms of hepatitis in 5-10% of patients. While most cases have been mild and resolved during treatment or after discontinuation, several cases of significant hepatotoxicity have been reported.

Adverse Effects
In clinical trials of adults, the most commonly reported adverse effects with posaconazole suspension or delayed-release tablets have been diarrhea, nausea, hypokalemia, rash, fever, or headache (each in 20-30% of patients), epistaxis, thrombocytopenia, hypomagnesemia, vomiting, decreased appetite, abdominal pain, cough, altered blood pressure, anemia, dyspnea, edema, constipation, and petechiae (each in 10-15%). Pediatric safety data from the studies published to date are similar to the adult clinical trial data.

Drug Interactions
Posaconazole may significantly impair the metabolism of drugs metabolized through CYP3A4, resulting in increased serum concentrations. Giving posaconazole to a patient taking sirolimus may increase sirolimus concentrations as much as 9-fold, and as a result the use of this combination is contraindicated. Use with calcineurin inhibitors (cyclosporine or tacrolimus) may result in significant drug accumulation leading to nephrotoxicity or leukoencephalopathy. If posaconazole is necessary in patients on these medications, it is recommended that the calcineurin inhibitor dose be reduced and serum monitoring increased.

Concomitant use of posaconazole with other drugs metabolized via CYP3A4, including calcium channel blockers (diltiazem, felodipine, nicardipine, nifedipine, or verapamil), digoxin, atazanavir, and ritonavir, may result in elevated plasma concentrations. Concomitant use with HMG-CoA reductase inhibitors metabolized through CYP3A4 may increase their plasma concentrations up to 10-fold, leading to rhabdomyolysis. Administration of posaconazole with midazolam may increase its serum concentrations up to 5-fold; similar results may occur with other benzodiazepines as well. Use of any of azole antifungal with ergot alkaloids may result in ergotism. Administration of azoles with vincristine has been reported to cause neurotoxicity, including seizures, peripheral neuropathy, and syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Administration of drugs that lower gastric acidity or increase gastric motility, such as such as histamine (H2) receptor antagonists, proton pump inhibitors, and metoclopramide, may reduce posaconazole absorption. It is recommended that these combinations be avoided to prevent breakthrough infections. Metabolism of posaconazole may be delayed if given with efavirenz, fosamprenavir, ribabutin, or phenytoin and these combinations should be avoided.

Availability and Dosing Recommendations
Posaconazole is available as a 40 mg/mL oral suspension, 100 mg delayed-release tablets, and a 300 mg/16.7 mL (18 mg/mL) injection. Oral forms of posaconazole should be taken with a full meal or a liquid nutritional supplement to increase oral absorption and optimize plasma concentrations. In patients not able to take their dose with food or a supplement, the dose may be given with an acidic carbonated beverage, such as ginger ale. The tablets should not be split,
crushed, or chewed. The oral suspension should be shaken thoroughly prior to use, and the dose should be measured using the spoon provided.

The recommended dose for prophylaxis of invasive Aspergillus or Candida infections in adolescents and adults using the delayed release tablet formulation is a loading dose of 300 mg (three 100 mg tablets) given twice daily on the first day, followed by a maintenance dose of 300 mg once daily starting the second day. In adolescents and adults taking the oral suspension, the dose is 200 mg (5 mL) three times daily. The duration of therapy should be based on signs of recovery from neutropenia or immunosuppression. Adolescents and adults taking posaconazole oral suspension for the treatment of OPC should receive a loading dose of 100 mg (2.5 mL) twice on the first day of treatment, followed by a maintenance dose of 100 mg once daily for 13 days. In patients with OPC refractory to other azole antifungals, duration of treatment should be based on clinical response and the patient’s underlying disease.

In the majority of papers published to date, the dose of posaconazole oral suspension for prophylaxis in children has been 12 mg/kg/day, divided and given every 8 hours. For pediatric patients requiring treatment for invasive fungal infections, doses of the oral suspension have ranged from 18-24 mg/kg/day, divided and given every 6 or 8 hours. In the 2017 paper by Döring and colleagues, posaconazole delayed-release tablets were used with doses of approximately 5-7 mg/kg twice daily on the initial day as a loading dose, followed by 5-7 mg/kg once daily. This was accomplished by giving 100 mg twice daily on day 1, then daily in patients weighing 15-21 kg, a dose of 150 mg twice daily on day 1, then daily for patients 22-30 kg, a dose of 200 mg twice daily on day 1, then daily for patients 31-35 kg, a dose of 250 mg twice daily, then daily for patients 36-40 kg, and 300 mg twice daily on day 1, then daily in those weighing more than 40 kg.

There are currently no dosing recommendations for using IV posaconazole in children. In adults requiring IV therapy, a loading dose of 300 mg should be given twice daily on day 1 of treatment, followed by a maintenance dose of 300 mg once daily. The dose should be administered through a 0.22 micron in-line filter via central venous access over 90 minutes. It should never be given as a bolus injection and should not be used in patients with moderate to severe renal impairment due to the risk for accumulation of betadex sulfobutyl ether sodium, the vehicle used in the preparation.

Summary

Posaconazole provides highly immunosuppressed patients with an effective option for antifungal prophylaxis or treatment. While still only approved for use in adolescents and adults, a number of case series and small-scale clinical studies support its use in children. As the use of posaconazole in pediatric patients becomes more common, healthcare providers should become familiar with its dosing, drug interactions, and adverse effect profile in order to optimize therapy.

References