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Use of Bosentan in Pediatric Pulmonary Hypertension

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The treatment options for children with pulmonary arterial hypertension (PAH) have expanded considerably over the previous decade, and include nitric oxide, prostacyclin analogues, phosphodiesterase inhibitors, and endothelin antagonists. Bosentan, the first endothelin antagonist on the market in the United States, was approved by the Food and Drug Administration (FDA) on November 20, 2001.[1,2] Although not currently approved for use in children, numerous case series and small-scale studies conducted over the past decade suggest a role for bosentan in this population.[3-7] This issue of *Pediatric Pharmacotherapy* will review these papers and provide recommendations for bosentan use in children.

Mechanism of Action

Endothelin-1 (ET-1) is a neurohormone which binds to endothelin A and B receptors (ET_A and ET_B) in the endothelium and vascular smooth muscle. In addition to producing vasoconstriction, ET-1 triggers proliferation of smooth muscle cells and inflammation. Circulating levels of ET-1 are known to be elevated in patients with PAH, with several studies suggesting a correlation between ET-1 levels and severity of disease. Bosentan, 4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(2-methyoxy-phenoxy)-[2,2′]-bipyrimidin-4-yl]-benzenesulfonamide monohydrate, is an oral ET-1 receptor antagonist. It is a dual endothelin antagonist, acting at both ET_A and ET_B receptor subtypes with a slightly higher affinity for ET_A receptors. Both endothelin receptor subtypes are believed to be involved in the development of PAH.[1-3]

Pharmacokinetics

Maximum plasma concentrations of bosentan are achieved within 3 to 5 hours after an oral dose. Bioavailability is approximately 50% and is not affected by food. Bosentan is highly protein bound (> 98%). In adults, the volume of distribution is 18 L, with an average elimination half-life of 5 hours. Bosentan undergoes hepatic metabolism via CYP2C9 and CYP3A4 to three metabolites. One of the metabolites is known to be pharmacologically active, providing 10-20% of the drug's effect. The metabolites are cleared by biliary excretion; less than 3% of a dose is excreted in the urine. Although mild hepatic impairment does not appear to affect bosentan clearance, the effects of moderate to severe hepatic impairment have not been studied.[1,2]

The pharmacokinetic profile of bosentan in children appears to be similar to that in adults.[4,5] In 2003, Barst and colleagues conducted a pharmacokinetic study as part of safety and efficacy trial in 19 children (3-15 years of age) with PAH.[4] The children were dosed according to weight group: 31.25 mg for those weighing 10-20 kg, 62.5 mg for those between 20 and 40 kg, and 125 mg (the standard adult dose) for those greater than 40 kg. All doses were given twice daily and titrated according to patient response over the 12-week study. Area under the plasma concentration-time curve (AUC) ranged from 5,453 to 10,777 ng•hr/mL on day 1 and from 3,496 to 6,124 ng•hr/mL at week 12, reflecting a decrease in concentrations after repeated exposure. This autoinduction had been reported previously in adults. The maximum serum concentration of bosentan on day 1 ranged from 959-1,709 ng/mL in the three dosing groups, with an average time to achieve the maximum ranging from 1 to 4 hrs. The average half-life ranged from 4.2 to 5.3 hrs, similar to that observed in adults.

In 2009, Beghetti and colleagues evaluated the pharmacokinetics of a new bosentan product in 36 children as part of the Formulation of Bosentan in Pulmonary Arterial Hypertension (FUTURE-1) study.[5] The children ranged in age from 2 to 12 years and included both those who had previously received bosentan and those who had not. Treatment consisted of a bosentan dose of 2 mg/kg twice daily for 4 weeks, followed by 4 mg/kg twice daily for 8 weeks. The new product, a 32 mg tablet with quadrisecting lines, can be easily split into halves or quarters and dispersed in water. The tablets contain a sweetener and flavoring, allowing the dissolved tablet to form an oral solution.

The two dosing strategies produced similar bosentan concentrations and clinical response. The mean maximum serum concentration was 583 ng/mL (95% CI 354, 961) with the 2 mg/kg dose and 649 ng/mL (444, 949) with the 4 mg/kg dose, lower than that reported in Barst's study. Mean AUC values were similar: 3,577 ng•hr/mL with the 2 mg/kg dose and 3,371 ng•hr/mL with the 4 mg/kg dose, suggestive of a plateau at higher doses. Time to maximum concentration occurred at 3 hours regardless of dose. Based on their results, the authors recommended initiating bosentan at 2 mg/kg twice daily in children.

Case Series and Clinical Trials

Since publication of the Barst study in 2003, more than two dozen papers describing the utility of bosentan in infants and children with PAH have appeared in the medical literature.[3,6-12] Because of the relative rarity of this diagnosis, there have been few prospective controlled studies; most of the papers published to date have been observational. In their original paper, Barst and colleagues studied 19 children New York Heart Association (NYHA) functional class II or III who had idiopathic PAH or PAH associated with congenital heart disease.[6] Bosentan produced hemodynamic improvement, with an overall change from baseline mean pulmonary artery pressure of -8.0 mm Hg (95% CI -12.2, -3.7 mm Hg) and in pulmonary vascular resistance index of -300 dyne•s•m^2/cm^5 (95% CI, -576, -24 dyne•s•m^2/cm^5).

Since that initial publication, other investigators have found similar improvement in function with bosentan using larger patient samples, longer treatment duration, or combination therapy. In their 2004 prospective observational study, Ivy and colleagues found that seven of the eight children who were started on bosentan were able to wean their intravenous epoprostenol dose and three were able to have their epoprostenol discontinued.[7] Bosentan was well tolerated by most of the children however one patient discontinued therapy due to elevated liver transaminases. The ability of bosentan to reduce the reliance on injectable medications for PAH is a significant benefit, providing the child and family with a more normal lifestyle.

Maiya and colleagues of the UK Pulmonary Hypertension Service conducted one of the first retrospective pediatric studies of bosentan in 2006.[8] They treated 40 children (ages 1-17 years) with IPAH or PAH associated with other conditions. All but one patient was World Health Organization (WHO) class III or IV. Twenty-five of the children received bosentan as their first treatment. The mean length of therapy was 12.7 months, with a range of 2-24 months. Of the 20 patients with IPAH, 19 demonstrated benefit. In spite of initial stabilization, however, 60% of these patients required epoprostenol. The patients with the least degree of benefit were all under 5 years of age. All 20 of the patients with secondary PAH showed clinical improvement, with improved 6 minute walk tests in the older children, improvement in WHO functional class, and weight gain.

In 2009, investigators from the same program reviewed their experience with 216 children with IPAH or secondary PAH.[9] In the patients with IPAH, monotherapy with bosentan or epoprostenol produced similar rates of survival, with an average of 3.9 years and 3.25 years, respectively. Survival rates were best (4.61 years), however, with combination therapy using bosentan and epoprostenol, with or without sildenafil. For comparison, the National Institutes of Health registry reports a mean survival of only 10 months after diagnosis of PAH in children, significantly shorter than that for adults. An additional paper from this program, published in 2010, provided further support for the use of combination therapy.[10]

In another 2010 paper, Ivy's group evaluated the long-term outcomes of bosentan in 86 children.[11] Early results in these children were published by Rosenzwieg et al. in 2005.[12] The patients (ages 9 months to 18 years) were treated at two centers, Columbia University in New York and the Children's Hospital in Denver. Thirty-six of the children had IPAH and the remaining patients had PAH associated with congenital heart disease or connective tissue disease. Bosentan was initiated as monotherapy or in combination with epoprostenol or treprostinil. Mean treatment duration was 24 months. At last assessment, 24 patients (31%) showed improvement in WHO functional class and 21 (27%) had worsened. Thirteen patients died prior the end of the observation period. All patients required additional therapies. Forty-three (50%) discontinued bosentan due to lack of improvement, PAH deterioration, increased liver transaminases or other adverse effects.

Contraindications and Precautions

Use of bosentan has been associated with teratogenic effects in animal studies. In rodents given approximately two times the recommended maximum human dose on a mg/m^2 basis, there was a higher rate of fetal death, malformations of the head and face, and abnormal vascular development. Based on these findings, the FDA made bosentan a category X drug (contraindicated during pregnancy). All females of child-bearing age must have a negative pregnancy test prior to initiating therapy and monthly thereafter. Adequate birth control measures must be used throughout therapy and for one month after discontinuing bosentan. Hormonal contraception alone (whether oral,

injectable, transdermal, or implantable) is not considered adequate and must be used in conjunction with a second method.[1-3]

Bosentan has been associated with increases in liver transaminases at least three-fold the upper limit of normal in 4-11% of patients during clinical trials in adults. Elevated bilirubin concentrations have also been described in a small number of patients after routine clinical use. Post-marketing surveillance has included rare reports of hepatic cirrhosis and liver failure in patients taking bosentan, but causality has not been clearly established in these cases. All patients treated with bosentan should have baseline and monthly monitoring of liver transaminases. Information on dosage adjustment in patients with elevated transaminases is provided in the Dosing Recommendations section below. Bosentan should be used with caution in patients with mild hepatic dysfunction. It should not be used in patients with moderate to severe liver disease. As a result of the drug's teratogenic and hepatotoxic potential, the FDA has required the manufacturer to develop a Risk Evaluation and Mitigation Strategy (REMS). The program components are described in the Availability section below.[1-3]

Use of bosentan has also been associated with a dose-dependent decrease in hemoglobin and hematocrit. In clinical studies of adults, the average decrease was 0.9 g/dL, with the greatest change occurring in the first 4 to 6 weeks of treatment. The mechanism for this decrease is not known. The manufacturer recommends that hemoglobin concentrations be evaluated at 1 and 3 months after starting therapy and every 3 months thereafter.[1-3]

Adverse Effects

In clinical trials conducted in adults, the most common adverse effects reported after bosentan administration were respiratory tract infections (in 22% of patients), headache (15%), edema (11%), syncope or chest pain (5%), flushing, hypotension, palpitations, sinusitis, and arthralgias (4%). Rates of these adverse effects were similar in study subjects receiving placebo. Hypersensitivity reactions, including angioedema, have been reported after bosentan use but appear to be rare.[1,2]

Safety studies in children receiving bosentan have provided similar results. In 2008, Beghetti and colleagues reviewed data from 146 children enrolled in a European post-marketing surveillance database maintained by the drug's manufacturer.[13] Median length of treatment was 29.1 weeks. Elevated liver transaminases were reported in four children, correlating to an annualized rate of 3.9%. For comparison, there was a 7.8% incidence in adults. All four pediatric cases occurred in the first 6 months and resolved with dose reduction or discontinuation. Only 2.7% of the children 2-5 years of age and 3.6% of those 6-11 years discontinued treatment because of adverse effects.

Drug Interactions

Bosentan is a substrate of CYP2C9 and CYP3A4 and is affected by the concomitant use of drugs that induce or inhibit these enzymes.[1,2] Administration of one or more inhibitors, such as amiodarone, fluconazole, itraconazole or ketoconazole, may produce clinically significant elevations in bosentan plasma concentrations and increase the risk for toxicity. Bosentan also induces CYP2C9 and CYP3A4 and may reduce plasma concentrations of other drugs metabolized by these enzymes. Other potential drug interactions are listed below.

Drug	Effect of Interaction
Clarithromycin	Increased risk for bosentan hepatotoxicity
Cyclosporine	Increased bosentan conc. and decreased cyclosporine conc. (use contraindicated)
Glyburide	Decreased conc. of both drugs
Rifampin	Increased bosentan conc. initially, followed by decrease
Ritonavir	Increased bosentan conc. (see prescribing information)
Sildenafil	Potential for increased bosentan conc. and decreased sildenafil conc.
Simvasatin	Increased conc. of simvastatin and metabolite; potential for similar effect with other statins
Tacrolimus	Increased bosentan conc.
Warfarin	Decreased warfarin conc. (29-38%); adjust as needed

Dosing Recommendations

The recommended starting dose for bosentan in adults is 62.5 mg twice daily for 4 weeks, followed by an increase to 125 mg twice daily for maintenance therapy.[1,2] Based on the available literature, an initial dose of 1-2 mg/kg twice daily appears appropriate for children.[4-12] After 4 weeks, the dose may be increased to 2-4 mg/kg twice daily. Bosentan may be taken with or without food.

In children requiring less than a full tablet, the tablet may be split with a pill cutter. Split tablets are stable for up to 4 weeks if stored in the original manufacturer's bottle. Because of the risk for teratogenic effects, splitting tablets or handling of split tablets should not be performed by women who are or may be pregnant. Bosentan tablets should not be crushed. For children unable to swallow tablets, or who require smaller doses, the tablet can be placed in

5-25 mL of water and allowed to disintegrate. The resulting suspension can be used to prepare an aliquot providing the correct dose. The suspension is stable at room temperature for up to 24 hrs. Bosentan should not be dissolved or mixed with acidic liquids such as fruit juices.[14]

Although limited information exists on the potential for rebound PAH with abrupt discontinuation, the manufacturer suggests reducing the dose by 50% for 3-7 days prior to discontinuation. Dosing must also be adjusted in patients with elevated liver transaminases. In those with transaminases 3-5 times the upper limit of normal, testing should be repeated and if the results are confirmed, the dose should be reduced to 62.5 mg twice daily in adults, half the starting dose in children, or stopped. Liver transaminases should be repeated every two weeks; therapy can be reintroduced when values return to baseline. In patients with transaminases 5-8 times the upper limit of normal, therapy should be stopped and not restarted until values are at baseline. When bosentan is re-introduced, it should be at the patient's initial dose. If transaminases are over 8 times the upper limit of normal, therapy should be discontinued.[1,2]

Availability

Bosentan (Tracleer®) is available in bottles of sixty 62.5 mg or 125 mg unscored film-coated tablets. Because of the teratogenic potential and risk for severe hepatotoxicity, bosentan prescribing requires compliance with a REMS program consisting of a Medication Guide for patient education to be dispensed with each new prescription or refill, specific patient monitoring requirements, and a restricted distribution program. Prescribers and pharmacies must be registered with the Tracleer® Access Program in order to prescribe or dispense bosentan. Details are available at www.tracleer.com or by calling 1-866-228-3546.[1,2]

Summary

Bosentan is a useful therapy for children with PAH. Studies have demonstrated benefit in children as young as 9 months of age. While effective, bosentan is associated with significant toxicity and must be closely monitored. Although the lack of a liquid dosage formulation makes use of bosentan difficult in children, twice daily oral administration is a considerable advantage compared to parenteral agents.

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Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their October meeting:

1. Belimumab (Benlysta®) was added to the Formulary for use in patients with lupus.
2. Ixabepilone (Ixempra®) was add for use in combination with capecitabine in patients with metastatic or locally advanced breast cancer.
3. Brentuximab vedotin (Adcetris™) was added for treatment of patients with Hodgkin lymphoma or systemic anaplastic large cell lymphoma who have failed prior therapies.
4. Nelarabine (Arranon®) was added for treatment of refractory acute lymphoblastic leukemia and lymphoblastic lymphoma.
5. Glatiramer (Copaxone®) was added for the treatment of patients with multiple sclerosis.

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