

# PEDIATRIC PHARMACOTHERAPY

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## Use of Serotonin Receptor Agonists in Adolescents with Migraines:

### Focus on Almotriptan

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Epidemiologic studies have shown an incidence of migraine headaches among adolescents ranging from 2 to 12%.<sup>1</sup> In a recent analysis of adolescent participants in the American Migraine Prevalence and Prevention study, the incidence of migraine meeting the International Classification of Headache Disorders (ICHD-II) criteria was 6.3%.<sup>2</sup> Treatment of migraines in adolescents remains controversial. While serotonin (5-HT<sub>1B/1D</sub>) receptor agonists, including almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan, have become an important part of treatment in adults, initial studies with these agents in adolescents have produced mixed results. Several studies have failed to demonstrate a significant treatment benefit, which has often been attributed to a high rate of response to placebo. More recent trials however, including two studies using almotriptan, have produced favorable results.<sup>3-7</sup>

Almotriptan was first approved by the Food and Drug Administration (FDA) in 2001 for the treatment of migraines in adults.<sup>8-10</sup> On June 3, 2009, the FDA extended the indication to include treatment of migraines in adolescents between 12 and 17 years of age, making it the first 5-HT<sub>1B/1D</sub> to be approved for pediatric patients. This issue of *Pediatric Pharmacotherapy* will describe the clinical trials which supported the FDA approval and review the pharmacology of almotriptan in the pediatric population.

#### Mechanism of Action

Almotriptan (1-[3-[2-(dimethylamino)-ethyl]-1H-indol-5-yl] methyl] sulfonyl] pyrrolidine) binds to 5-HT<sub>1D</sub>, 5-HT<sub>1B</sub>, and 5-HT<sub>1F</sub> receptors. It has weak affinity for 5-HT<sub>1A</sub> and 5-HT<sub>7</sub> receptors, but no activity at other serotonergic, adrenergic, adenosine, angiotensin, dopamine, endothelin, or tachykinin (NK<sub>1</sub>, NK<sub>2</sub>, and NK<sub>3</sub>)

receptors. Like other serotonin receptor agonists, almotriptan appears to relieve migraine symptoms through activation of 5-HT<sub>1B</sub> receptors on intracranial and extracerebral blood vessels. Activity at these sites produces vessel constriction, inhibits neuropeptide release, while activity at 5-HT<sub>1D</sub> reduces transmission through trigeminal pain pathways.<sup>8-11</sup>

#### Pharmacokinetics

The bioavailability of almotriptan after oral administration is approximately 70%, with peak blood levels occurring 1 to 4 hours after a dose. Administration with food does not significantly alter its absorption. Almotriptan is approximately 35% protein bound and has a mean volume of distribution in adults of 180 to 200 L. Approximately 40% of a dose is excreted unchanged in the urine. The remainder is metabolized through monoamine oxidase-mediated oxidative deamination to an indoleacetic acid metabolite. In addition, hydroxylation via cytochrome P450 3A4 and 2D6, followed by oxidation by aldehyde dehydrogenase, results in production of a gamma-aminobutyric acid metabolite. Neither metabolite is pharmacologically active. The mean half-life of almotriptan in adults is 3-4 hours. The clearance of almotriptan is decreased by approximately 60% in adult patients with severe renal or hepatic dysfunction.<sup>8-12</sup>

The pharmacokinetic profile of almotriptan has also been assessed in adolescents. In 2004, Baldwin and colleagues conducted an open-label single-dose study in 18 healthy adults and 18 adolescents (12-17 years of age).<sup>13</sup> Each patient was given a 12.5 mg dose after an overnight fast. Mean area under the plasma concentration-time curve (AUC) results were similar between the groups (320.4±76.8 ng-h/mL for the adolescents and 350.8±56.3 ng-h/mL for the adults). There was also no significant difference in the

maximum concentration or time to reach maximum concentration (55.3±19.0 ng/mL versus 52.4±8.4 ng/mL and 1.9±0.7 hr in both groups). Although elimination half-life was similar between the adolescents and adults (5.1±1.5 hrs and 5.1±0.9 hrs), mean weight-corrected oral clearance was 32% higher in the adolescents (0.672±0.127 L/hr/kg versus 0.518±0.144 L/hr/kg,  $r=1.32$ , 90% CI 1.16, 1.51). Based on their results, the authors suggest that no dosage adjustment is necessary in adolescents and that treatment with a dose of 12.5 mg is appropriate.

#### Clinical Trials with Almotriptan

Two studies of almotriptan have been conducted in adolescents.<sup>3,4</sup> In 2006, Charles published the results of an open-label pilot study of almotriptan in 15 adolescents with a history of migraines (14 females and 1 male between 11 and 17 years of age).<sup>3</sup> Two patients who weighed less than 50 kg were given almotriptan 6.25 mg and the remaining patients, all weighing more than 50 kg, received 12.5 mg to be taken at the onset of a migraine. Patients were allowed to take a second dose for recurrence of symptoms. Eight patients were pain-free within 2 hours; three were pain-free within 3 hours and two within 4 hrs. Almotriptan was ineffective in two patients. None of the patients who responded to treatment required re-dosing within 24 hours. All patients continued to use almotriptan as needed, with efficacy documented for over a year after initiation of therapy.

In the October 2008 issue of *Headache*, Linder and colleagues reported the results of their multicenter, randomized, double-blind, placebo-controlled trial of almotriptan in adolescents.<sup>4</sup> A total of 866 patients between 12 and 17 years of age were enrolled at 93 sites throughout the United States, Argentina, Colombia, and Mexico. All patients had at least a one year history of migraines. Patients were randomized to receive almotriptan at a dose of 6.25 mg, 12.5 mg, or 25 mg, or placebo to be taken at the onset of migraine symptoms. The primary end-point of the study was pain relief at 2 hours post-dose, along with assessment of nausea, photophobia, and phonophobia at 2 hours as additional outcomes.

The percentage of patients reporting pain relief at 2 hours was significantly higher in all treatment groups compared to placebo, with 71.8% of the 6.25 mg group, 72.9% of the 12.5 mg group, and 66.7% of the 25 mg group reporting pain relief compared to only 55.3% of the controls ( $p<0.05$  for each comparison). The number of patients with sustained pain relief

(continuing for 24 hours) was also significantly different in the treatment groups, with response rates of 67.2% in the 6.25 mg group, 66.9% in the 12.5 mg group, and 64.5% in the 25 mg group, versus 52.4% in the controls (all  $p<0.05$ ). Subanalysis by age group revealed a significantly lower incidence of photophobia and phonophobia at 2 hours with almotriptan compared to placebo in the 15 to 17 year olds. In the 12 to 14 year old patients, only the reduction in phonophobia achieved statistical significance. Overall, the 12.5 mg dose was associated with the best patient response. There were no significant adverse effects reported. Based on their results, the authors concluded that almotriptan was an effective, well tolerated treatment for migraines in the adolescent patient population.<sup>4</sup>

#### Other 5-HT<sub>1B/1D</sub> Agonist Trials in Adolescents

Several other 5-HT<sub>1B/1D</sub> agonists have also been studied in adolescents with migraines. In the last three years, new studies have demonstrated the efficacy of sumatriptan, rizatriptan, and zolmitriptan in patients less than 18 years of age.<sup>5-7</sup> In 2006, Winner and colleagues studied sumatriptan nasal spray in a randomized, double-blind, placebo-controlled trial of 738 adolescents.<sup>5</sup> A 20 mg sumatriptan dose produced significantly greater headache relief than placebo at 30 minutes (42% versus 33% of patients,  $p=0.046$ ) and at 2 hours (68% versus 58%,  $p=0.025$ ). Sustained pain relief over 24 hours was not significantly different.

Also in 2006, Ahonen and colleagues conducted a randomized, double-blind, placebo-controlled cross-over trial of rizatriptan in 96 patients between 6 and 17 years of age.<sup>6</sup> Each patient was treated during three migraine attacks, receiving rizatriptan on two episodes and placebo for another. Patients less than 40 kg received a 5 mg dose, while larger patients received 10 mg. Pain relief at 2 hours was achieved in 74% of patients after their first rizatriptan dose and in 73% after the second dose, compared to only 36% of patients after receiving a placebo dose ( $<0.001$ ). Results were still significant at 3 and 4-hour assessments.

Lewis and colleagues found similar benefit with zolmitriptan 5 mg nasal spray in a multicenter, single-blind, placebo challenge study of 171 children (mean age 14.2 years, range 12-17 years).<sup>7</sup> Pain relief occurred within 15 minutes in 37% of the migraine attacks treated. At one hour, zolmitriptan nasal spray produced a significantly higher rate of pain relief than placebo (response in 58.1% of attacks versus 43.3%). Zolmitriptan was also associated with

significant improvement in pain intensity, sustained resolution of headache, and associated symptoms (photophobia, phonophobia, nausea, and vomiting).

#### Contraindications and Precautions

Prior to initiating therapy with a 5-HT<sub>1B/1D</sub> agonist, all patients should be carefully assessed to rule out the presence of cerebrovascular disease. Attributing patient symptoms to migraine, with subsequent initiation of 5-HT<sub>1B/1D</sub> agonist therapy, has resulted in delays in the diagnosis of cerebral hemorrhage and stroke.<sup>8,9</sup>

All 5-HT<sub>1B/1D</sub> agonists, including almotriptan, can produce coronary vasospasm. As a result, these drugs are considered contraindicated in patients with ischemic heart disease, a history of myocardial infarction, coronary artery vasospasm, hypertension, arrhythmias, or other significant cardiovascular disease. In patients with risk factors for coronary artery disease but no history, it is recommended that the first dose of a 5-HT<sub>1B/1D</sub> agonist be given under the supervision of a health care provider with resources to respond to an adverse reaction. It has also been suggested that these patients have an electrocardiogram prior to treatment.<sup>8,9</sup>

Patients who develop symptoms of tightness, pain, or pressure in the chest, throat, neck, or jaw should be closely evaluated for the possibility of coronary artery vasospasm. Signs of vasospasm in other vessels may include abdominal pain and bloody diarrhea resulting from colonic ischemia and Reynaud's syndrome resulting from decreased perfusion in the extremities. While unlikely in the adolescent population, the patient and his/her family should be aware of the need to report any significant adverse effects.<sup>8,9</sup>

While no data are available in pregnant women, animal studies suggest that almotriptan may produce fetal death or defects. Female patients should be aware of the potential risk involved with therapy and the need to avoid pregnancy during treatment.<sup>8,9</sup>

#### Adverse Effects

Almotriptan is generally well tolerated. The most commonly reported adverse effects with almotriptan use in adolescents have been nausea, dizziness, somnolence, paresthesia, flushing, fatigue, and stiffness (reported in 1 to 2% of patients). All of these reactions were considered mild and resolved without treatment during clinical trials.<sup>3,4</sup> Other reactions to almotriptan (occurring in 0.1 to 2% of adult patients in pre-marketing clinical trials) include vasodilation, arrhythmias, hypertension, tremor, changes in

mood or behavior, diaphoresis, rash, vomiting, diarrhea, dry mouth, arthralgias or myalgias, laryngitis, difficulty breathing, ear or eye pain, flu-like symptoms, fever, or photosensitivity reactions.<sup>8-11</sup>

#### Drug Interactions

In order to avoid additive effects, patients receiving almotriptan should not be given any other 5-HT<sub>1B/1D</sub> agonists or ergot-containing drugs within 24 hours of treatment. Administration of almotriptan with selective serotonin reuptake inhibitors (SSRIs) may produce weakness or loss of coordination.<sup>8-12</sup>

Ketoconazole, as well as other drugs which inhibit CYP3A4 activity, may reduce the clearance of almotriptan. Administration of almotriptan in patients taking ketoconazole at standard doses resulted in a 50 to 60% increase in almotriptan plasma concentrations. It is recommended that these agents not be used together. At this time, there have been no studies to evaluate the extent of the interaction with other potent CYP3A4 inhibitors such as erythromycin, itraconazole, or ritonavir. Studies with verapamil, a less potent inhibitor of CYP3A4, have shown a 20 to 24% increase in almotriptan concentrations, which was considered clinically insignificant.<sup>8-12</sup>

Concomitant administration of almotriptan and monoamine oxidase inhibitors may produce a decrease in almotriptan clearance. Studies with moclobemide have resulted in a 27% reduction in almotriptan clearance. In order to adjust for this clearance in reduction, lower doses of almotriptan should be used in patients taking monoamine oxidase inhibitors.<sup>8-12</sup>

#### Dosing Recommendations

The recommended dose of almotriptan in adolescents and adults is 6.25 to 12.5 mg. A dose should be taken when migraine symptoms occur. Almotriptan should not be used as migraine prophylaxis. In patients who initially respond to therapy, but have a return of their symptoms, a second dose may be taken at 2 hours. The maximum recommended daily dose is 25 mg and the treatment frequency should be limited to no more than four episodes per month. In patients with renal or hepatic dysfunction, the recommended starting dose is 6.25 mg, with a suggested maximum of 12.5 mg during a 24-hour period.<sup>8,9</sup>

#### Availability and Cost

Almotriptan (Axert®, Ortho-McNeil) is available in 6.25 mg and 12.5 mg tablets.<sup>8,9</sup> The average wholesale price (AWP) of a package of six 6.25

mg tablets is \$139.23. A package of twelve 12.5 mg tablets has an AWP of \$278.48.<sup>14</sup> The cost of almotriptan is comparable to the other drugs in class, with the exception of sumatriptan which is now available in generic preparations.

### Summary

The 5-HT<sub>1B/1D</sub> receptor agonists have become a mainstay in the management of patients with migraine headaches. While several studies have examined their efficacy in adolescents, the results have been mixed. Recent research supporting the effectiveness of almotriptan in this population has led to it becoming the first drug within the class to be approved for use in adolescents.

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### Pharmacology Literature Update

#### Cystic Fibrosis Review

This review focuses on drugs currently under investigation in the management of patients with cystic fibrosis. The authors begin with a discussion of antibacterials, including new

preparations of older drugs such as colistin and ciprofloxacin which may improve delivery into the lungs. They then cover anti-inflammatory agents including glutathione and phosphodiesterase-5 inhibitors such as sildenafil, simvastatin, and methotrexate. There is also a review of three investigational ion channel modulating agents, lancovotide, denofosol, and GS 9411, a sodium channel antagonist. The article concludes with investigational agents designed to correct the dysfunctional CFTR and gene therapy. Jones AM, Helm JM. Emerging treatments in cystic fibrosis. **Drugs** 2009;69:903-10.

#### Sapropterin Review

Sapropterin (Kuvan<sup>®</sup>) was approved on December 13, 2007 for the management of BH4-responsive phenylketonuria (PKU). This agent is a synthetic form of tetrahydrobiopterin (BH4), and serves as a cofactor to phenylalanine hydroxylase in the liver to aid in the hydroxylation of phenylalanine to tyrosine. The authors of this new review describe the development of sapropterin and the results of the three primary clinical trials demonstrating its efficacy. They also address the limitations of these trials and the need for additional research to provide data on long-term efficacy and adverse effects. Hegge KA, Horning KK, Peitz GJ, et al. Sapropterin: a new therapeutic agent for phenylketonuria. **Ann Pharmacother** 2009;43:1466-73.

#### Formulary Update

The next meeting of the Pharmacy and Therapeutics Committee will be held on 11/19/09.

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