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Montelukast: A Review of Recent Studies in Pediatric Asthma and Allergic Rhinitis

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Montelukast was approved by the Food and Drug Administration (FDA) on February 20, 1998 for the treatment of asthma in children and adults. It has gained widespread acceptance as an adjunct to inhaled corticosteroids and beta-adrenergic agonists in the treatment of asthma in children and adults. By 2010, worldwide sales of montelukast exceeded $5 billion with $3 billion of that in the United States.[1] The availability of generic montelukast since 2012 and the extension of the approved indications to include treatment of allergic rhinitis and exercise-induced bronchoconstriction have added to the drug's continued growth.[2]

Mechanism of Action

Montelukast is a selective cysteinyl leukotriene type 1 ($CysLT_1$) receptor antagonist.[2] The cysteinyl leukotrienes are products of arachidonic acid metabolism and are released from mast cells and eosinophils. The $CysLT_1$ receptor is found in airway smooth muscle cells and airway macrophages, as well as on eosinophils. Leukotriene-mediated effects include the airway edema, smooth muscle contraction, and inflammation associated with asthma and exercise-induced bronchoconstriction. Cysteinyl leukotrienes are also released from the nasal mucosa after allergen exposure during both early and late-phase reactions. Montelukast has been shown to be effective in moderating these symptoms in children as well as adults. In infants and young children, administration of montelukast may also improve respiratory symptoms associated with viral bronchiolitis.[3]

Pharmacokinetics

The pharmacokinetic profile of montelukast has been studied in infants, children, and adults.[2] It is rapidly absorbed after oral administration, with a mean peak plasma concentration (C_{max}) of 353 ng/mL (range 180-548 ng/mL) in adults occurring within 2-4 hours. Oral bioavailability ranges from 64% with the tablets to 73% with the 5 mg chewable tablet when taken in a fasted state. Administration of the oral granules with low-fat foods does not affect the pharmacokinetics of the drug, but administration with a high-fat meal has been shown to decrease C_{max} by 35% and prolong the time to peak concentration in adults from 2 hours to 6.4 $\pm$ 2.9 hrs. Montelukast has a volume of distribution of 8-11 L in adults and is more than 99% bound to plasma proteins. There is minimal distribution of the drug across the blood-brain barrier. Montelukast is extensively metabolized through cytochrome P450 (CYP) 3A4, CYP2C8, and CP2C9. In a pre-marketing study of adults, the mean area under the concentration-time curve (AUC) was 2,689 ng•hr/mL, with a range of 1,521 to 4,595 ng•hr/mL. Elimination half-life ranged from 2.7 to 5.5 hours.

Pharmacokinetic parameters in children 2 to 14 years of age have been shown to be similar to those in adults. Studies in infants and toddlers, however, have shown considerable differences.[2,4,5] In children 6 to 11 months of age, administration of the 4 mg oral granules resulted in higher plasma montelukast concentrations and greater variability among patients, with a mean AUC of 4,296 ng•hr/mL (range 1,200-7,153 ng•hr/mL), 60% higher than that of adults. Likewise, the mean C_{max} of 667 ng/mL (range 201-1,058 ng/mL), was 89% higher than that of adults.[2] Children 12 to 23 months of age showed less variability, but still had higher values than adults, with an AUC 33% higher (3,574 ng•hr/mL, range 2,229-5,408 ng•hr/mL) and a C_{max} 60% higher (562 ng/mL, range 296-814 ng/mL).

Although not currently approved for use in infants less than 6 months of age, two small studies have examined the pharmacokinetics and safety of montelukast in this population using the commercially available 4 mg granules. Knorr and colleagues reported that a mean AUC of 3,644.3 $\pm$ 481.5 ng•hr/mL and a C_{max} of 561.1 $\pm$ 78.0 ng/mL in 14 infants between 3 and 6 months of age, similar to the values in the study of 6- to 11-month-old infants.[4] However, in 12 infants between 1 and 3 months of age with bronchiolitis, a 4 mg dose of the montelukast

granules resulted in a significantly larger mean AUC of 13,195.7 ± 2,309.8 ng•hr/mL and a C_{max} of 1,234.6 ± 196.4 ng/mL.[5] The authors suggest that these elevated values likely reflect the lower levels of CYP2C9 and uridine diphosphate glucuronosyltransferase activity in young infants necessary for metabolism. Although this dose was well tolerated by the patients when given once daily for 7 days, further work is need to determine a dose in this population that would more closely approximate serum montelukast concentrations in adults.

Recent Clinical Trials

Several studies from the past 2 years have addressed the role of montelukast as monotherapy or an adjunctive treatment in pediatric asthma management. In 2014, Berube and colleagues reported the results of a 12-week multicenter open-label observational study conducted in 328 children (mean age 6.9 years) with uncontrolled asthma.[6] Fifty-eight clinics across Canada took part in this study to evaluate the utility of montelukast in a more realistic clinical setting. Seventy-six patients (23%) were treated with montelukast alone, while the rest received montelukast and inhaled corticosteroids. At 4 weeks, 61% of the monotherapy group and 53% of the combination group had achieved asthma control. At 12 weeks, the numbers had increased to 75% and 70%. Clinically and statistically significant reductions were seen in asthma control questionnaire (ACQ) scores: from 1.67 ± 069, to 0.71 ± 0.70 at 4 weeks, and 0.50 ± 0.52 at 12 weeks in the monotherapy group and from 2.02 ± 0.83 to 0.90 ± 0.86 at 4 weeks and 0.64 ± 0.86 at 12 weeks in the combination group (goal ≤ 0.75). Twenty percent of patients were able to have their corticosteroid dose tapered. Pediatric Asthma Caregivers Quality of Life Questionnaire scores also demonstrated significant benefit.

Another trial of montelukast in the clinical setting was performed in the urban poor of the "Los Erasos" area of Caracas.[7] The authors conducted a prospective, double-blind, placebo-controlled trial of montelukast in children and adults with asthma who had limited access to inhaled corticosteroids. Sixty-four patients were analyzed. Adherence in both groups remained at 80-90% at 6 months. At both 3 and 6-month follow-up, patients receiving montelukast had significantly fewer asthma exacerbations than the placebo group (16 versus 46, $p < 0.03$, and 10 versus 43, $p < 0.04$, respectively). The differences were no longer significant at 12 months, possibly because of the high attrition rate. The authors concluded that montelukast may be a relatively simple method to reduce asthma exacerbations in patients with minimal resources and limited access to health care.

The utility of montelukast in children with stable asthma on inhaled corticosteroids remains controversial.[8] While observational studies like the ones just described have shown benefit, clinical trial results have not been as favorable. A 2013 meta-analysis of clinical trial data concluded that the addition of leukotriene receptor antagonists was not associated with a significant reduction in inhaled corticosteroid doses or the need for oral corticosteroids.[9] Recent studies have begun to focus on identifying patient characteristics which may dispose a patient towards greater benefit. Earlier this year, Stelmach and colleagues conducted a randomized double-blind, placebo-controlled trial to evaluate the effects on montelukast added to low-dose inhaled corticosteroids for exercise-induced asthma.[10] Seventy-six children (6-14 years of age) with stable asthma and dust mite allergy were enrolled. While asthma control test scores and mean corticosteroid doses were not significantly different between the groups, there was a significantly lower frequency of asthma exacerbations in the montelukast group (mean 4.5 in the placebo group versus 3 in the montelukast group, $p = 0.004$).

Contraindications and Precautions

In December 2008, prompted by postmarketing case reports, the FDA mandated that a warning be added to the product labeling stating a possible risk for neuropsychiatric symptoms with montelukast use. After several revisions, the warning currently includes agitation, aggressive behavior or hostility, anxiousness, depression, disorientation, inattentiveness, dream abnormalities, hallucinations, insomnia, irritability, memory impairment, restlessness, somnambulism, suicidal thinking or behavior, and tremor.[2]

Studies of the relationship between these symptoms and montelukast use have had mixed results. In 2009, an analysis of reports in the Swedish adverse drug reaction database between 1998 and 2007 identified 48 cases of psychiatric disorders in children receiving montelukast.[11] The most frequent symptoms reported included nightmares (in 15 children), anxiety (11), aggressiveness (11), sleep disorders (10), insomnia, irritability, hallucinations, and hyperactivity (3 each). Twenty-three children (48%) were 3 years of age or younger. Eighty percent of the reactions occurred within one week of drug initiation. A 2014 analysis of postmarketing adverse effect reports submitted to the European adverse drug reaction database,

EudraVigilance from 2007 to 2011, provides a more recent assessment of potentially serious reactions in clinical practice.[12] Fifty-four reports of montelukast adverse effects were filed over the 5-year period, with the majority (20%) being for psychiatric symptoms. This was also true for budesonide and fluticasone.

In contrast, an analysis of controlled clinical trials of montelukast has found no higher incidence of neuropsychiatric symptoms in the patients receiving montelukast. Philip and colleagues evaluated data from 35 adult and 11 pediatric studies, with a total of 11,673 patients given montelukast, 8,827 patients given placebo, and 4,724 given an active control.[13] Rates of a behavior-related adverse effect were 2.73% in the montelukast group and 2.27% in the controls groups (OR 1.12, 95% CI 0.93, 1.26). The frequency of discontinuation for a behavior-related adverse effect was 0.07% and 0.11%, respectively.

In February 2015, Ali and colleagues published the results of a matched nested case-control study of insurance claim data designed to evaluate the association between montelukast and neuropsychiatric symptoms in children.[14] A sample of claims from children with asthma treated with montelukast between January 1998 and December 2009 provided 1920 subjects. Patients with a prior history of neuropsychiatric or developmental disorders were excluded. Using conditional logistic regression, children exposed to montelukast were found to have an adjusted odds ratio of 1.01 (95% CI 0.88, 1.14) for experiencing a neuropsychiatric symptom. Exposure to montelukast was not associated with a higher risk of neuropsychiatric disturbances, developmental disorders, or the need for psychiatric medications. The only significant positive finding of the study was a relationship between exposure to high cumulative doses (> 1.080 mg) and neuropsychiatric symptoms (OR 0.67, 95% CI 0.48, 0.93).

Evaluating the available studies as a whole, a causal relationship between montelukast use and the development of neuropsychiatric symptoms has not been demonstrated. While families should know that it appears unlikely that montelukast use is associated with development of these symptoms, it should be noted that these studies do not completely exclude the possibility of causation for an individual patient. Patients and their families should be aware of the need to discuss onset of any neuropsychiatric symptoms with a health care provider.

Montelukast has been associated with systemic eosinophilia, including Churg-Strauss syndrome (systemic eosinophilia with a vasculitic rash which may progress to worsening pulmonary or cardiac symptoms or neuropathy).[2] A causal relationship with montelukast has not been established, as this condition has also been associated with a reduction in oral corticoid therapy which may occur when montelukast is started in patients with asthma.

Families of patients with phenylketonuria should be aware that the 4 mg and 5 mg chewable montelukast tablets contain 0.674 mg and 0.842 mg phenylalanine per tablet.[2]

Adverse Effects

The adverse effects reported with montelukast in pediatric clinical trials have been comparable in the treatment and placebo groups. Those reported in at least 5% of children include headache (13-33%), pharyngitis (12-26%), rash (11%), diarrhea (10-11%), fever (8-27%), wheezing (7%), cough (6-19%), sinusitis (5-20%), abdominal pain (5-11%), bronchitis (5%), nasal congestion (4-12%), viral infections (2-57%), and emesis (1-16%).[2,15]

Although rare, hepatotoxicity has been associated with montelukast in several case reports, including two in children. A recent case described a 3-year-old boy with allergic asthma who developed hepatocellular injury after taking 5 mg montelukast daily for 5 months.[16] He was admitted after developing abdominal pain, a rash, and pruritus. Upon admission, he was noted to have hepatomegaly and his laboratory values included alanine aminotransferase of 1197 IU/L, asparagine aminotransferase of 490 IU/L, alkaline phosphatase of 305 IU/L, and gamma-glutamyl transferase of 78 IU/L, all significantly above the upper limit of the reference range. Bilirubin was within range at 0.82 mg/dL, as were prothrombin time, albumin, and leukocyte count. All assessments for viral hepatitis were negative. After further evaluation, montelukast was considered a possible cause and discontinued. With little change after 2 weeks, a biopsy was done which showed a dense lymphohistiocytic infiltration of the portal tract. Gradual improvement occurred, with normalization of laboratory values over a period of 3 months. No residual adverse effects were noted on long-term follow-up.

Drug Interactions

Concomitant administration with phenobarbital, a potent CYP enzyme inducer, may result in a reduction in the montelukast AUC of approximately 40%.[2] In spite of the reduction, no

dosage adjustment is recommended. Although not studied, rifampin may produce a similar reduction in montelukast concentrations.

Administration with itraconazole, a strong CYP3A4 inhibitor, did not produce a significant increase in montelukast concentrations.[2] Use with gemfibrozil, an inhibitor of both CYP2C8 and 2C9, increased the montelukast AUC 4- to 5-fold. Although the manufacturer recommends no dosage adjustment, investigators assessing the interaction suggest that the dose of montelukast should be reduced by 50% to 80% in patients requiring long-term therapy with both agents.[17]

Administration

Montelukast is available in 10 mg tablets, 4 mg and 5 mg chewable tablets, and packets of 4 mg oral granules.[2] Oral granules may be given directly into the mouth or mixed with 5 mL of formula, breastmilk, or a soft food such as applesauce, pureed carrots, rice cereal, or ice cream. The recommended dose of montelukast for adults and adolescents 15 years of age and older with asthma or allergic rhinitis is 10 mg daily. The dose for children 6 to 14 years of age is 5 mg daily and for children 2 to 5 years is 4 mg daily. A dose of 4 mg is also recommended for children 6 to 23 months of age with allergic rhinitis. Patients 15 years of age and older with exercise-induced bronchoconstriction should take a 10 mg dose at least 2 hours prior to exercise, while those 6 to 14 years of age should take a 5 mg dose. Only one dose should be taken per 24-hour period.

Summary

As we approach 20 years of montelukast use in the United States, a number of new studies are adding to our understanding of its efficacy and safety in children. Many of these recent reports, as well as the outcomes of several ongoing projects, will allow pediatric health care providers to make more informed decisions about the use of montelukast in their patients.

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