Pediatric Pharmacotherapy

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Montelukast: a selective leukotriene receptor antagonist

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Pharmacology Literature Reviews

Formulary Update

Asthma is the most frequent admitting diagnosis for children and a leading cause of chronic illness. For many years, bronchoconstriction was thought to be the primary mechanism of this disease. However, chronic inflammation has now been recognized as the major cause of asthma exacerbations.[1,2] Current recommendations for the treatment of chronic asthma now include consistent treatment of inflammation as a primary goal. Research is being focused on developing drugs to inhibit inflammatory mediators. Montelukast is among the new agents targeted at reducing inflammation in hopes of alleviating asthma symptoms.

Mechanism of Action

Montelukast is a selective, reversible leukotriene receptor antagonist.[3] Leukotrienes were first discovered in the 1930's as potent mediators of inflammation and given the name slow-reacting substance of anaphylaxis.[4] Bronchoconstriction, increased mucous formation, and increased vascular permeability with edema formation are all possible mechanisms of airflow obstruction secondary to leukotrienes.[5]

The cysteinyl leukotrienes (LTC_4, LTD_4, and LTE_4) are products of arachadonic acid metabolism which are released by mast cells, monocytes, eosinophils, and basophils. Studies have shown LTD_4 to be 140 to 6,000 times more potent than histamine as a bronchoconstrictor. Montelukast binds with high affinity to the LTD_4 receptor, inhibiting bronchoconstriction. In clinical trials, montelukast has been found to inhibit bronchoconstriction at doses ranging from 5 to 250 mg, when administered four hours prior to a nebulized LTD_4 challenge.[1-5]

Current Indications

Montelukast is indicated for the prophylaxis and chronic treatment of asthma in patients greater than six years of age. Unlike the other leukotriene antagonists, zafirlukast and zileuton, montelukast is approved by the Food and Drug Administration (FDA) for use in young children. Approval for exercise-induced asthma has not yet been established.[6,7]

Use in Children

Even with the recent approval of montelukast by the FDA, clinical experience is still very limited. Only one large-scale study has been published to date in children with chronic asthma.[8] The study by Knorr and colleagues included 336 children between the ages of 6 and 14 years with a history of intermittent or persistent asthmatic symptoms requiring inhaled beta-adrenergic agonists on an as needed basis. Patients were randomized in this multi-center, double-blinded study to receive either montelukast 5 mg given once daily or placebo.

The primary endpoint of the study was the change in the forced expiratory volume (FEV_1) from baseline, with each patient serving as his/her own control. The montelukast group had a significant improvement in FEV_1 versus placebo (8.23% versus 3.57% increase), with a resulting p value of < 0.001. The montelukast group also had a significantly greater decrease in the frequency of beta-adrenergic agonist use and number of asthma exacerbations than the placebo group during the 2 month evaluation period.

In a study published in the September issue of *The Journal of Pediatrics*, Kemp and co-workers examined the efficacy of montelukast in mitigating the symptoms of exercise-induced asthma.[9] Once again, the patients included in the study were between the ages of 6 and 14 years. Only 27 children participated in this double-blind, crossover, multi-center study. Patients were randomized initially to receive either montelukast 5 mg or placebo for 2 days and then given an exercise challenge 20 to 24 hours after the last dose. After a minimum 4 day wash-out period, the children were crossed over to the other treatment group, and the testing was repeated. Endpoints assessed included the area above the post-exercise percent fall in FEV_1 versus time curve ($AAC_{0\text{-}60\ min}$), the maximum percent fall in FEV_1 from baseline, and time to recovery. Montelukast significantly reduced both the $AAC_{0\text{-}60\ min}$ and the maximum percent fall in FEV_1 versus placebo. In addition, montelukast provided a faster time to recovery of baseline (non-exercise) lung function. Based on these results, the authors concluded that montelukast attenuates exercise-induced bronchoconstriction and should be considered in the therapy of children with this condition.

Pharmacokinetics

Montelukast is rapidly absorbed following oral administration, reaching peak levels 2 to 2.5 hours after administration of the 5 mg tablet and 2 to 4 hours after administration of the 10 mg tablet.[7,10,11] Bioavailability varies between the two tablet strengths. The 10 mg tablet is approximately 64% bioavailable, regardless of whether it is administered with food. The 5 mg tablet is 73% bioavailable in the fasting state, but bioavailability declines to 63% when it is taken with food. Montelukast is 100% protein bound.[7,8,10]
Montelukast undergoes extensive metabolism in the liver by the cytochrome P450 enzyme system, specifically CYP3A4 and CYP2C9, and is excreted into the bile.[10,12,13] The mean plasma half-life of the drug is 2.7 to 5.5 hours. Patients with mild to moderate hepatic dysfunction and evidence of cirrhosis have been shown to have a decrease in metabolism and a resulting increase in AUC of 40% with a prolonged elimination half-life. Despite these effects, dosage adjustment has not been required for patients with liver disease. Dosage adjustments are also not necessary for patients with renal dysfunction.[7]

Drug Interactions

Phenobarbital, which acts as a potent cytochrome P450 enzyme inducer, may decrease the AUC of montelukast by up to 40%. However, this interaction has not been shown to be clinically significant. It is important to note that other P450 inducers, such as rifampin or valproate, may also induce the metabolism of montelukast, but the clinical effects of these interactions are not well established.[7] More research is needed in this area.

Adverse Effects

Montelukast appears to be well tolerated. In clinical trials, the most common adverse effect reported was headache, occurring in approximately 18% of patients. Rash, dyspepsia, dizziness, and abdominal pain were all reported in less than 2% of patients. Elevated liver transaminases have been reported with montelukast use, but not at a greater incidence than with placebo. A small percentage of pediatric patients have experienced diarrhea, sinusitis, and otitis media during montelukast clinical trials.[6,7]

Pregnancy and Lactation

Montelukast is classified as pregnancy category B. The drug has been shown to cross the placenta of pregnant rats and rabbits, but there have been no reports of its use in pregnant women. Montelukast is also known to be excreted into breastmilk, but only limited information is available on the significance of this finding. Caution should be used prior to initiating montelukast therapy in nursing mothers.[6,7]

Dosing Recommendations

Montelukast is currently available as Singulair® , manufactured by Merck. It is available as a 5 mg chewable tablet and a 10 mg film-coated tablet. Currently, there is no parenteral form of the drug. The recommended dosage for children 6 to 14 years of age is one 5 mg chewable tablet daily in the evening. For patients $\geq$ 15 years of age, the usual dosage is 10 mg daily in the evening. The maximum daily dose of montelukast is 10 mg, although doses as high as 250 mg have been found to be safe in clinical trials. Higher doses, however, have not been found to improve efficacy.[14]
Patients should be advised to take montelukast even if they are asymptomatic and not to change the dose without the recommendation of a physician. Patients should also be reminded that this

agent is not to be used for an acute asthma attack. Although montelukast functions as an anti-inflammatory, it should not be abruptly substituted for inhaled corticosteroids. Phenylketonurics should not receive the 5 mg chewable tablets, as that dosage form contains phenylalanine.[6,7]

Conclusion

The treatment of chronic asthma has seen many changes in the past 15 years. The National Institute of Health's current guidelines for the diagnosis and management of asthma recommend daily anti-inflammatory therapy as the most effective method to control chronic asthma.[15] Leukotrienes have been shown to be mediators in the inflammatory process and excellent targets for therapy aimed at reducing chronic symptoms.

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Pharmacology Literature Review

ADHD Review

While many reviews of therapies for attention deficit/hyperactivity disorder have been published in the past three years, few cover as many alternatives as this concise article by Cyr and Brown from the University of Tennessee. All of the standard treatments are presented, as well as newer alternatives such as the selective serotonin reuptake inhibitors, bupropion, clonidine, and antipsychotics. Cyr M, Brown CS. Current drug therapy recommendations for the treatment of attention deficit hyperactivity disorder. **Drugs 1998;56:215-23.**

Budesonide for Asthma

Budesonide is one of the newest corticosteroids available for the management of asthma. In the powder form for inhalation, it offers a high ratio of local to systemic effects. The authors present a review of budesonide use in both children and adults. A cost comparison to other inhaled steroids is included. Davis KC, Small RE. Budesonide inhalation powder: A review of its pharmacologic properties and role in the treatment of asthma. **Pharmacotherapy 1998;18:720-8.**

Otitis Media Review

This extensive review covers the pathophysiology and treatment of otitis media, one of the most common pediatric illnesses. The authors provide a thorough discussion of bacterial resistance, then follow with a description of 11 of the most frequently prescribed oral antibiotics for resistant strains. Clinicians may find the most useful parts of this review to be the tables, one providing a cost comparison and one summarizing the results of two dozen clinical trials. Hoppe HL, Johnson CE. Otitis media: Focus on antimicrobial resistance and new treatment options. **Am J Health-Syst Pharm 1998;55:1881-97.**

Sedation Review

This paper updates a previous review from Dr. Bhatt-Mehta published several years ago. The authors review the agents in common use, then divide the remainder of the article into different procedures requiring sedation. Each section describes recent clinical trials comparing sedatives and summarizes current opinion on drug choices. Several tools for monitoring and adjusting medication doses developed by Dr. Rosen at West Virginia University are provided as tables. A brief discussion on preventing withdrawal symptoms is also included. Bhatt-Mehta V, Rosen DA. Sedation in children: Current concepts. **Pharmacotherapy 1998;18:790-807.**

Tacrolimus as Rescue Therapy

The authors present a retrospective review of tacrolimus use in children who failed cyclosporine therapy after liver transplantation. Charts were reviewed for 21 children (median age 5 years) who were transplanted during the period from May 1993 to January 1997. The indications for switching to tacrolimus were acute rejection (62%), chronic rejection (33%), and cyclosporine toxicity (5%). All patients had started therapy with a dose of 0.2 to 0.3 mg/kg given twice daily, with dosage adjustment based on clinical response and maintenance of a serum concentration between 5 and 15 ng/ml. Of the 17 patients with follow-up data available for 2 years, a significant difference was found in the average dose required to maintain target serum concentrations. In the first month of treatment, the average dose was 0.32 mg/kg, whereas by

the end of the follow-up period, it was only 0.14 mg/kg. The authors theorize that the effects of growth and graft function played a role in this decline in dose. Interestingly, the authors also found a significant difference in dose requirements between patients with a history of hepatitis C and those without the disease. The mean daily dose in hepatitis C patients at follow-up was 0.08 mg/kg compared to 0.24 mg/kg for children transplanted for other reasons. Further study is clearly needed to determine if separate tacrolimus dosing recommendations are needed for children with hepatitis C. Moreno M, Manzanares C, Castellano F, et al. Monitoring of tacrolimus as rescue therapy in pediatric liver transplantation. **Ther Drug Monit 1998;20:376-9.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 9/25/98:

1. Palivizumab (Synagis®) was added to the formulary for the prevention of respiratory syncytial virus infections in high-risk infants. For more information about this agent, please refer to the September issue of *Pediatric Pharmacotherapy*.
2. Tolterodine (Detrol®) was also added to the formulary. This agent is used to treat urinary incontinence, as an alternative to oxybutinin.
3. Imiquimod (Aldara®) was added for the treatment of genital warts.
4. A combination of ribavirin and interferon alfa (Rebetron®) was approved for use in patients with Hepatitis C.
5. Famciclovir (Famvir®), an antiviral used to manage herpes infections, was also added to the formulary.
6. Tirofiban (Aggrastat®), a glycoprotein IIb/ IIIa receptor inhibitor with antiplatelet effects, was added for the management of patients with acute coronary syndrome.
7. Lansoprozole (Prevacid®), a proton pump inhibitor similar to omeprazole, was also added.

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