Montelukast Sodium – *Singulair*®, Merck

Development and Pharmacology:[1]

Asthma is a chronic inflammatory disease of the airways that is complicated by episodes of acute inflammation. Even patients with mild disease show airway inflammation, including infiltration of the mucosa and epithelium with activated T cells, mast cells, and eosinophils. T cells and mast cells release cytokines that promote eosinophil growth and maturation and the production of IgE antibodies, and these, in turn, increase microvascular permeability, disrupt the epithelium, and stimulate neural reflexes and mucus-secreting glands. The result is airway hyperreactivity, bronchoconstriction, and hypersecretion, manifested by wheezing, coughing, and dyspnea. Traditionally, asthma has been treated with oral and inhaled bronchodilators which alleviate the acute symptoms of asthma, but do nothing for the underlying inflammation. Recognition of the importance of inflammation in the etiology of asthma has led to the increased use of corticosteroids in recent years, but many patients continue to suffer from uncontrolled asthma. It is estimated 13 million Americans have asthma, and asthma mortality has risen 40% over the past 15 years. Over the past several years the FDA has approved the first of a new class of antiasthma drugs called the anti-leukotrienes with the potential to interfere with the initial steps in the inflammatory cascade. The potential market for the new leukotriene inhibitors and antagonists is estimated to be billions of dollars.

The role of leukotrienes in inflammatory disease has been realized since the late 1970s when the so-called "slow reacting substance of anaphylaxis" (SRS-A) was identified as an arachidonic acid derivative and given the name "leukotriene C." Since that time, it has been determined that there are a number of leukotrienes (LTs), now labeled as A, B, C, D, and E subtypes, and some of these play a critical role in the pathology of asthma. The so-called cysteinyl or peptidoleukotrienes (LTC_4, LTD_4 and LTE_4) are present in higher levels in asthmatics and released from mast cells, basophils, eosinophils and macrophages in human airways during antigen challenge. Once released through interactions with specific receptors they cause bronchoconstriction, increased vascular permeability, edema, enhanced mucus production, reduced mucociliary transport, and inflammatory cell infiltration. Like the related prostaglandins, leukotrienes are biosynthesized from arachidonic acid in the cell membrane. Arachidonic acid in mast cells, macrophages, monocytes, eosinophils, and basophils is released from membrane phospholipids by the activation of phospholipase A_2. After its release, arachidonic acid undergoes metabolism via two major pathways: the cyclooxygenase pathway, which produces various prostaglandins and thromboxanes, and the 5-lipoxygenase pathway which produces leukotrienes. The prostaglandins, thromboxanes, and leukotrienes are known collectively as eicosanoids.

For the past 15 years considerable effort has been expended by the pharmaceutical industry to develop novel drug therapies for asthma which function by inhibiting the biosynthesis of LT, or block the actions of LTs at there receptors. These efforts resulted in the introduction of two drug products over the past several years, zileuton (*Zyflo*®) and zafirlukast (*Accolate*®). Zileuton (*Zyflo*®), the first anti-leukotriene drug approved, functions as a selective inhibitor of 5-lipoxygenase (no inhibition of cyclooxygenase) and the resultant decrease in leukotriene formation has been shown to significantly improve breathing

performance in asthmatic patients. This advance was followed by the introduction of several leukotriene receptor antagonist (LTRAs) for asthma, including zafirlukast (*Accolate*®) several years ago and now montelukast (*Singulair*®). These LTRAs are potent and selective in their pharmacologic action, binding with high affinity to cysteinyl leukotrine ($CysLT_1$) receptors in preference to other important airway targets such as prostanoid, cholinergic or beta-adrenergic receptors. In human trials montelukast in doses as low as 5 mg have been shown to inhibit the bronchoconstriction induced by inhaled LTD_4 in asthmatics. Currently zafirlukast is approved for use only in adults and children 12 years and older and the recommended dose is 20 mg twice daily. The new agent, montelukast, is indicated to treat asthma in adults and children 6 years of age and older, and can be administered in single daily doses of 5 or 10 mg.

Therapeutics:[2-6]

The efficacy of montelukast (10 mg) in the treatment of chronic asthma in adolescents and adults was documented in two placebo-controlled 3 month studies involving more than 1500 patients with mild to moderate ranging in age from 15 to 85 years. In these trials the patients treated with montelukast demonstrated significant improvement (10-15% increase) versus placebo in the primary study endpoint, forced expiratory volume in one second (FEV_1). Montelukast-treated patients also showed statistically significant improvments in secondary trial endpoints including morning and evening peak expiratory flow rates (increased by 18-25%), "as-needed" beta-agonist use (decreased by 26%) and asthma-related nocturnal awakenings (reduced 2%). Furthermore, in "quality-of-life" assessments the montelukast treated patients reported significant improvements in their asthma symptoms, emotional well-being and their overall activity, and a reduction in the effects of environment stimuli on their disease. In similar controlled trials with pediatric asthmatics (ages 6-14), montelukast was found to displayed comparable efficacy based on these primary, secondary and quality of life therapeutic endpoints. In all trials significant therapeutic benefit was observed with the first dose of montelukast and remained essentially unchanged over the treatment period. In extended trials, montelukast efficacy was maintained up to one year. Also, withdrawal of montelukast after 3-months of continuous use did not result in rebound worsening of asthma symptoms. In a comparative study with beclomethasone, montelukast had a more rapid onset of initial response, but beclomethasone displayed a greater therapeutic effect when using FEV_1, and number of asthma attacks were used as the evaluative criteria. At present time there are no controlled studies comparing montelukast to other antileukotriene drugs, theophylline, cromolyn sodium (*Intal*®), salmeterol xinafoate (*Serevent*®) or other inhaled steroids. Currently montelukast is indicated for the prophylaxis and chronic treatment of asthma and adults and pediatric patients 6 years of age and older.

Adverse Reactions:[2-6]

In the clinical trials to date the overall incidence of adverse reactions associated with montelukast therapy was comparable to placebo. Most reactions were mild and did not require discontinuation of drug therapy. In adults and adolescent patients (15 years of age and older) the primary adverse experiences included headache (18%), influenza (4%), abdominal pain (3%), cough (2.7%) and dyspepsia (2.1%). Other less frequent reactions (but >1%) included fever, asthenia, GI infection, dizzines, nasal congestion, rash and elevated liver

enzymes (ALT and AST). The adverse reaction profile in pediatric patients (6-14 years of age) was generally similar to the adult/adolescent profile with the exception of diarrhea; laryngitis; pharyngitis; nausea; otitis; sinusitis; viral infection which occurred at a frequency of 2% or greater. In both adult and pediatric patients the adverse experience profile did not significantly change with prolonged montelukast therapy.

Drug Interactions:[2-6]

The administration of montelukast with other drugs used routinely to manage the symptoms of asthma does not appear to increase the incidence of adverse reactions. Also, no clinically significant adverse experiences were noted in drug interaction studies with theophylline, prednisone, prednisolone, oral contraceptives, terfenadine, digoxin or warfarin. Based on it's metabolic profile, monitoring is recommended when potent cytochrome P450 enzyme inducers, such as phenobarbital or rifampin, are coadministered with montelukast. For example, phenobarbital, which induces hepatic metabolism, decreases the AUC of montelukast » 40%. However, no dosage adjustment for montelukast is recommended when these drugs are used concurrently.

Pharmacokinetics:[7]

Montelukast is rapidly absorbed following oral administration. The mean oral bioavailability of the 10 mg tablet in adults is 64%, and the mean peak plasma concentration (C_{max}) is achieved in 3-4 hours (T_{max}). Oral bioavailability and C_{max} of the tablet are not significantly influenced by a morning meal. The mean oral bioavailability of the 5 mg chewable tablet is 73% in the fasted state vs 63% when administered with a morning meal. For the chewable tablet the mean C_{max} is achieved in 2 to 2.5 hours. Montelukast is > 99% bound to plasma proteins and the steady-state volume of distribution averages 8 to 11 L. Studies in animals indicate minimal distribution across the blood-brain barrier. Montelukast is extensively metabolized primarily by cytochrome P450 isozymes 3A4 and 2C9. Approximately 86% of an oral dose is recovered in feces over 5 days and < 0.2% is recovered in urine. These elimination data, coupled with estimates of montelukast oral bioavailability, indicate that montelukast and its metabolites are excreted almost exclusively via the bile. The mean plasma half-life of montelukast ranges from 2.7 to 5.5 hours in healthy young adults and the pharmacokinetics are nearly linear for oral doses up to 50 mg. The pharmacokinetic profile and the oral bioavailability of montelukast are similar in elderly and younger adults, but the plasma half-life of montelukast is slightly longer in the elderly. Patients with mild-to-moderate hepatic insufficiency and cirrhosis display higher (41%) mean montelukast area under the plasma concentration curve (AUC) as a result of decreased metabolism and slower clearance. However, no dosage adjustment is recommended in patients with mild-to-moderate hepatic insufficiency.

Administration and Dosage:[2-7]

Montelukast is supplied as 10 mg tablets and 5 mg chewable tablets. The recommended dose and dose schedule for adults and adolescents (≥15 years of age) is one 10 mg tablet daily, taken in the evening. Pediatric patients (6 to 14 years of age) are advised to take one 5 mg chewable tablet daily in the evening. No dosage adjustment within this age group is necessary. The safety and efficacy in pediatric patients < 6 years of age have not been established. At present there have been no clinical trials evaluating the relative efficacy of morning vs evening dosing. Patients should be advised to take montelukast daily as prescribed and that it is not for the treatment of acute asthma attacks; patients should have appropriate short-acting inhaled beta-agonist medication available to treat asthma exacerbations and should seek medical attention if short-acting inhaled bronchodilators are needed more often than usual. Montelukast is not indicated for use in the reversal of bronchospasm in acute asthma attacks, including status asthmaticus.It also should not be used as monotherapy for the treatment and management of exercise-induced bronchospasm. Patients with known aspirin sensitivity should avoid aspirin or non-steroidal anti-inflammatory agents while taking montelukast. Also phenylketonuric patients should be warned that the chewable tablet contains phenylalanine.

References:

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3. Reiss TF, Chervinsky P. Edwards T, et al. Montelukast (MK-0476), a CysLT-1 receptor antagonist, improves asthma outcomes over a three month treatment period. *Am. J. Respir. Crit. Care. Med.*. Apr 1997; 155 (4): A662.
4. Knorr BA, Matz J, Sveum RJ et al. Montelukast (MK-0476) improves asthma over 6 months of treatment in 6-14 year old patients. Eur. Respir.J. 1997, 10 (Suppl 25): P1429.
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6. Kelloway JS, Wyatt RA, Adlis SA. Compairson of patients' compliance with prescribed oral and inhaled asthma medications. Arch. Intern. med. June 27, 1994, 154(12):1349-1352.
7. Zhao JJ, Rogers JD, Holland SD et al. Pharmacokinetics and bioavailability of montelukast sodium (MK-0476) in healthy young and elderly volunteers. Biopharm. Drug Dispos. 1997, 18(9):769-777.

1. The recommended dosage regimen for Montelukast sodium (*Singulair*®) forchronic asthma in adults is:

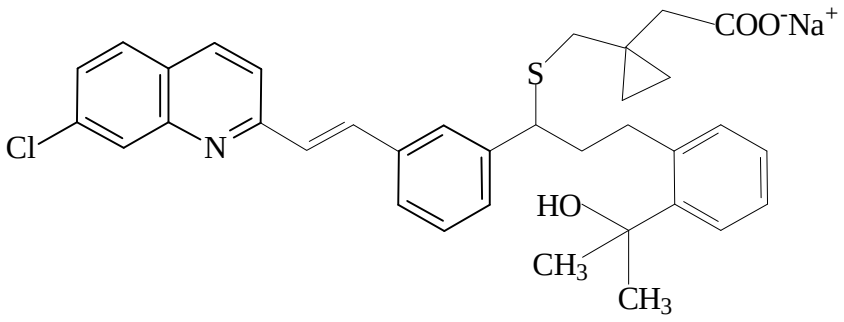
   (A) 5 mg oince daily in the morning
   (B) 10 mg once daily in the morning
   (C) 5 mg twice daily
   (D) *10 mg once daily in the evening*

2. Montelukast sodium (*Singulair*®) produces its therapeutic effects via:

   (A) Agonist actions at beta-adrenergic receptors
   (B) Inhibition of cyclooxygenase
   (C) Blockade of leukotriene receptors
   (D) Inhibition of 5-lipoxygenase

3. The most common adverse reactions (>2%) associated montelukast sodium (*Singulair*®) therapy include:

   (A) Headache
   (B) Influenza
   (C) GI tract pain and dyspepsia
   (D) *All of the above*



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