

THE CLINICAL UTILITY OF MONTELUKAST IN PAEDIATRIC RESPIRATORY DISEASES

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ABSTRACT

The arachidonic acid metabolism via 5-lipoxygenase gives rise to a family of biologically active lipids known as leukotrienes. The role of cysteinyl leukotrienes in the pathogenesis of bronchial asthma is well established. Randomized controlled trials (RCTs) have confirmed the efficacy of leukotriene receptor antagonists (LTRAs), when used as monotherapy or added to inhaled corticosteroids (ICS), in improving bronchial outcome including lung function, symptoms, bronchial asthma exacerbation and health related quality of life. Although, current guidelines place LTRAs as therapeutic option at a range of levels of bronchial asthma severity, there is uncertainty among clinicians about their role in relation to other therapies. Montelukast is a potent, specific, oral cystinyl leukotriene₁ (cysLT₁) receptor antagonist which improves bronchial asthma control and reduces inhaled corticosteroids requirement.^c This review provides an overview of evidence for the use of montelukast in patients with bronchial asthma and exercise induced asthma sleep disorder, respiratory syncytial virus (RSV), bronchiolitis and cystic fibrosis.

KEY WORDS: Montelukast, bronchial asthma, exercise-induced asthma, respiratory syncytial virus, Bronchiolitis, allergic rhinitis, sleep disordered breathing.

Pak J Med Sci October - December 2007 (Part-II) Vol. 23 No. 6 962-969

INTRODUCTION

Over the past three decades, drugs used in the treatment of bronchial asthma such as corticosteroids, beta 2-agonists and theophylline have changed a little. Inhaled corticosteroids, when used as first-line preventive therapy, are now well established in the management of the

disease, and this is primarily driven by a greater understanding of the importance of the underlying inflammatory process.¹ However, inhaled corticosteroids have a shallow dose-response curve for antiasthmatic efficacy and a steeper curve for systemic adverse effects, although the clinical relevance of the latter remains uncertain.² Concern about potential systemic side effects of inhaled corticosteroids have become more prominent because of a tendency to prescribe higher doses when initiating treatment, along with a failure to taper to the lowest effective maintenance dose. The addition of a second drug, such as long-acting beta 2-agonists or theophylline to reduce the doses of inhaled corticosteroids, may offer an alternative to monotherapy when higher doses of steroids are used.¹ This approach in turn focuses the attention on the need for other strategies to block the effects of inflammatory mediators such as the cysteinyl leukotrienes. The latter are the subject of this review.

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* Received for Publication : August 29, 2007

* Revision Received : September 3, 2007

* Revision Accepted : November 17, 2007

Leukotrienes are chemical mediators of inflammation that are secreted by eosinophils, mast cells, neutrophils, lymphocytes, macrophages and basophils.³ Arachidonic acid metabolism via the 5-lipoxygenase gives rise to a family of biologically active lipids (Fig-1). The leukotriene B₄ is a potent activator of leukocytes chemotaxis and cysteinyl leukotrienes (leukotriene C₄, D₄ and E₄) account for the spasmogenic activity described as SRS-A (Slow-reacting substance of anaphylaxis). After an allergen challenge, a large increase in the production in these cysteinyl leukotrienes is detectable in bronchoalveolar lavage (BAL) fluid and urine of people who are suffering from bronchial asthma.⁴⁻⁶

The discovery of leukotrienes dates back to 1938 when the term SRS was coined to describe substances which possess the capability of a

pronounced contraction of smooth muscle which is slower in onset and longer in duration than that produced by histamine.⁷ In 1940, SRS-A was shown to be released during anaphylactic shock. Despite research over the next 40 years, the identity of SRS-A remained elusive. By late 1970, a variety of biochemical and physical chemical properties of this substance had been discovered. It was shown that SRS-A contained a conjugate triene and sulphur was present in the molecule and SRSs could be formed in a variety of cells including leukocytes and arachidonic acid was a precursor of SRS-A formation. Hence, the term leukotriene was coined to indicate that these products are formed in leukocytes and that they contain conjugated trienes.⁸ The term CYSLT1 was introduced in 1995, based on pharmacological characterization of smooth muscle tissues, but

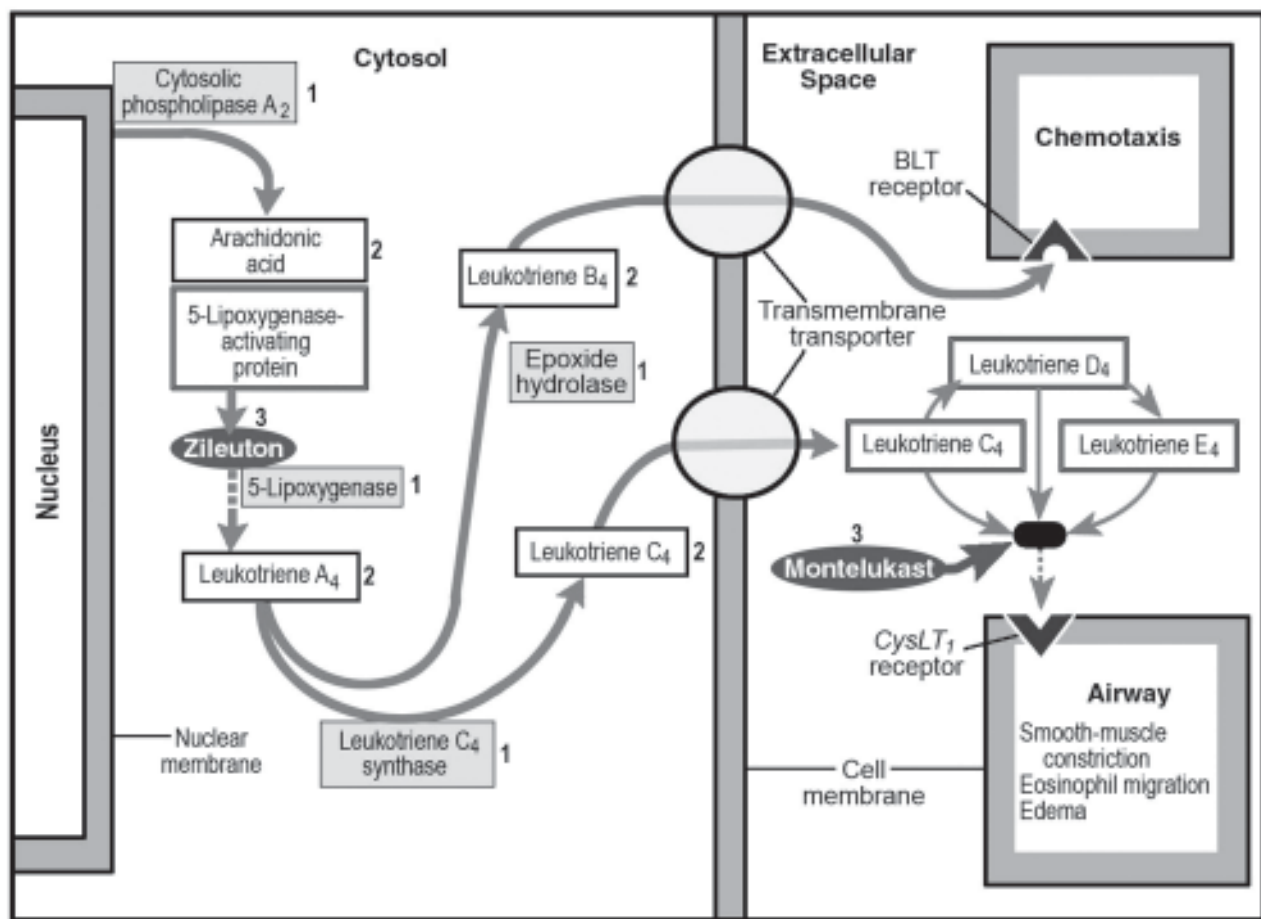


Figure-1: 1 = Enzymes, 2 = Products, 3 = Drugs

it was not until 1999 that molecular cloning led to the identification of a 336 amino acid, G-protein-coupled membrane protein which exhibited the pharmacological properties of a CYS-LT1 receptor.^{8,9}

The action of leukotrienes depend on their binding to cellular receptors. Drugs that thwart the asthmatic process by blocking the action of leukotrienes at their receptors are known as leukotrienes antagonists. Three drugs of this class are known at present namely, zafirlukast, pranlukast and montelukast. All three are specifically active against the cysteinyl leukotrienes by blocking their receptor, (CysLT1) (Fig-1). Montelukast is the only agent used in pediatrics and has been extensively studied in children.

Pharmacodynamics of montelukast: Montelukast is a potent and selective antagonist of leukotriene D₄ (LTD₄) at the cysteinyl leukotriene receptor (CysLT1), in the lungs and bronchial tree. This reduces the bronchoconstriction otherwise caused by the leukotrienes, and results in less inflammation. Studies on montelukast in the paediatric population found that it is well tolerated.¹⁰⁻¹³ The majority of reported adverse effects were mild and included headache, ear infection, nausea, abdominal pain and pharyngitis.^{14,15} It was apparent from clinical trials that the incidence of these adverse effects was higher than with the placebo.¹⁴⁻¹⁶ The Churg-Strauss syndrome which occurs when steroid doses are reduced had not been causally related to montelukast.¹⁷⁻¹⁹ One case report of pulmonary eosinophilia which is associated with a cysteinyl leukotriene type 1 receptor antagonist other than zafirlukast suggests that the syndrome may be related to the effect of antileukotriene drugs at leukotriene receptors.²⁰

It has been reported that no dose adjustments are necessary when montelukast is used for patients with renal and mild to moderate hepatic dysfunction. However, there was a case report of montelukast-induced acute hepatitis in a 75 years old man and another of cholestasis which had been linked to the use of montelukast.²¹⁻²³ Moreover, it has been also

demonstrated that treatment with montelukast increased the phagocytic and intracellular killing activity of polymorphonuclear leukocytes in patients with asthma.²⁴ There were reports which had shown CysLT1 receptor antagonists to have significant anti-inflammatory effects on allergen-induced lung inflammation and fibrosis in an animal model reflective of the airway remodeling changes observed in patients with persistent asthma. Thus the potent anti-inflammatory effects of CysLT1 receptor blockers may be beneficial in the long-term management of bronchial asthma.²⁵

Pharmacokinetics: Montelukast is available in 4mg chewable tablet or granules for children between 2-5 years; 5mg chewable tablet and 10mg oral tablet (Merck & Company, INC, 1998). The 5mg chewable tablet is recommended for patients 6 to 14 years of age and the 10 mg tablet is for patients \geq 15 years of age, and the dose is given once daily.¹⁴⁻¹⁶

The dose for montelukast for 6-14 years old children was selected by identifying the chewable tablet dose of montelukast yielding a single-dose area under the plasma concentration time curve (AUC) comparable to that achieved with the adult 10mg film-coated tablet dose. Based on this approach which included dose normalization of data from several pediatric pharmacokinetic studies, a 5mg chewable tablet dose of montelukast was selected for use in clinical efficacy studies in 6-14 year old children with asthma.¹⁰⁻¹² Montelukast is rapidly absorbed following oral administration. For the 10mg film-coated tablet, the mean peak plasma concentration (C_{max}) is achieved within three hours (T_{max}) after administration in adults in the fasting state.^{10,11,15,16} The mean oral bioavailability is 66%. The oral bioavailability and C_{max} are not influenced by standard meals. For the 5mg chewable tablet the C_{max} is achieved in two hours after administration in adults in the fasting state.^{10,11,12,15,16} The mean oral bioavailability is 73% and it is decreased to 63% by the standard meal. After administration of the 4 mg chewable tablet to pediatric patients 2 to 5 years of age in the fasting

state, peak plasma concentration is achieved 2 hours after administration.^{10,11,13}

Montelukast is more than 99% bound to plasma proteins and the steady state volume of distribution of montelukast averages 8-11 liters.¹⁰⁻¹³ In studies with therapeutic doses, plasma concentration of metabolites of montelukast are undetectable at steady state in adults and children.¹⁴ Various studies have provided the pharmacokinetic basis for the selection of the 4 mg dose for children 2-5 years of age.¹² Migoya et al, evaluated the pharmacokinetics comparability of a 4mg dose of montelukast oral granules in patients between 6 to 24 months old to the 10mg approved dose in adults.¹¹ The authors observed that the area under the curve estimate ratio (pediatric/adult 10mg film coated tablet) and the 95% confidence interval (CI) for children compared with adults were within the predefined comparability bounds. The observed plasma concentrations were also, similar.

Montelukast and bronchial asthma in children: The incidence of asthma has increased substantially in many countries during the last two decades in both children and adults.¹ Previous studies have suggested that physician-diagnosed asthma occurs in 4-17% of urban Saudi children.^{26,27}

Most of the concepts regarding the pathogenesis of asthma are derived from studies performed in young adults. Obvious ethical reasons, have limited the application of invasive methods, in particular bronchoscopy, for evaluation of inflammation in airways of asthmatic children. However, from the available studies, the pathological findings of inflammation at the site of the airway in asthmatic children appears to be similar to that observed in adult patients, as suggested by studies of bronchoalveolar lavage (BAL), induced sputum, and exhaled nitric oxide (FeNO).²⁸⁻³⁰

Several randomized double blind(RCT) comparative studies in pediatric patients concerning the therapeutic efficacy of montelukast have been conducted.³¹⁻⁴² The severity of asthma was mild to moderate or persistent in these trials. Two of these studies were in patients less than

two years of age.^{31,43} The results from these studies depicted significant improvements in multiple parameters of asthma with montelukast when compared to placebo in the context of day and overnight asthma symptoms. There was a significant improvement in forced expiratory volume in first second (FEV1) from baseline for montelukast group as compared to the placebo group and it was found to have a positive effect on lung function, reduction of airway inflammation and symptoms scores in very young children with early childhood asthma. A study by Bisgaard et al showed that montelukast effectively reduced viral-induced asthma exacerbations in 2-5 years old patients with intermittent asthma over 12 months of treatments and also delayed the median time to first exacerbation by approximately 2 months.³² Two RCTs demonstrated that it have a beneficial effect on lung function, airway inflammation, and symptoms scores in very young children with early childhood asthma.^{31,42} Strauch et al studied asthmatic children aged 6 to 14 years, who had been taking inhaled corticosteroids (400-800mic/day budesonide) regularly for at least 12 weeks. They were randomized to receive additional treatment with either montelukast (5mg orally, once daily) or placebo over a 4-week period. It was concluded that the add-on treatment with montelukast can suppress sputum ECP in children with steroid-dependent asthma, while at the same time an improvement in quality of life items occurred.³⁵ Nitric oxide in exhaled air (FeNO) is increased in patients with asthma and correlates with asthma severity, sputum eosinophils, methacholine reactivity, as well as peak flow variability and this is, probably, related to airway inflammation. Although the precise mechanism that links nitric oxide with airway inflammation remains to be elucidated, it has been utilized as a useful marker of asthma control, and as a noninvasive measure of the effect of pharmacologic intervention on airway inflammation. FeNO was measured during single-breath exhalation. There was a significant reduction in FeNO in the montelukast arm.⁴⁰

Recent published RCTs concluded that montelukast was comparable to fluticasone in increasing the percentage of asthma rescue-free days. Montelukast was also found to be advantageous over inhaled corticosteroids.^{41,42} Children with low pulmonary function or high levels of inflammatory markers had a better response to inhaled corticosteroid therapy.⁴³ Migoya et al, Adelsberg et al, found that montelukast 4mg oral granules was well tolerated over a period of the study treatment.^{11,44}

Montelukast in exercise - induced asthma: Exercise induced bronchoconstriction (EIB) occurs in 80 to 90 percent of patients with bronchial asthma. EIB is especially limiting for children because it may interfere with activities important for physical and social development. The cause of EIB is incompletely understood. However; airway cooling and drying are hypothesized to stimulate the release of inflammatory mediators such as the cysteinyl leukotrienes (leukotriene C₄, D₄ and E₄) which are excreted in urine as leukotriene E (a stable metabolite of leukotriene C₄ and D₄) after exercise challenge.⁴⁵ Few long-term studies, however, exist in children with EIB. One study showed that, following 8 weeks of treatment with montelukast, asthma symptoms score and FEV₁ significantly improved in patients with EIB.⁴⁶ Peroni et al found that Montelukast attenuate the immediate and late phase responses to exercise challenge in asthmatic children and the timing of drug administration was crucial and the maximum protective effect of montelukast was observed after 12 hours of administration.⁴⁷ A recent study, also, showed that montelukast was effective in EIB when given either in the morning or in the evening.⁴⁸

Does montelukast have a role in acute asthma in children? Corticosteroids have become the standard of care in the emergency department for the management of acute asthma. Although corticosteroids are believed to be the most potent anti-inflammatory agents available, they do not suppress some inflammatory processes such as leukotrienes release.⁴⁹

Studies are presently exploring the efficacy of intravenous montelukast in the management of moderate-severe acute asthma in adults but no study was done to evaluate its effects in pediatric patients. LTRAs may be more effective in acute severe asthma in adult studies, since cysteinyl leukotriene concentrations are significantly higher in subjects with acute severe asthma than in patients with milder asthma.^{50,51} Montelukast has the potential to be a new adjunct in the therapy of acute asthma in adults but pediatric studies are still lacking.

Montelukast for sleep disordered breathing in children: Obstructive sleep apnea (OSA) is a common and highly prevalent disorder in the pediatric age range, affecting 2-3% of all children.⁵² This disorder is usually due, at least in part, to adenotonsillar hypertrophy.^{52,53} If left untreated OSA, can result in serious morbidity, primarily affecting the neurobehavioral and cardiovascular systems.⁵⁴ Thus, adenotonsillectomy is currently the most common treatment for children with OSA. A link between obstructive sleep apnea and airway inflammation has been demonstrated in children with OSA having significantly higher expression of the leukotriene (LT) 1 and 2 receptors and higher concentration of LT C₄, LT E₄, and LT B₄ in adenotonsillar tissues than children with recurrent rhinitis who have no OSA. This explains the efficacy of treatment of OSA with montelukast, a LTI receptor antagonist, alone or in combination with corticosteroids.⁵⁵

Montelukast for respiratory syncytial viral bronchiolitis: RSV bronchiolitis is the most common cause of pneumonia and bronchiolitis in infants and is a major health burden worldwide.⁵⁶ The steep rise during winter months of hospital admissions for pneumonia and bronchiolitis in infants and young toddlers is the landmark of RSV. In Saudi Arabia, RSV appears in November and the seasonal peak occurs during January and February.⁵⁶ RSV bronchiolitis is commonly followed by reactive airway disease which is characterized by recurrent wheeze and other asthma-like symptoms

which can persist for up to 11 years.⁵⁷ The β_2 -adrenergic agonists and corticosteroids, whether oral or inhaled, have little to offer to the acute course of the illness.⁵⁸ The beneficial effects of antiviral or anti-inflammatory therapy for lower respiratory tract infections caused by RSV is still debatable. A Study on the effect of inhaled glucocorticoids found that may have a prolonged effect on subsequent asthmatic symptoms after termination of treatment in children with recurrent obstructive episodes after acute bronchiolitis.⁵⁹ Studies had shown that cysteinyl leukotrienes produced by both bronchial epithelial cells and macrophages, are increased in the wheezing disease induced by RSV.^{60,61} Bisgaard et al⁶² recruited infants with RSV bronchiolitis and suggested that regular LTR antagonists provide clinical improvements of RSV post-bronchiolitis-reactive airways disease.

Role of Montelukast in Cystic fibrosis: Cystic fibrosis (CF) is the most common autosomal recessive lethal hereditary disorder globally including Saudi.⁶³ The prognosis of the disease is substantially dependent on chronic respiratory infection and inflammation; a hallmark of CF. *Pseudomonas aeruginosa* is the dominant pathogen in patients with CF. This is a major cause of mortality and morbidity. Neutrophils are the primary effector cells responsible for the progressive deterioration of lung function. Peptido-leukotriene B4 receptor antagonists, which are new anti-inflammatory agents that block the neutrophil-dominated inflammation, may have the potential for long-term use. Schmitt-Grohe´ et al have shown that montelukast reduces eosinophilic inflammation in cystic fibrosis (CF).⁶⁴

CONCLUSIONS

Montelukast is indicated for the prophylaxis of chronic asthma in adults and children. It may be considered for use as first-line therapy in patients with mild persistent asthma or for additional control in patients who are still symptomatic while receiving treatment with inhaled corticosteroids. Moreover, treatment with montelukast can provide additional

control of symptoms during exercise, but inhaled beta 2-agonists remain the first-line drugs for prophylaxis and treatment. Research, however, has shown that montelukast, although efficacious as compared to placebo but is not superior to inhaled steroids.

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