Leukotriene receptor antagonists in childhood asthma

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Leukotriene receptor antagonists (LTRAs) may provide a satisfactory alternative to sodium cromoglycate and to low dose inhaled corticosteroids in children with frequent episodic and mild persistent asthma.

Asthma is now the most common chronic disease of childhood. Much of this disease is frequent episodic virus-triggered and mild persistent disease. These two patterns of asthma primarily involve children between the ages of 2 and 7 years, with children older than 7 years more represented in moderate to severe persistent disease.

Leukotrienes in asthma

Asthma is an inflammatory disease of the airways that involves a number of inter-related inflammatory cascades. For 40 years, 'slow reacting substance of anaphylaxis' (SRSA) has been known to produce acute bronchoconstriction and mucous hypersecretion in patients with asthma. SRSA is now known to be the cysteinyl leukotrienes. These are highly reactive metabolites of arachidonic acid that are released from activated eosinophils and mast cells in both immediate and delayed airway inflammation in asthma. The cysteinyl leukotrienes bind to target receptors in the bronchial smooth muscle and airway mucous glands, resulting in acute bronchoconstriction and hypersecretion. This particular inflammatory pathway appears not to be impacted in a major way by either oral or inhaled corticosteroid therapy. Moreover, this pathway may play a prominent part in the airway inflammation of a significant number of asthmatic children.

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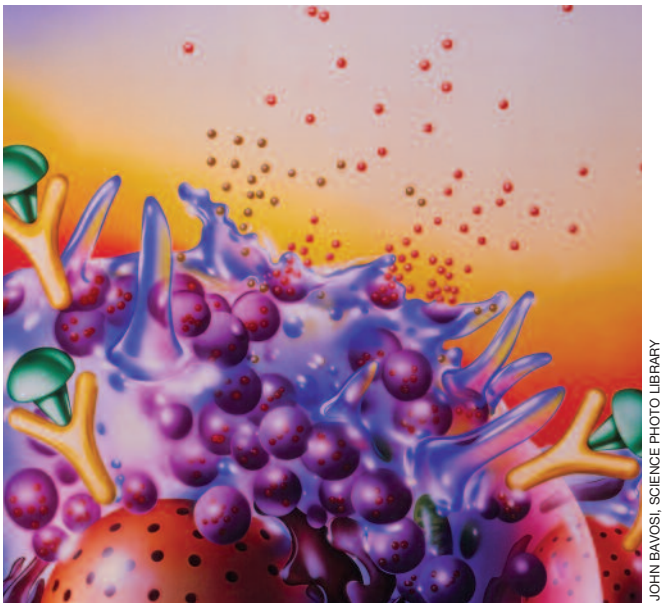

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Figure. Activated mast cell releases mediators of inflammation.

Leukotriene receptor antagonists

Leukotriene receptor antagonists (LTRAs) are a relatively new class of asthma medications that block the receptor sites for cysteinyl leukotrienes in the airways. The only available LTRA in Australia is montelukast (Singulair), a specific blocker of cysteinyl leukotriene receptor 1.

LTRAs appear to have both anti-inflammatory and anti-bronchoconstrictive properties in children with asthma. They appear to be more effective in some children than in others, suggesting that the importance of the inflammatory pathway associated with leukotrienes is not equal in all children with asthma.

Efficacy

In many studies, LTRAs have been shown to be effective in children between the ages of 2 and 14 years with frequent episodic asthma and mild persistent asthma. Compared with placebo, LTRAs lead to improvement in the control of asthma, and they also appear to confer an anti-inflammatory effect similar to a small dose of inhaled corticosteroid (50 to 100 μg budesonide equivalent). In children with frequent episodic or mild persistent disease, there is also a modest reduction in exercise induced asthma. Studies of infants and children with moderate to severe persistent asthma using LTRAs in combination with inhaled corticosteroid therapy have shown a significant steroid sparing effect in some cases.

The therapeutic effect of the LTRAs is thought to be rapid, often within 24 to 48 hours following administration. A current study is investigating the efficacy of LTRAs as acute therapy

in occasional episodic asthma but these results are not yet at hand.

Since not only asthma but also allergic rhinitis and eczema may involve the release of cysteinyl leukotrienes, it is possible that LTRAs may be of some benefit in these other conditions, but there is little information in the literature.

Patient selection

The most obvious therapeutic niches for these agents in childhood asthma are in that significant proportion of children with troublesome frequent episodic disease and in those with mild persistent disease, particularly exercise related symptoms. Children with either of these patterns of asthma are generally aged less than 7 years. Previously, these children would have used sodium cromoglycate (Intal, Intal Forte), nedocromil sodium (Tilade) or perhaps a small dose of inhaled corticosteroid for control of their disease on a seasonal or a perennial basis.

The use of sodium cromoglycate has been diminishing, mainly because of the need for three or four times daily dosing and difficulties with the new non-CFC propellant. Nedocromil sodium has also been poorly tolerated, predominantly because of its taste. Meanwhile, parental concern regarding the use of inhaled corticosteroids in children with mild asthma is familiar to all of us and frequently leads to poor adherence to treatment.

In many cases, a single daily dosage of a palatable, chewable tablet containing no corticosteroid and with a good safety profile is preferable to the above preventive therapies. Although no direct comparisons of efficacy exist between sodium cromoglycate and LTRAs, patient preference and improved compliance with LTRAs has been well documented.

Dosing guidelines

Montelukast sodium is licensed for use in children aged from 2 to 14 years and for adults (over 14 years of age). Presentation is in 4 mg chewable tablets for children aged 2 to 5 years, 5 mg chewable tablets for children 6 to 14 years, and 10 mg nonchewable tablets for those over the age of 14 years. The medication is taken once daily, usually at bedtime, and its efficacy is not affected by food. There is not an exact bioequivalence between the 5 mg and the 10 mg tablet because of differing release characteristics of each formulation.

Prescribing restrictions

Montelukast is available as a private prescription (but is expensive) or as an authority PBS prescription. The approved indications for authority relate to the 4 mg and 5 mg chewable tablets for children aged 2 to 14 years, and require that the medication is used as a first line preventer and only as a single medication. There is no allowance for combination with inhaled corticosteroids, although this may be useful in more severe chronic asthma as a steroid sparing strategy.

The authority restrictions and the expense clearly place significant limitations on the therapeutic use of LTRAs, particularly in more severe disease. At the present time, montelukast is targeted as an alternative to sodium cromoglycate.

Drug interactions

Although in high doses (16 times therapeutic) montelukast competitively induces the cytochrome P450 system, at normal doses this is not a consideration. Compatibility with oral and inhaled corticosteroids and with bronchodilators has been clearly demonstrated.

Adverse reactions

Adverse reactions to montelukast tend to be mild and self-limiting and usually do not require discontinuation of therapy. In most studies, the overall incidence of adverse events is not significantly higher than that seen with placebo. Thirst, headache and gastrointestinal upsets, such as nausea and abdominal pain, may occur occasionally but are usually mild. In rare cases, in adults, particularly those concurrently taking high doses of oral corticosteroids, a systemic eosinophilic syndrome (Churg–Strauss syndrome) may occur, but whether this relates to the medication directly or to the concomitant reduction of the corticosteroid doses is unclear.

Summary

Montelukast sodium appears to have a place in the management of mild persistent and frequent episodic asthma, particularly in those children with significant exercise induced asthma, although short acting salbutamol may still be needed. The drug's benefit, however, is not universal and an alternative preventer should be considered if children have not improved using montelukast within a four to eight week period.

The single daily dosage and favourable safety profile make montelukast an appealing alternative to currently available prophylaxis for mild disease. However, authority prescribing limitations and expense do not allow it to be widely used as a steroid sparing agent in more significant persistent disease at this time. Likewise, back titration to montelukast during low risk seasons in children on inhaled corticosteroids is difficult as the two medications are not permitted on authority to be used simultaneously. It is hoped that a future broadening of the prescribing limitations will lead to more widespread use of LTRAs, and hence their full therapeutic potential can be explored. MT