THORAX

Editorials

Leukotrienes and aspirin induced asthma

Leukotrienes are lipid mediators formed from the oxidative metabolism of arachidonic acid via the 5-lipoxygenase enzyme cascade.[1] The sulphidopeptide leukotrienes comprise leukotriene (LT) C_4, and LTD_4, and LTE_4. These molecules are responsible for the activity previously recognised as slow reacting substance of anaphylaxis.

The sulphidopeptide leukotrienes are potent constrictors of the smooth muscle of the airways,[2] and may also contribute to the bronchial hyperresponsiveness characteristic of asthma.[3] Lam *et al* used fast atom bombardment mass spectroscopy to analyse bronchoalveolar lavage fluid for the presence of leukotrienes.[4] LTE_4 was the predominant leukotriene recovered, although LTD_4 was also identified. Significant quantities of LTC_4 have been detected by radioimmunoassay in the bronchoalveolar lavage fluid of symptomatic asthmatic patients compared with normal control subjects,[5] and increased quantities of leukotrienes have been detected in bronchoalveolar lavage fluid after local endobronchial challenge with allergen.[6]

In man LTC_4 is converted enzymatically in the blood to LTD_4 and LTE_4 which is excreted in the urine. After infusion of radiolabelled LTC_4 12–20% appears in the urine, of which 4–6% of the total infused dose is seen as LTE_4.[7] Measurement of the urinary LTE_4 concentration may therefore act as a marker for the systemic release of the sulphidopeptide leukotrienes. Urinary LTE_4 levels are increased during acute severe asthma,[8] following allergen challenge,[8 9] and in aspirin induced asthmatic responses.[10]

There is compelling evidence that aspirin induced asthma is mediated by 5-lipoxygenase pathway products and, in particular, by the sulphidopeptide leukotrienes. A proportion of patients with asthma are intolerant of aspirin.[11] In these individuals aspirin ingestion is followed by the onset of wheezing, rhinitis, urticaria, or anaphylaxis. These symptoms may occur singly or in combination. It has been suggested that aspirin induced asthma may relate to the inhibition of cyclooxygenase, resulting in the "shunting" of arachidonate metabolism to the 5-lipoxygenase pathway. This, in turn, will lead to the increased generation of leukotrienes in susceptible individuals.[12] While there is increasing evidence for the enhanced generation of leukotrienes in aspirin induced asthmatic responses, the evidence that this is a result of shunting of arachidonic acid metabolism from the cyclooxygenase to the 5-lipoxygenase pathway is lacking.

Ferreri *et al* measured mediator release in the nasal lavage fluids of aspirin sensitive asthmatic patients after aspirin challenge.[13] The release of LTC_4 into nasal secretions was noted but there was no decrease in the levels of prostaglandin E_2 (PGE_2). Urinary levels of LTE_4 have also been measured before and after aspirin provocation in patients with aspirin sensitivity. The baseline LTE_4 levels are significantly raised in asthmatic patients with aspirin sensitivity compared with those who are tolerant of aspirin.[14] Following provocation with oral aspirin there is a further fourfold increase in urinary LTE_4 excretion in aspirin sensitive individuals.[14–17] Urinary concentrations of the thromboxane A_2 metabolite, 11-dehydrothromboxane B_2, were unchanged.[17] Increased release of LTE_4 into the urine of patients with aspirin sensitivity is also seen after asthma induced by lysine-aspirin in susceptible subjects,[17 18] suggesting a pulmonary source of the leukotrienes. These cumulative observations strongly support the view that there is an upregulation of arachidonate metabolism in aspirin sensitive patients resulting in the augmented production of the sulphidopeptide leukotrienes.

If sulphidopeptide leukotrienes play a significant part in the pathogenesis of asthma, then attempts to inhibit their generation or antagonise their action should be of some benefit. A number of selective leukotriene receptor antagonists and 5-lipoxygenase inhibitors have now been developed and many are undergoing clinical trials in patients with disease. These assessments are still in their early stages, but several studies have shown bronchodilatation after administration of leukotriene antagonists and 5-lipoxygenase inhibitors in asthmatic patients but not in normal subjects, suggesting that leukotrienes may contribute to the resting airways tone in asthma.[19–22] Furthermore, leukotriene receptor antagonists inhibit asthmatic responses induced by aspirin,[23 24] exercise,[25 26] and allergens.[27 28] In one study leukotriene receptor antagonism reduced allergen induced enhancement in bronchial hyperresponsiveness.[27] Zileuton, a novel 5-lipoxygenase inhibitor, protected against asthma induced by hyperventilation[29] and attenuated aspirin induced asthmatic responses.[30]

Only limited data are available on the effects of leukotriene antagonism and 5-lipoxygenase inhibitors in chronic asthma. Preliminary evidence suggests that these new classes of drugs produce a significant mild improvement in airways function and a reduction in symptoms.[31–35]

The interesting study reported by Dahlén and colleagues in this issue of *Thorax* (pp 1205–10) in aspirin intolerant patients[36] extends the previous observations on the bronchodilating properties of sulphidopeptide leukotriene antagonists. Eight subjects were studied on two separate days, when they received 825 mg MK-0679 or placebo, orally, in a double blind randomised crossover study. MK-0679 elicited bronchodilatation which lasted for at least nine hours. The maximal improvement in FEV_1 ranged from 5% to 34% above predrug baseline values, and the degree of bronchodilatation correlated with the severity of asthma and aspirin sensitivity. These findings provide further evidence that leukotriene dependent tone may be an important component of the persistent airway obstruction in asthmatic patients. In view of the clinical heterogeneity of bronchial asthma, it would be interesting to define a subgroup of individuals who respond particularly well to leukotriene antagonism. In this regard it would be informative to

evaluate whether there is a correlation between the bronchodilating effect of MK-0679 and basal urinary LTE_4 concentrations. Although there is strong evidence for the involvement of leukotrienes in aspirin induced asthma, it is not possible to establish from the study by Dahlén *et al* whether it was the severity of asthma or the degree of aspirin sensitivity which was the critical determinant of the bronchodilator response to MK-0679. Nevertheless, the present findings support the view that leukotriene receptor antagonists offer promise in the treatment of patients with asthma; patients with aspirin induced asthma may be particularly helped by these drugs. The recent observation that inhalation of LTE_4 results in eosinophilic accumulation in asthmatic airways[37] has suggested that this new class of therapeutic agents may have anti-inflammatory and steroid-sparing potential.

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