

EDITORIAL

Aspirin-induced early and late asthmatic responses

Aspirin-induced asthma refers to the development of bronchoconstriction in asthmatic individuals following ingestion of aspirin. These patients constitute approximately 8-20% of the asthmatic population [1,2]. Since Samter and Biers [3] published their work in 1968 on aspirin-sensitive reactions, there has been much interest in the mechanisms of this clinical problem. Substantial evidence now exists for the involvement of cysteinyl leukotrienes as mediators of aspirin-induced bronchoconstrictor responses.

Cysteinyl leukotrienes are derived from arachidonic acid via the 5-lipoxygenase pathway. Arachidonic acid released from membrane phospholipids by the action of phospholipase A₂ can be metabolized by the lipoxygenase or the cyclo-oxygenase pathway. The 5-lipoxygenase pathway results in the generation of cysteinyl leukotrienes and leukotriene B₄, whereas the cyclo-oxygenase pathway produces prostaglandins and thromboxane A₂. Aspirin and non-steroidal anti-inflammatory drugs inhibit the cyclo-oxygenase pathway. Cyclo-oxygenase inhibition is an essential property of drugs which precipitate asthmatic responses in patients who are intolerant of aspirin [4].

Provocation with aspirin, either orally or by inhalation of lysine-aspirin solutions produce airflow obstruction in intolerant individuals. The bronchoconstrictor response is accompanied by the release of cysteinyl leukotrienes into the urine [5,6], in nasal lavage [7,8] or bronchoalveolar lavage fluid [9]. No clinical symptoms or abnormal release of urinary cysteinyl leukotrienes are detectable in asthmatic individuals who are aspirin-tolerant [5]. The efficacy of leukotriene receptor antagonists [10,11] and more recently 5-lipoxygenase inhibitors [12,13] in blocking the asthmatic response following aspirin provocation in sensitive individuals adds compelling support to the critical role of these mediators in aspirin-sensitive asthma.

Apart from aspirin-induced asthma, cysteinyl leukotrienes are now believed to play a role in clinical asthma [14] and in asthma provoked by allergen [15,16] and exercise [17]. Allergen challenge in sensitized atopic subjects results in an immediate bronchoconstrictor response within minutes. This is followed by recovery and in approximately half the subjects, a non-immediate and more prolonged phase of airflow limitation develops. The finding that there is an increased excretion of cysteinyl leukotrienes in the urine of patients during the acute bronchoconstrictor responses following allergen challenge [18] and the finding that cysteinyl leukotriene receptor antagonists inhibit the non-immediate

asthmatic response [19,20], adds strong support for the role of cysteinyl leukotrienes in this reaction.

If cysteinyl leukotrienes have a role in inducing the non-immediate phase bronchoconstrictor reaction in allergen challenge, one may expect the development of late-phase responses following other types of provocation which lead to the release of cysteinyl leukotrienes. In this issue Park *et al.* report that non-immediate decrements in FEV₁ occur several hours following lysine aspirin challenge [21], adding further support to the view that cysteinyl leukotrienes predispose to the development of a non-immediate asthmatic reaction. Inhalation of cysteinyl leukotrienes can also produce a mild increase in bronchial hyperresponsiveness [22]. It is therefore interesting to note that the development of bronchial hyperresponsiveness is also a feature following both allergen [23] and lysine aspirin provocation [24]. These results are different from those reported by Phillips *et al.* who were unable to document a late-phase reaction [25]. The reason for the discordance is not known, but may be related to patient selection. In both allergen and aspirin challenge, only a certain proportion of individuals develop non-immediate reactions.

If leukotrienes have a role in inducing non-immediate responses following allergen and aspirin challenges, it is notable that there are no reports of the development of late-phase reactions following inhalation of cysteinyl leukotrienes themselves. There may be several explanations. These include the possibility that late-phase responses have not been studied in any detail following leukotriene inhalation. Whilst this cannot be excluded, it seems unlikely. If non-immediate reactions occurred, they must have been extremely mild, since many centres which have participated in such work have never observed any severe bronchoconstrictor sequelae many hours after leukotriene inhalation. Secondly, lack of documented late-phase responses after leukotriene inhalation may be related to the small dose of leukotriene inhaled, which is limited by the magnitude of the early-phase response. Leukotriene inhalation is usually stopped when there is only a minor decrease in lung function in the immediate phase, such as a 35% decrease in specific airways conductance. This dose may be insufficient to induce a non-immediate reaction. Finally, leukotriene release in the airways following allergen and aspirin challenge may induce a cascade of events resulting in the development of the late-phase response, but these events cannot be duplicated simply by the deposition of leukotrienes on the surface of the

airways. The mechanism by which cysteinyl leukotrienes provoke a non-immediate reaction may be due to their ability to recruit eosinophils into the airways [26].

Lysine-aspirin has been used as an alternative to oral aspirin as a bronchoprovocation test for the screening of aspirin sensitivity. The advantages of using lysine-aspirin stem from the ability to use it exclusively for provoking either a nasal or a bronchial reaction. The bronchoconstriction induced by lysine-aspirin is reproducible to within a single doubling concentration [25]. During screening of 22 asthmatics suspected of aspirin-sensitive asthma Dahlen *et al.* [27] found that inhaled lysine-aspirin had the same sensitivity as oral aspirin challenge, with a quicker reaction time of 20 min vs 60 min for oral aspirin. The symptoms experienced by the aspirin-sensitive subjects were limited to the airways and therefore easily reversed by bronchodilators as opposed to the systemic symptoms exhibited during oral aspirin challenge. The specificity was similar between oral and lysine-aspirin provocation with none of a control group of 19 asthmatics tolerant to aspirin responding to lysine-aspirin. The present data emphasizes the need to address the safety of lysine-aspirin inhalation challenges. Clearly, the period of observation following inhalation challenge with these solutions for research and for diagnosis of aspirin sensitivity must now be carefully re-evaluated.

Acknowledgments

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References

- McDonald JR, Mathison DA, Stevenson DD. Aspirin intolerance in asthma, detection by oral challenge. *J Allergy Clin Immunol* 1972; 50:198–204.
- Spector SL, Wangaard CH, Farr RS. Aspirin and concomitant idiosyncracies in adult asthmatic patients. *J Allergy Clin Immunol* 1979; 64:500–6.
- Samter M, Biers RF. Intolerance to aspirin: Clinical studies and consideration of its pathogenesis. *Ann Intern Med* 1968; 6:975–83.
- Szczeklik A, Gryglewski RJ, Czerniawska-Mysik G. Relationship of inhibition of prostaglandin biosynthesis by analgesics to asthma attacks in aspirin-sensitive patients. *Br Med J* 1975; 1:67–9.
- Christie PE, Tagari P, Ford-Hutchinson AW *et al.* Urinary leukotriene E₄ concentrations increase after aspirin challenge in aspirin-sensitive asthmatic subjects. *Am Rev Respir Dis* 1991; 143:1025–9.
- Christie PE, Tagari P, Ford-Hutchinson AW *et al.* Urinary leukotriene E₄ after lysine-aspirin inhalation in asthmatic subjects. *Am Rev Respir Dis* 1992; 146:1531–4.
- Ferreri NR, Howland WC, Stevenson DD, Spiegelberg ML. Release of leukotrienes, prostaglandins and histamine into nasal secretions of aspirin-sensitive asthmatics during reactions to aspirin. *Am Rev Respir Dis* 1988; 137:847–54.
- Ortolani C, Mirone C, Fontana A *et al.* Study of mediators of anaphylaxis in nasal wash fluids after aspirin and sodium meta-bisulphite nasal provocation in intolerant rhinitic patients. *Ann Allergy* 1987; 59:106–12.
- Sladek K, Dworski R, Soja J *et al.* Eicosanoids in bronchoalveolar lavage fluid of aspirin-intolerant patients with asthma after aspirin challenge. *Am J Resp Crit Care Med* 1994; 149:940–6.
- Christie PE, Smith CM, Lee TH. The potent and selective sulphidopeptide leukotriene antagonist SK&F 104353, inhibits aspirin-induced asthma. *Am Rev Respir Dis* 1991; 144:957–8.
- Dahlén B, Kumlin M, Margolskee DJ *et al.* The leukotriene-receptor antagonist MK-0679 blocks obstruction induced by inhaled lysine-aspirin in aspirin-sensitive asthmatics. *Eur Respir J* 1993; 6:1018–26.
- Israel E, Fischer AR, Rosenberg MA *et al.* The pivotal role of 5 lipoxygenase-products in the reaction of aspirin-sensitive asthmatics to aspirin. *Am Rev Respir Dis* 1993; 148:1447–51.
- Nasser SMS, Bell GS, Foster S *et al.* Effect of the 5-lipoxygenase inhibitor ZD2138 on aspirin-induced asthma. *Thorax* 1994; 49:749–56.
- Drazen JM, O'Brien J, Sparrow D *et al.* Recovery of leukotriene E₄ from the urine of patients with airway obstruction. *Am Rev Respir Dis* 1992; 146:104–8.
- Taylor GW, Black P, Turner N *et al.* Urinary LTE₄ after antigen challenge and in acute asthma and allergic rhinitis. *Lancet* 1989; 8638:584–8.
- Smith CM, Hawksworth RJ, Thien FCK, Christie PE, Lee TH. Urinary leukotriene E₄ in bronchial asthma. *Eur Respir J* 1992; 5:693–9.
- Manning PJ, Watson RM, Margolskee DJ *et al.* Inhibition of exercise-induced bronchoconstriction by MK-571, a potent leukotriene D₄ receptor antagonist. *N Engl J Med* 1990; 323:1736–9.
- Westcott JY, Smith HR, Wenzel SE *et al.* Urinary leukotriene E₄ in patients with asthma. *Am Rev Respir Dis* 1991; 143:1322–8.
- Taylor IK, O'Shaughnessy KM, Fuller RW, Dollery CT. Effect of cysteinyl leukotriene receptor antagonist ICI 204,219 on allergen-induced bronchoconstriction and airway hyperreactivity in atopic subjects. *Lancet* 1991; 337:690–4.
- Rasmussen JB, Eriksson L-O, Tagari P, Stahl EG, Andersson K-E. Reduced nonspecific bronchial reactivity and decreased airway response to antigen challenge in atopic asthmatic patients treated with the inhaled leukotriene D₄ antagonist, L648,051. *Allergy* 1992; 47:604–9.
- Park HS. Early and late onset asthmatic responses following lysine aspirin inhalation in aspirin-sensitive asthmatic patients. *Clin Exp Allergy* 1994; 24:38–40.
- O'Hickey SP, Hawksworth RJ, Fong CV *et al.* Leuko-

- trienes C4, D4 and E4 enhance histamine responsiveness in asthmatic airways. *Am Rev Respir Dis* 1991; 144:1053-7.
- 23 Cartier A, Thompson NC, Frith PA, Roberts R, Hargreave FE. Allergen-induced increase in bronchial responsiveness to histamine: relationship to the late asthmatic response and change in airway caliber. *J Allergy Clin Immunol* 1982; 70:170-5.
- 24 Melillo G, Padovano A, Masi C, Melillo E, Cocco G. Aspirin induced asthma and bronchial hyperresponsiveness. *Allergie et Immunologie* 1991; 23: 423-7.
- 25 Phillips GD, Foord R, Holgate ST. Inhaled lysin-aspirin as a bronchoprovocation procedure in aspirin-sensitive asthma: Its repeatability, absence of a late-phase reaction and the role of histamine. *J Allergy Clin Immunol* 1989; 84:232-41.
- 26 Laitinen LA, Laitinen A, Haahtela T, Vilkkla V, Spur BW, Lee TH. Leukotriene E4 and granulocytic infiltration into asthmatic airways. *Lancet* 1993; 341:989-90.
- 27 Dahlen B, Zetterstrom O. Comparison of bronchial and per oral provocation with aspirin in aspirin-sensitive asthmatics. *Eur Respir J* 1990; 3:527-34.

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