

EDITORIAL

Aspirin sensitive asthma

Introduction

Aspirin intolerance is marked by the development of symptoms including bronchospasm, nasooocular symptoms, urticaria, angioedema and anaphylaxis. These symptoms may occur in isolation or in any combination [1]. The prevalence of aspirin sensitivity in asthma is estimated to be between 10-30%. Symptoms generally appear after the third decade of life and are frequently associated with chronic rhinitis, sinusitis and nasal polyposis. These patients are typically non-atopic, and often have persistent asthma, requiring regular treatment with either inhaled or oral corticosteroids [2,3]. A genetic association with HLA-DQw2 has been described, although this has yet to be confirmed [4].

Diagnosis

Diagnosis based on history may be confirmed by challenge with either oral aspirin, or inhaled lysine aspirin [3,5]. This is only advisable if the baseline FEV₁ is greater than 70% of the predicted normal value. For oral aspirin challenge, patients ingest 10 mg aspirin and measurements of FEV₁ are made at 15 minute intervals for 2 hr. If the fall in FEV₁ is less than 15% from baseline then incremental doses of aspirin (30 mg, 60 mg, 120 mg, 300 mg and 600 mg) are given at 2 hr intervals until the FEV₁ has fallen by more than 15% from the baseline value, or 600 mg of aspirin has been tolerated. Bronchospasm typically develops 30-45 min following ingestion and may be accompanied by systemic side-effects. Ideally, a placebo challenge should also be performed at least 1 week later.

An alternative method for confirming aspirin sensitivity is to challenge the patient with inhaled lysine-aspirin. Following baseline measurements of FEV₁, 1 ml of a nebulized solution of 1.25 mg/ml lysine-aspirin is inhaled. Measurements of FEV₁ are made at 15 min intervals for 30 min following inhalation. If the fall in FEV₁ is less than 10%, doubling concentrations are inhaled at 30 min intervals until a greater than 10% fall is induced or the maximum concentration of 25 mg/ml has been tolerated. Onset of bronchospasm occurs within 30 min and is associated with fewer systemic side-effects than challenge with oral aspirin. More recently Schapowal *et al.* have used nasal challenge with lysine-aspirin as an alternative technique for detecting aspirin sensitivity [6]. Lysine-aspirin at doses described above are applied to the inferior turbinate and nasal flow measurements made with anterior rhinomanometry at 10, 20 and 30 min. Threshold

doses of lysine-aspirin for nasal challenge are 20-fold lower than those for bronchial challenge and 1000-fold lower than for oral provocation. Nasal provocation is not accompanied by systemic side-effects or bronchopulmonary reactions and may therefore be a preferable technique to use in patients where poor lung function precludes oral or inhalation challenge with aspirin.

Patients can be desensitized to aspirin by the administration of oral aspirin given in incremental doses provided continuous aspirin is tolerated with no systemic side-effects [7-9]. In some cases this may lead to improvement of asthma and rhinitis, and may be worth considering as a form of therapy in aspirin sensitive asthmatics. The patient is given the dose which has previously been shown to induce a 15% fall in FEV₁, and measurements of FEV₁ are made at 15 min intervals up to 2 hr as previously described. On succeeding days the protocol is repeated starting with the maximal dose of aspirin tolerated the previous day and progressing with doubling doses until the patient is able to tolerate 600 mg aspirin with no symptoms. Tolerance to aspirin continues as long as patients continue to take 650 mg aspirin and do not discontinue this for longer than 48 hr. It should be noted that both aspirin challenge and desensitization to aspirin can be hazardous. The procedure should be performed by experienced personnel, skilled in resuscitation techniques, with full resuscitation equipment at hand.

Mechanism

The mechanism of aspirin sensitivity is unknown. Patients with aspirin sensitivity are also intolerant of other non-steroidal anti-inflammatory drugs (NSAIDs), and the capacity of these agents to provoke asthma is related to their potencies as inhibitors of cyclo-oxygenase [10]. As well as cross-reactivity to other NSAIDs, there is also cross-tolerance to NSAIDs following successful desensitization. The NSAIDs are a class of drugs with diverse chemical structures, but which share the property of cyclo-oxygenase inhibition. Such diversity of chemical structure makes immunological cross-reactivity unlikely, and IgE dependent mechanisms unlikely to explain aspirin sensitivity. It is inhibition of cyclo-oxygenase that appears to be central to the mechanism of aspirin intolerance.

Arachidonic acid released from cell membrane phospholipids is metabolized by the cyclo-oxygenase pathway to the prostaglandins and thromboxane A₂ or by the 5-lipoxygenase pathway to leukotrienes [11]. The sulphido-

peptide leukotrienes LTC₄, LTD₄ and LTE₄ are potent spasmogens for non-vascular smooth muscle and comprise the activity previously recognized as the slow-reacting substance of anaphylaxis, or SRS-A [12–15]. It has been suggested that inhibition of cyclo-oxygenase by aspirin and other cyclo-oxygenase inhibitors could divert the metabolism of arachidonic acid from the cyclo-oxygenase pathway to the 5-lipoxygenase pathway, thereby increasing the generation of leukotrienes.

Although there is considerable evidence to suggest that cyclo-oxygenase inhibition increases synthesis of LTC₄ in aspirin-sensitive asthmatic subjects, there is little evidence to suggest that this occurs as a result of diversion from the cyclo-oxygenase pathway at the relatively low doses of aspirin required to induce the response.

The observation that pre-treatment of sensitized human airways *in vitro* with indomethacin results in increased generation of LTC₄ following IgE-dependent challenge supports the theory that cyclo-oxygenase inhibition enhances increased leukotriene release [16]. Similarly, in the guinea-pig model of antigen-induced anaphylaxis, pretreatment of animals with indomethacin resulted in an augmentation of the pulmonary mechanical response to intravenous antigen which was accompanied by an increased generation of LTB₄ [17].

Leukotriene release *in vivo* in man

Although the relevance of these findings in the absence of aspirin intolerance is questionable, studies in humans with aspirin sensitivity also indicate that increased generation of leukotrienes may contribute to the mechanism of aspirin-induced asthma. Ferreri *et al.* demonstrated that in patients who developed naso-ocular symptoms following ingestion of aspirin, concentrations of both LTC₄ and histamine from nasal lavage fluid increased significantly from baseline values, whilst levels of LTB₄ remained unchanged [18]. It is interesting to note that there was no decrease in PGE₂ at the low doses of aspirin required to induce the response. After desensitization, challenge with 650 mg of aspirin no longer resulted in an increase in concentrations of LTC₄ and histamine in nasal lavage fluid, although concentrations of PGE₂ decreased by a mean of 75% at this higher dose. Thus naso-ocular symptoms were associated with increased production of LTC₄ locally, but were unrelated to PGE₂ synthesis. Intranasal challenge with lysine-aspirin is also associated with increased concentrations of histamine and LTC₄ in aspirin-sensitive subjects, but not in aspirin-tolerant subjects [19].

Urinary concentrations of LTE₄ have also been used to reflect systemic synthesis of LTC₄ following both oral challenge with aspirin and bronchial challenge with

inhaled lysine-aspirin. Christie *et al.* reported that ingestion of aspirin which produced a greater than 15% fall in FEV₁ was associated with a mean fourfold increase in urinary LTE₄. Placebo challenge in the same individuals, and aspirin challenge in normal subjects and asthmatic subjects tolerant of aspirin, were not associated with a change in FEV₁ or increments in urinary LTE₄ concentrations [20]. Dahlen *et al.* have also reported a significant rise in urinary LTE₄ following bronchial challenge with inhaled lysine-aspirin. Urinary concentrations of the thromboxane A₂ metabolite 11-dehydro thromboxane B₂ were unchanged [21].

Leukotriene antagonism

Christie *et al.* demonstrated recently that the potent and specific LTD₄ antagonist SKF 104353 attenuated the response to aspirin ingestion by between 43 and 74% in five of six subjects studied [22]. There was no effect of SKF 104353 in one subject. This may have been due to variability in aerosol deposition or inadequate dosage, and further studies are indicated. It is possible that the failure to completely attenuate the response was due to the fact that other mediators contribute to the bronchoconstriction induced by aspirin. In this regard, naso-ocular symptoms induced by either oral aspirin or inhaled lysine-aspirin are associated with histamine release into nasal lavage fluid. Recently, Bosso *et al.* reported that histamine and tryptase release in venous blood samples occurred in three of 14 aspirin sensitive asthmatic subjects following aspirin challenge. These three subjects experienced bronchospasm which was accompanied by gastrointestinal and/or skin reactions. No increase was seen in the remaining patients who developed bronchospasm, but did not experience extrapulmonary symptoms [23].

Abnormal arachidonate metabolism at rest

It is not clear why some individuals are intolerant of aspirin. It may relate to a fundamental abnormality in arachidonic acid metabolism, or perhaps to defective handling of cyclo-oxygenase inhibitors. There is evidence to suggest that there may be abnormal arachidonate metabolism in aspirin sensitive patients even in the absence of aspirin challenge. Christie *et al.* have reported that baseline concentrations of urinary LTE₄ are significantly higher in aspirin-sensitive asthmatics than those measured in either aspirin-tolerant asthmatic subjects or normal subjects [20]. This finding has recently been confirmed by Dahlen *et al.* [21] and Smith *et al.* [24].

It has been reported that circulating levels of PGF_{2x} are raised in subjects with aspirin-induced asthma [25,26]. However, this finding was not confirmed by Williams *et*

al. who were unable to demonstrate elevated $\text{PGF}_{2\alpha}$ in the plasma of aspirin-sensitive subjects compared with non-aspirin-sensitive asthmatics [27]. There was an increase in $\text{PGF}_{2\alpha}$ from the plasma of aspirin-sensitive subjects when aspirin was added and this was not observed in non-aspirin-sensitive asthmatics. PGE_2 levels remained unchanged in the absence or presence of aspirin in aspirin-sensitive and non-aspirin-sensitive asthmatics. They suggested that the albumin binding property of analgesic drugs was more important than cyclo-oxygenase inhibition and that prostaglandins such as $\text{PGF}_{2\alpha}$, which is highly protein bound, may be released from albumin by aspirin giving rise to aspirin-induced bronchoconstriction. However, it is difficult to explain the target organ specificity of the aspirin-induced responses using this hypothesis.

Target organ sensitivity

Altered target organ sensitivity may contribute to the mechanism of aspirin-sensitivity. Although sensitivity to inhaled histamine is the same in asthmatic patients with and without aspirin-induced asthma, Arm *et al.* reported that sensitivity to inhaled LTE_4 in a group of aspirin sensitive asthmatics was approximately 20-fold higher than in the control group of non-aspirin-sensitive asthmatic controls [28]. Following desensitization with oral aspirin, sensitivity to histamine remained unchanged, but sensitivity to LTE_4 in the aspirin-sensitive subjects was reduced such that it was no longer different from that seen in non-aspirin-sensitive asthmatics.

Orehek *et al.* studied the bronchial response to inhaled $\text{PGF}_{2\alpha}$ in patients with and without aspirin sensitive asthma and did not observe any difference in the two groups [29]. In contrast Szczeklik *et al.* investigated airway response to $\text{PGF}_{2\alpha}$ in three groups of asthmatic subjects, namely aspirin-sensitive, atopic and intrinsic respectively. Atopic patients were reactive to low doses of histamine and $\text{PGF}_{2\alpha}$ [30]. Aspirin-sensitive asthmatics had similar airway responses to histamine but tolerated higher doses of $\text{PGF}_{2\alpha}$. In patients with intrinsic asthma larger doses of histamine and $\text{PGF}_{2\alpha}$ were necessary to induce bronchoconstriction. The response to PGE_2 was similar in all three groups of asthmatics but in aspirin sensitive asthmatics peak bronchodilatation occurred at the end of PGE_2 inhalation unlike the response in the atopic and intrinsic asthmatics where bronchodilatation occurred up to 30–60 min later.

Cellular source

The cellular source for the augmented LTC_4 synthesis is unknown. It has been suggested that the increased release

of sulphidopeptide leukotrienes by cyclo-oxygenase inhibition in susceptible patients may result from an interaction between platelets and other leucocytes. Ameison *et al.* reported that *in vitro* stimulation of platelets from aspirin-sensitive subjects with various NSAIDs generated a cytotoxic supernatant and a burst of chemiluminescence associated with the release of oxygen-derived free radicals. These effects were not demonstrated in platelets taken from non-aspirin-sensitive subjects or normal subjects, nor could they be demonstrated in leucocytes from the aspirin sensitive subjects. Following aspirin desensitization, the platelets from aspirin-sensitive subjects no longer demonstrated these abnormalities [31]. Cyclo-oxygenase inhibition occurs in platelets at relatively low concentrations of NSAIDs, and it is possible that with cyclo-oxygenase inhibition, platelets of aspirin-sensitive patients may provide a stimulus for the release of LTC_4 from other leucocytes, such as mast cells and basophils. Alternatively, platelets are able to synthesize LTC_4 if the precursor LTA_4 is donated by inflammatory leucocytes such as eosinophils, neutrophils and mast cells. This might explain why cyclo-oxygenase inhibition in aspirin-sensitive subjects results in increased synthesis of LTC_4 without any evidence of decreased prostaglandin or thromboxane A_2 synthesis at the doses of aspirin required to elicit responses in these patients.

The finding that there is a functional abnormality of platelets from aspirin-sensitive asthmatics has been debated. Pearson and Suarez-Mendez reported that substantial bursts of chemiluminescence could be found in only 20% of the aspirin-sensitive asthmatic subjects they studied [32]. Similarly, Williams *et al.* reported that there was no difference in chemiluminescence in platelet suspensions from aspirin-sensitive and non-aspirin-sensitive asthmatics after aspirin challenge [25].

Nizankowska *et al.* measured 5- and 12-hydroxyeicosatetraenoic acid (5- and 12-HETE) and LTB_4 production by polymorphonuclear leucocytes in aspirin-sensitive and non-aspirin-sensitive asthmatics before and during aspirin-induced reactions [33]. The increase in 12-HETE was similar in both groups and 5-HETE and LTB_4 remained unchanged suggesting that regulation of eicosanoid metabolism was similar in aspirin-sensitive and non-aspirin-sensitive asthmatics.

The formation of leukotrienes and thromboxane B_2 from peripheral blood monocytes of aspirin-sensitive, non-aspirin-sensitive asthmatics and normal controls has been investigated to determine whether these patients have abnormalities of arachidonic acid metabolism. Although aspirin sensitive asthmatics demonstrate elevated LTB_4 and TXA_2 secretion at baseline compared to non-aspirin-sensitive asthmatic patients and normal controls, after addition of aspirin there was no difference in

the fall in TXA_2 and increase in LTB_4 from monocytes of aspirin-sensitive, non-aspirin-sensitive asthmatics and normal controls [34].

Okuda *et al.* recently demonstrated that there was no difference in PAF-induced histamine release from leucocytes of aspirin-sensitive asthmatics and atopic subjects although this was significantly higher than histamine release from leucocytes of normal control subjects [35].

Viral infection

Another mechanism that has been proposed is that chronic viral infection may lead to the production of a population of cytotoxic T lymphocytes. Since these cells are usually suppressed by PGE_2 production from alveolar macrophages, cyclo-oxygenase inhibition may prevent this regulatory mechanism [36]. However, there is no evidence to suggest that PGE_2 is suppressed at the doses of aspirin required to elicit the response.

Szczeklik and colleagues have recently measured IgG subclass concentrations in 100 patients with aspirin-induced asthma and 80 healthy control individuals [37]. The aspirin-induced asthmatic patients demonstrated a significant elevation of IgG₄ which was not related to corticosteroid therapy or serum IgE levels. The increase in IgG₄ was accompanied by a statistically significant decrease in IgG₁ concentrations. There were no significant changes of IgG₂ and IgG₃ concentrations in the aspirin-sensitive patients. The authors have suggested that the elevation of IgG₄ may be the result of chronic antigenic stimulation, possibly of viral origin, in the aspirin-sensitive individuals. It would have been informative to have compared aspirin-sensitive asthmatic subjects with asthmatic subjects who did not have aspirin sensitivity, to evaluate whether the finding is specific to aspirin sensitivity or to asthma.

Conclusion

Although it is generally accepted that inhibition of cyclo-oxygenase is central to the mechanism of aspirin-induced asthma, the mechanism remains unclear. The demonstration of increased leukotriene release, increased airway responsiveness to LTE_4 and the effect of the leukotriene receptor antagonist SKF 104353 in attenuating aspirin induced asthma suggest that the sulphidopeptide leukotrienes have a role in the pathogenesis of aspirin sensitivity and that leukotriene receptor or biosynthesis inhibitors may have a role in the treatment of aspirin sensitive asthmatics.

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