Aspirin-sensitive asthma and rhinosinusitis

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Ingestion of aspirin or an NSAID induces a reproducible reaction in sensitive patients with asthma. The reaction characteristically occurs within 30 to 120 minutes. In any individual the form of the reaction is consistent and any combination of symptoms may occur including systemic upset with facial flushing, perspiration and intense lethargy rhinorrhoea, nasal congestion, conjunctivitis and respiratory symptoms of cough and bronchospasm. Some patients experience gastrointestinal symptoms with vomiting, diarrhoea and abdominal discomfort. In more sensitive individuals, or if a large dose has been taken, a severe reaction may ensue with the development of respiratory arrest and shock.

Despite the association between aspirin-sensitivity and asthma the relationship is not causal and indeed the patient may have never taken aspirin or NSAIDs. Therefore, for patients with this profile, the term aspirin-sensitive asthma (ASA) or aspirin-intolerant asthma is preferred to aspirin-induced asthma, which should be reserved for acute reactions precipitated by aspirin ingestion and not the chronic day-to-day syndrome experienced by these patients. This is a severe subtype of asthma and often very difficult to treat.

Typically, patients complain of severe asthma frequently requiring maintenance therapy with oral corticosteroids. They usually have rhinosinusitis with prominent nasal congestion, anosmia and loss of taste resulting from intractable nasal polyposis. The nasal symptoms may be resistant to therapy and require treatment with corticosteroids together with repeated surgical removal of nasal polyps. Avoidance of NSAIDs does not have a beneficial or detrimental effect on the course of the chronic asthma or rhinosinusitis. The relationship between symptom and aspirin-sensitivity is often not appreciated by the patient or physician thereby potentially restricting treatment options.

The diagnosis of ASA should be suspected in a patient with a characteristic symptom profile even if there is no history of an aspirin/NSAID-induced reaction. Skin prick tests to aspirin or NSAIDs in these patients are of no value as IgE plays no role in this condition. There are no other *in vitro* tests for aspirin-sensitivity and therefore aspirin challenge may be required to confirm or exclude the diagnosis if there is any doubt from the history. The preferred challenge route is to use inhaled lysine-aspirin as an alternative to oral aspirin and thereby provoke either a localized nasal or a bronchial reaction. With lysine aspirin the symptoms experienced are limited to the airways and therefore easily reversed by bronchodilators as opposed to the systemic symptom elicited during oral aspirin challenge. The challenge

comprises the administration of doubling doses of lysine-aspirin at thirty-minute intervals using a hand-held nebulizer linked to a breath-actuated dosimeter. The challenge is continued until there is a decrease in FE_{1} of 20% compared to baseline. Nasal provocation can be used in patients suspected of aspirin-intolerant rhinitis or where poor lung function precludes bronchial challenge.

It is unusual for ASA patients to develop dermatological manifestations and aspirin-induced urticaria or angioedema should be considered a different disorder.

All NSAIDs, which cross-react with aspirin to cause intolerant reactions in ASA have anti-cyclooxygenase (COX) activity and the potency of a drug to inhibit COX *in vitro* correlates well with its ability to induce intolerant reactions.¹ Paracetamol (acetaminophen) is a weak inhibitor of cyclooxygenase and is generally well tolerated but at doses of between 150 and 600 mg induces symptoms in approximately 6% of aspirin-sensitive subjects. Our own experience and that from recent published trials have demonstrated that selective cyclooxygenase-2 (COX-2) inhibitors such as rofecoxib and celecoxib are likely to be safe in the majority of patients with ASA strongly implicating inhibition of the COX-1 isoenzyme of cyclooxygenase as the initiating event for ASA reactions.² Subjects with ASA have urinary leukotriene (LT)₄ levels that are several-fold higher than in normals or in aspirin-tolerant asthmatics. However, there is substantial overlap of LT₄ levels between these groups and therefore urinary LT₄ cannot be used to diagnose aspirin sensitivity in an individual with asthma.³ Upon challenge with aspirin, patients with ASA exhibit a further 4-fold increase in urinary LT₄ excretion accompanied by a decrease in FE_{1} . Pretreatment with an inhibitor of leukotriene synthesis not only inhibits this increase in cysteinyl leukotriene release but also blocks the symptoms and signs resulting from aspirin ingestion.⁴ The cysteinyl leukotrienes are potent bronchoconstrictors, and stimulate bronchial mucus secretion, increase permeability and increase airway hyperresponsiveness in asthmatic individuals and are therefore capable of producing all the symptoms and signs experienced by these subjects. Eosinophils and mast cells are found in greater numbers in the bronchial mucosa of ASA patients⁵ and eosinophils in these patients have a greater capacity to generate cysteinyl leukotrienes compared to aspirin-tolerant asthmatics because there is increased expression of CT₄ synthase, the terminal enzyme for the synthesis of cysteinyl leukotrienes.⁶ Therefore these cell types are likely to be the source for the enhanced cysteinyl leukotriene release in ASA.

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Therefore, inhibition of the iso-enzyme COX-1 is the "affecter" or initiating event and cysteinyl leukotrienes are the "effectors" for the pathophysiological processes leading to the symptoms and signs following aspirin ingestion and for a significant proportion of the chronic symptoms in ASA. However the connecting steps between COX-1 inhibition and activation of the 5-lipoxygenase pathway to generate cysteinyl leukotrienes have not been fully elucidated. It has been suggested that in ASA there is a relative deficiency of the bronchodilator prostaglandin PGE₂ in the respiratory tract compared to PGF₂ α , which increases bronchial smooth muscle tone. Although there is no direct evidence for a relative deficiency of PGE₂, inhaled PGE₂ has been shown to completely protect patients with ASA to a challenge with inhaled lysine-aspirin and to prevent the increase in urinary ET₄.⁷ The simplest hypothesis for the pathogenesis of ASA maintains that because both enzymes have arachidonic acid as their substrate, inhibition of COX-1 leads to a diversion from the cyclooxygenase to the 5-lipoxygenase pathway. Although attractive there are a number of valid objections to this concept as it does not explain why inhibition of COX-1 does not precipitate bronchoconstriction in aspirin-tolerant asthmatics and does not explain the severe chronic symptoms experienced by patients with ASA. However, a combination of these hypotheses may lead to a plausible theory. For example, a relative deficiency of PGE₂ could result in upregulation of CT₄ synthase and therefore explain the chronic symptoms due to elevated basal cysteinyl leukotrien levels. Any additional decrease in PGE₂ by COX-inhibition would then divert arachidonic acid to the 5-lipoxygenase pathway leading to a further increase in cysteinyl leukotriene synthesis and to the acute symptoms experienced by subjects with ASA following aspirin ingestion.

Patients with ASA and rhinosinusitis should be warned to avoid the large number of drugs with COX-1 inhibitory activity. Selective cyclooxygenase 2 (COX-2) inhibitors should be considered if treatments are required for inflammatory disorders but should only be introduced with caution until there is wide experience of these drugs in ASA. Aspirin desensitization in ASA is an effective method of controlling symptoms of rhinosinusitis and the regrowth of nasal polyps and may reduce systemic corticosteroid requirements with the possibility of an improvement in asthma control.⁸ Patients considered for desensitization are usually on large doses of intranasal and inhaled corticosteroids for rhinosinusitis and asthma and are likely to require frequent courses of oral corticosteroids. Typically, desensitization takes from 2 to 4 days and the patient continues on a daily maintenance dose of 600 mg. The state of desensitization is made possible because after each dose of aspirin there is a refractory period during which time a further equivalent dose produces no symptoms. The mechanism of this refractory period and hence aspirin desensitization may be explained by a combination of a downregulation of leukotrien airway receptor sensitivity during acute desensitization and reduced leukotriene production in response to

aspirin administration with chronic therapy.⁹ The refractory period is individual to each patient and may last from less than 2 days to more than 7 days and it is therefore essential to continue taking aspirin 600 mg daily in order to prevent resensitization. Aspirin desensitization is a resource-intensive procedure with attendant risks and should only be carried out in a hospital setting. Therefore, patients must be selected carefully and warned to discontinue aspirin if they develop gastro-intestinal or other adverse effects.

Although one would envisage that salicylate-free diet would be useful in ASA, these have proved disappointing in ASA, but it is unclear whether this is due to poor compliance or the lack of accurate dietary advice. In addition, foods may also contain non acetylated salicylates, which do not inhibit cyclooxygenase and *in vitro* studies have demonstrated that some of these may actually prevent aspirin from acetylating cyclooxygenase thereby potentially blocking aspirin-induced reactions. The patient's asthma should be treated in the usual way with bronchodilators and inhaled corticosteroids. Anti-leukotrienes are a vital component in the management of patients with ASA. The two major classes of anti-leukotrienes act either by blocking the effect of cysteinyl leukotrienes at the CysLT₁ receptor (e.g. zafirlukast, montelukast and pranlukast) or by preventing their biosynthesis by inhibition of the enzyme 5-lipoxygenase (e.g. zileuton - not available in the U.K.). A number of studies have established the efficacy in inhibiting aspirin-induced bronchoconstriction confirming the key role played by cysteinyl leukotrienes in the acute reaction. There is also evidence for clinical improvement with more prolonged use of anti-leukotrienes resulting in an increase in respiratory function, fewer nasal symptoms and a reduction in the number of asthma exacerbations.¹⁰

Despite optimal treatment, a significant proportion of patients with ASA will still require regular oral corticosteroids for control of symptoms compared to patients with other forms of asthma. The most troublesome nasal symptom is congestion and this usually requires treatment with topical corticosteroid and intermittent topical decongestants and may require occasional courses of oral corticosteroids. The addition of oral or nasal antihistamines may provide additional relief. Surgery for the removal of nasal polyps may be required on a regular basis and some patients may require polypectomies every few years. Intractable cases should be referred to a specialist allergy clinic or a respiratory physician with experience of this condition. ■

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