Aspirin sensitivity and the nose

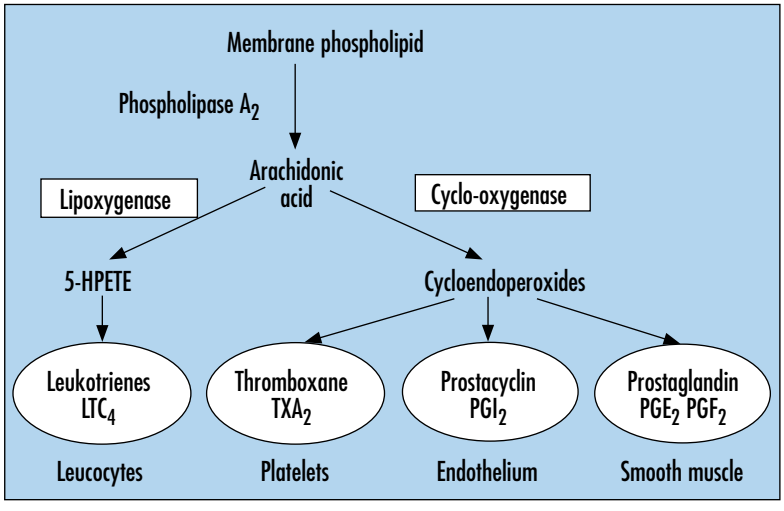
There is a well-recognized association of aspirin sensitivity, aspirin-induced asthma, nasal polyposis or sinusitis, known as Samter's triad. This article outlines the pathogenesis and clinical features of this condition and reviews current management options.

Aspirin is the commonly used term for acetylsalicylic acid. The association of aspirin sensitivity, aspirin-induced asthma and nasal polyposis was first published in 1922 (Widal et al, 1922), but the full clinical presentation of aspirin intolerance was not reported until 1968, after which it became colloquially known as Samter's triad (Samter and Beers, 1968).

A wide variety of terms have been used to describe this triad, including aspirin-sensitive asthma, aspirin-induced asthma and aspirin hypersensitivity. The current accepted terminology is aspirin-exacerbated respiratory disease. This is an acquired disorder characterized by chronic hyperplastic eosinophilic sinusitis with nasal polyposis, asthma and airway reactivity exacerbated by the ingestion of cyclo-oxygenase-1 inhibitors (COX-1) such as aspirin and other non-steroidal anti-inflammatory drugs (Williams and Woessner, 2008).

The condition is characteristically associated with severe nasal polyposis, asthma that is more challenging to control and acute attacks that are induced by ingesting aspirin. It is caused by a biochemical anomaly and is not an immunoglobulin-related allergy as is often incorrectly assumed.

Figure 1. Arachidonic acid pathway. 5-HPETE = 5-hydroperoxyeicosatetraenoic acid.



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Pathophysiology

The pathogenesis of aspirin intolerance is related to the abnormal metabolism of arachidonic acid. Aspirin inhibits the activity of the cyclo-oxygenase enzyme within the soft tissues in susceptible individuals and diverts the metabolism of arachidonic acid to the lipooxygenase pathway (*Figure 1*). This altered metabolism results in decreased production of prostaglandins, particularly the anti-inflammatory prostaglandin PGE_2. This is accompanied by simultaneous production of pro-inflammatory cysteinyl leukotrienes increased by over-expression of the enzyme leukotriene synthase (Szczeklik et al, 1975). In a low PGE_2 environment, these potent inflammatory mediators induce acute tissue inflammation, bronchoconstriction, excess mucus secretion, eosinophilia within the airways and nasal mucosal oedema.

Nasal polyps in patients with aspirin-exacerbated respiratory disease are consistent with the reduced rate of apoptosis of local inflammatory cells (Kowalski et al, 2002). Polyps are probably the end result of an infectious agent triggering the activation of nasal mucosal cells within a background of chronic inflammation.

Clinical presentation

In most patients, aspirin-exacerbated respiratory disease evolves in a predictable clinical pattern: sinonasal symptoms typically start approximately 2 years before the onset of asthma unless there has been pre-existing asthma from childhood (McGeehan and Bush, 2002). Chronic rhinosinusitis presents with chronic nasal congestion, hyposmia and rhinorrhoea, probably being triggered by a respiratory viral infection (Berges-Gimeno et al, 2003). Once rhinosinusitis is induced in aspirin-intolerant patients, severe hyperplastic eosinophilic rhinosinusitis with sinonasal polyposis often ensues.

Ingestion of aspirin induces an acute reaction that varies in severity and may be delayed for a period of approximately 3 hours. The reaction is characterized by acute rhinitis (rhinorrhoea, nasal congestion, sneezing and nasal itching), bronchospasm (coughing, wheezing, dyspnoea, chest tightness) and/or laryngospasm (stridor or dysphonia). Extra-respiratory manifestations include orbital oedema, conjunctival injection, urticaria, flushing, angioedema, abdominal pain, nausea and vomiting (Williams and Woessner, 2008). Aspirin sensitivity is normally a lifelong condition although sporadic cases of resolution of intolerance have been reported (Rosado et al, 2003).

Prevalence

The true prevalence of aspirin-exacerbated respiratory disease is unknown and it is likely that this is underestimated. Accurate estimation is challenging because of variation in the timing, severity and clinical features of the condition. Patients with a mild reaction will not always correlate their symptoms to aspirin ingestion.

A multicentre European study of asthmatic patients who were unaware of their aspirin status found that 15% reacted to an oral challenge to aspirin (Szczeklik and Nizankowska, 2000). A meta-analysis of 15 prospective studies of patients with nasal polyps and asthma demonstrated a combined prevalence of aspirin intolerance in 21% in adults and 5% of children (range 14–29% of adults and 0–14% of children) (Jenkins et al, 2004). These findings show that aspirin-exacerbated respiratory disease is quite common in asthmatic patients but may go unrecognized.

Conversely, patients with asthma and nasal polyps may be incorrectly diagnosed as having aspirin-exacerbated respiratory disease when based on history alone, and a subsequent oral aspirin challenge has been shown to be negative in 14–16% of patients (Pleskow et al, 1983).

The prevalence of nasal polyps in the general population is estimated as 4% but polyps have been described in 70% of patients who are intolerant to aspirin (Szczeklik and Nizankowska, 2000). The recurrence rate after surgery is almost three times higher in patients with aspirin-exacerbated respiratory disease than in aspirin-tolerant asthmatics (Jantti-Alanko et al, 1989).

Diagnosis

As yet, no valid in-vitro test for aspirin intolerance exists and the diagnosis is often based on clinical history alone. Patients with aspirin-exacerbated respiratory disease often have significant recurrent nasal polyps and regular severe asthma attacks. A specific history of episodic acute exacerbation of asthma associated with profuse rhinorrhoea following ingestion of non-steroidal anti-inflammatory drugs is highly suggestive of aspirin-exacerbated respiratory disease.

It is important to differentiate aspirin-exacerbated respiratory disease patients from other causes of chronic rhinosinusitis such as IgE-mediated allergic sensitization, infectious sinusitis and extra-oesophageal manifestations of gastro-oesophageal reflux. Many asthmatics who suffer from rhinosinusitis are not aspirin sensitive and further investigation is ideally indicated to confirm the diagnosis before considering the therapeutic options.

The only definitive means of confirming aspirin intolerance is to provoke the patient with an aspirin challenge or another non-steroidal anti-inflammatory drug. This inevitably carries a risk that can be significant and dangerous if not managed properly. Patients undergoing oral challenge tests need to be admitted and managed in specialist units. Highly sensitive aspirin oral challenge protocols have been developed but the time and cost implications for providing a diagnostic service are considerable (Szczeklik and Stevenson, 2003).

Concomitant inhalational allergy is common in patients with aspirin-exacerbated respiratory disease: allergies can exacerbate the symptoms of aspirin-exacerbated respiratory disease but they are also eminently treatable.

Medical treatment options

The management of asthma in patients with aspirin-exacerbated respiratory disease should follow the standard guidelines, using regular inhaled corticosteroids, short and long-acting beta-agonists, and other therapeutic options according to clinical need. Similarly, conventional treatments can be effective in the management of upper airway disease. Intranasal steroids supplemented when necessary by systemic corticosteroids are used to reduce mucosal inflammation and polyp formation (Fokkens et al, 2007).

The role of cysteinyl leukotrienes in the pathophysiology of chronic inflammation in aspirin-exacerbated respiratory disease is now well established. Specific leukotriene-modifying drugs were developed and introduced into clinical practice in the 1990s. Montelukast, a cysteinyl leukotriene receptor type 1 antagonist, and zileuton, a 5-lipoxygenase inhibitor, are established in the management of asthma. Evidence regarding the long-term use of these medications in controlling the symptoms of aspirin-exacerbated respiratory disease is inconclusive, although a decreased polyp recurrence rate in patients receiving montelukast has been reported (Parnes, 2003).

The paradoxical finding that aspirin-sensitive patients experience a refractory period after an oral aspirin challenge was reported in 1922 (Widal et al, 1922). Despite this, the potential for therapeutic benefit went unrecognized for more than 50 years. Aspirin-sensitive patients were then reported to have a 3-day refractory period after an oral aspirin challenge (Zeiss and Lockey, 1976). A clinical improvement in sinonasal symptoms in patients with aspirin-exacerbated respiratory disease following aspirin desensitization was subsequently reported (Stevenson et al, 1980). There is good evidence to support the clinical effectiveness of aspirin desensitization and continued aspirin therapy in patients with aspirin-exacerbated respiratory disease (Macy et al, 2007). In a double-blind, randomized, placebo controlled crossover study, a significant improvement in nasal symptoms was described in patients with aspirin-exacerbated respiratory disease who had undergone aspirin desensitization and aspirin maintenance (Stevenson et al, 1984). Subsequent observational studies support the finding that desensitization and aspirin therapy is associated with a significant reduction in the number of sinus infections, the dose of systemic and nasal steroids and need for sinus surgery. A highly significant reduction in the number of hospital admissions per year for acute asthma exacerbations following the use of this protocol has been reported (McMains and Kountakis, 2006).

There has been debate regarding the dose of aspirin therapy required to maintain the clinical benefits following desensitization. In an observational cohort study of 172 aspirin-exacerbated respiratory disease patients, 46 (27%) discontinued aspirin therapy during the first year after desensitization: 24 (14%) did so because of gastritis, gastrointestinal bleeding, urticaria or epistaxis (Berges-Gimeno et al, 2003). The use of lower doses of aspirin and alternative routes of administration has been investigated in an attempt to limit the adverse effects. Evidence suggests that there is no additional clinical benefit in the established dose of 650 mg twice daily over a lower dose of 325 mg twice daily (Lee et al, 2007). Doses as low as 100 mg once daily have been proposed but more studies are required to confirm the clinical benefits (Gosepath et al, 2002).

Intravenous aspirin desensitization has been proposed as a safer route of administration: the ability to terminate the infusion in the event of a severe systemic reaction may offer an advantage over oral administration (Pfaar and Klimek, 2006).

It has been suggested that aspirin desensitization followed by aspirin therapy should be considered when the symptoms of aspirin-exacerbated respiratory disease persist despite the optimal use of conventional treatments, or when a patient requires treatment with aspirin or non-steroidal anti-inflammatory drugs for an alternative clinical indication (Macy et al, 2007). Suitable patients include the following:

- Moderate or severe asthma and/or intractable nasal symptoms that are uncontrolled with topical corticosteroids and leukotriene-modifying drugs
- Severe extensive 'aggressive' nasal polyps
- Requirement for daily or frequent courses of systemic corticosteroids to control nasal symptoms and/or asthma
- Additional medical indications for aspirin such as atherosclerotic cardiovascular disease
- Medical indication for other COX-1 enzyme inhibiting medication such as arthritic pain refractory to regular paracetamol.

Topical lysine-aspirin, administered endonasally, has shown encouraging results in the management of nasal polyposis in aspirin-exacerbated respiratory disease. The effect of intranasal lysine-aspirin administration on resistant nasal polyps of asthmatic, aspirin-intolerant patients, when used in addition to routine therapy, was examined in a well-structured but small prospective study. Thirteen patients with asthma and intolerance to aspirin were recruited. All but one had undergone numerous polypectomies and were uncontrolled on standard therapy with intranasal corticosteroids, leukotriene receptor antagonists and nasal douching. Aspirin treatment involved one drop (100 µl) of 30 mg/ml lysine-aspirin solution applied to each nostril, initially daily, increased every 2 or 3 days up to a maximum of 18 drops (54 mg lysine-aspirin) a day. Nasal symptoms, nitric oxide level, nasal inspiratory peak flow rate, peak expiratory flow rate and nasendoscopic grading were assessed before therapy and 3 months later. This open study suggested that intranasal lysine-aspirin administration reduces nasal polyp volume in aspirin-intolerant patients, without any adverse affect on concomitant asthma (Ogata et al, 2007). Previous studies have confirmed a reduction in polyp size following lysine-aspirin administration but the overall nasal symptom scores have shown no significant improvement (Parikh and Scadding, 2005).

Salicylic acid is present naturally in fruits and vegetables, with herbs and spices being a particular rich source. Salicylates can also be found in medication and cosmetics. Some examples of salicylate-containing food include fruits such as apples, avocados, blueberries, peaches, raspberries; vegetables such as cauliflower, cucumbers, mushrooms, radishes; beverages such as coffee, wine, beer, orange juice; and nuts such as pine nuts, peanuts, pistachios and almonds. Patients with severe aspirin intolerance should be made aware of which food may precipitate their symptoms (Flower, 2003).

Surgical management

Despite the chronic inflammatory nature of aspirin-exacerbated respiratory disease, many patients who undergo functional endoscopic sinus surgery to alleviate sinonasal symptoms achieve good results. The prevalence of aspirin-exacerbated respiratory disease in all patients undergoing functional endoscopic sinus surgery for chronic rhinosinusitis was 4.8%, 9.4% in those with polypoidal chronic rhinosinusitis and 25.6% in those with nasal polyps and asthma (Kim and Kountakis, 2007). Many patients with aspirin-exacerbated respiratory disease present with nasal symptoms before the diagnosis of lower respiratory tract disease.

Patients with aspirin-exacerbated respiratory disease generally have poorer symptom control and higher rates of recurrence than the comparable aspirin-tolerant group. The frequency of revision functional endoscopic sinus surgery is also higher in patients with aspirin sensitivity and asthma (Kim and Kountakis, 2007). Despite these findings, evidence suggests that sinonasal symptoms are significantly improved in the postoperative period following functional endoscopic sinus surgery in patients with aspirin-exacerbated respiratory disease, although the benefit of surgery may be short lived (Awad et al, 2008). With regard to improved olfaction following functional endoscopic sinus surgery, aspirin-exacerbated respiratory disease is a significant predictor of a worse outcome when compared to patients with allergic rhinitis and nasal polyposis (Katotomichelakis et al, 2009). The conductive impairment of nasal airflow associated with aspirin-exacerbated respiratory disease is thought to be attenuated by higher eosinophilic infiltration of the nasal mucosa, thus compromising the recovery of the olfactory neuroepithelium following surgery.

Studies into the long-term effects following aspirin desensitization suggest that the surgical outcome is better in patients who maintain continuous aspirin therapy. In one cohort of patients who underwent aspirin desensitization therapy, the need for functional endoscopic sinus surgery was reduced from once every 3 years to once every 10 years.

Conclusions

Aspirin-exacerbated respiratory disease is a debilitating and potentially life-threatening condition and a severe acute asthmatic episode can be induced by aspirin ingestion. In patients with aspirin sensitivity and persistent severe nasal polyposis, control is best achieved by intensive medication, sometimes combined with endoscopic sinus surgery. However, the duration of the effect of surgery may be relatively short and needs to be considered on an individual basis when deciding upon the management strategy.

The mainstay of therapeutic control is topical steroid administration to the nose and lower airways combined with intermittent systemic steroids when necessary. The effectiveness of anti-leukotriene medication is uncertain and its role in overall management is controversial. Aspirin desensitization is effective but the inherent risk limits this strategy to a few specialist centres, although topical nasal lysine aspirin may offer a safer alternative. **BJHM**

Conflict of interest: none.

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KEY POINTS

- Samter's triad is a well-recognized association of aspirin sensitivity, aspirin-induced asthma, and nasal polyposis or sinusitis.
- The prevalence of nasal polyps in the general population is estimated as 70% in patients who are intolerant to aspirin. The recurrence rate of polyps after surgery is almost three times higher in these patients.
- The mainstay of therapeutic control is topical steroid administration to the nose and lower airways combined with intermittent systemic steroids when necessary.
- Control is achieved by intensive medication, sometimes combined with endoscopic sinus surgery. However, the duration of the effect of surgery may be relatively short and needs to be considered on an individual basis when deciding upon the management strategy.
- Aspirin desensitization is effective but the inherent risk limits this strategy to a few specialist centres.