

Aspirin desensitization in aspirin intolerance: update on current standards and recent improvements

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Purpose of review

This review provides an overview of sensitivity to aspirin (acetylsalicylic acid) and its management. In particular, it focuses on current standards and recent improvements in aspirin desensitization. Recent publications on various desensitization protocols and routes of administration are discussed.

Recent findings

The incidence of aspirin hypersensitivity in the general population ranges from 0.6–2.5%, but that in adult asthmatics ranges from 4.3–11%. Carefully controlled challenge tests with aspirin or other non-steroidal anti-inflammatory drugs are performed as the diagnostic tool of choice. Aspirin desensitization therapy has demonstrated therapeutic effects. Various protocols and routes of administration have been elaborated in the last two decades. Oral administration by means of an initial desensitization with incremental doses of aspirin, followed by daily high-dose therapy, has proven clinical efficacy and safety. Immunological mechanisms of aspirin desensitization therapy are also discussed.

Summary

The full clinical picture of aspirin intolerance – the association of aspirin-induced bronchial asthma (with severe acute asthma attacks), aspirin sensitivity and nasal polyps – is commonly summarized as the 'Samter triad'. This condition is related to the abnormal metabolism of arachidonic acid, implicating both the lipoxygenase and the cyclooxygenase pathways. Knowledge concerning mechanisms and clinical features of aspirin intolerance has grown rapidly in recent years. Research has focused on new strategies of aspirin desensitization therapy, especially oral administration using high-dosage protocols.

Keywords

acetylsalicylic acid, aspirin desensitization, aspirin intolerance, aspirin sensitivity, nasal polyps, Samter triad

Abbreviations

AIA	aspirin-induced asthma
ASA	aspirin (acetylsalicylic acid)
COX	cyclooxygenase
NSAID	non-steroidal anti-inflammatory drug

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Introduction

Shortly after aspirin (acetylsalicylic acid; ASA) was developed more than 100 years ago by Felix Hoffmann, a German chemist, for the treatment of his father's arthritis, cases of severe attacks of asthma after ingestion of ASA began to be described. In 1922, the association of ASA sensitivity, aspirin-induced asthma (AIA) and nasal polyposis was described by Widall *et al.* [1]. This full clinical picture of ASA intolerance was subsequently pointed out in the studies of Samter and Beers [2], and is nowadays commonly summarized as the 'Samter triad'. The triad can be incomplete, however, and nasal polyposis can be the first clinical symptom of ASA sensitivity.

Although the exact mechanisms of ASA intolerance, as well as those behind therapy by ASA desensitization, remain unclear, evidence exist that the pathogenesis of ASA intolerance is not an IgE-mediated reaction, but is related to abnormal metabolism of arachidonic acid, implicating both the lipoxygenase and the cyclooxygenase (COX) pathways [3]. In addition to pharmacological options, ASA desensitization is a valuable therapeutic option in most patients with AIA, especially in those patients suffering from recurrent nasal polyposis [4].

This paper gives an overview of the prevalence, diagnosis and clinical presentation of ASA intolerance, as well as proposed pathophysiological mechanisms. Moreover, it focuses on recent improvements and current standards in the management of ASA intolerance, for example the development of ASA-desensitization therapy.

Prevalence and clinical presentation

The incidence of ASA hypersensitivity ranges in the general population from 0.6–2.5%, and in adults with asthma from 4.3–11% [5,6]. Nevertheless, ASA intolerance seems to be under-reported. In a population of 500 patients with AIA studied in the European Network of Aspirin-Induced Asthma (AIANE), 18% were unaware of ASA intolerance before having ASA challenge tests [7]. In

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addition, approximately 34% of patients suffering from both asthma and concomitant rhinosinusitis were unaware of their condition before testing [5,8]. This indicates that under-reporting of ASA sensitivity may be due to the lack of routine ASA challenge testing of asthmatic patients who do not report a positive history of ASA sensitivity.

In most cases, sensitivity to ASA develops according to a typical pattern: rhinitis is the first clinical sign during the third decade, often after a viral respiratory infection. Usually, these initial symptoms result subsequently in chronic nasal congestion, hyposmia and chronic rhinorrhoea after some months [7,8]. In addition, nasal polyps might be evaluated by endoscopic examination. Finally, the disease results in AIA: 20% of AIA patients suffer from mild and intermittent asthma, 30% are moderate asthmatics whose condition can be controlled with inhaled steroids, whereas 50% have a chronic, severe corticoid-dependent asthma.

In these patients, ingestion of ASA or non-steroidal anti-inflammatory drugs (NSAIDs) leads to an acute asthma attack within hours, which may be life-threatening. In a prospective 6-year follow-up study by Marquette *et al.* [9] of 145 adult asthmatics requiring emergency ventilation in an acute asthma attack, 25% revealed sensitivity to ASA. In general, the asthma attack is accompanied by profuse rhinorrhoea, orbital oedema, conjunctival injection and an erythema reaction (flush) of the head and neck. Once developed, sensitivity to ASA continues throughout life, although sporadic disappearance of intolerance has been described [10].

Rhinosinusitis

In a multi-centre European study including 500 patients, rhinosinusitis was described as the typical first symptom of AIA, at an average age of 30 years, often as a result of a viral respiratory infection [11]. The discharge from the nose was perennial and often watery, while hyposmic sensations were found in 55% of cases. On average, the first asthmatic symptoms appeared 2 years later; however, AIA was proven by challenge testing 4 years later.

Nasal polyps

In the general population, the overall prevalence of nasal polyps is about 4%, whereas in ASA-sensitive patients nasal polyps are present in 70% of cases [11,12]. They are usually not limited to the nasal cavity, but spread and involve all paranasal sinuses bilaterally [13]. In an American survey, pansinus affection could be proven radiologically in almost all patients with AIA by means of computed tomography (CT) scans [8].

The high prevalence of nasal polyps in patients with AIA might be due to differences in HLA genes [14] or a

reduced rate of apoptosis of cells involved in local inflammation, such as eosinophils [15]. Additionally, there is evidence that infectious agents such as viruses, bacteria and fungi may be potential primary factors that activate nasal epithelial cells [16]. This inflammation process is mediated by pro-inflammatory cytokines such as eotaxin and growth factors that play important roles in the persistence of mucosal inflammation associated with nasal polyps [12,17]. Other studies have revealed a differential role of COX-1 and COX-2, which have special regulator functions in the pathogenesis of nasal polyps [18].

After resection of the polyps, the recurrence rate is almost three times higher in patients with AIA than in non-intolerant intrinsic asthmatics [19]. In a prospective study of 227 patients operated on for nasal polyposis between 1993 and 2001 [20], a significantly higher rate of recurrence was revealed in the AIA group compared with patients tolerant to ASA.

Pathomechanisms of aspirin-induced asthma

Evidence has been obtained that intolerance to ASA and other NSAIDs is not an IgE-mediated allergic reaction, but is related to abnormal metabolism of arachidonic acid [3,5]. By inhibiting the COX pathway, ASA diverts metabolites to the lipoxygenase pathway, resulting in a decrease in the levels of the anti-inflammatory prostaglandins, especially prostaglandin E₂, and an increase in the synthesis of cysteinyl leukotrienes, particularly leukotrienes A₄, B₄, C₄ and D₄ (Fig. 1). Moreover, patients intolerant to ASA were revealed to have an increased leukotriene C₄ synthase activity in their bronchial mucosa [21]. Together, these changes in the arachidonic acid metabolic pathways result in excessive leukotriene production which is responsible for the inflammatory reaction.

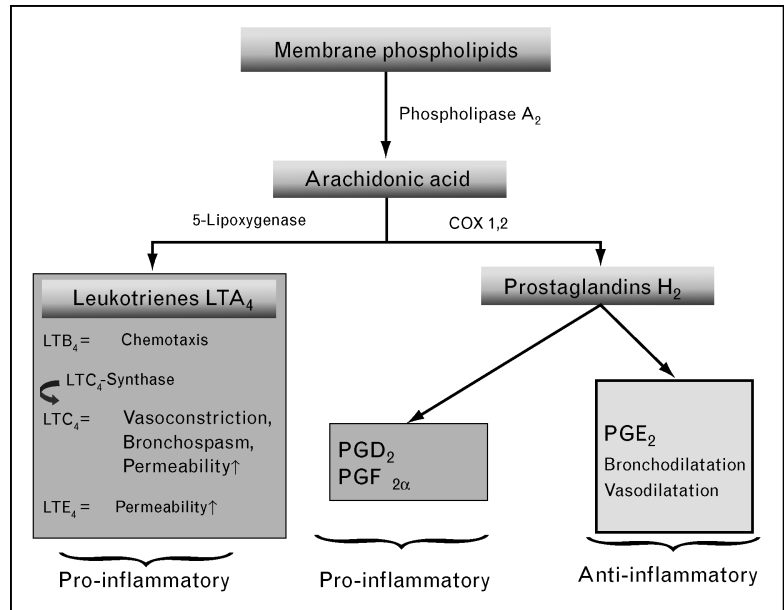
Diagnosis

On clinical presentation, four typical findings in the patient's history might indicate an intolerance to ASA and other NSAIDs [3,7,22]: (i) typical symptoms of respiratory reactions after ASA challenge; (ii) asthma attacks accompanied by chronic nasal congestion and watery, profuse rhinorrhoea; (iii) a high frequency of nasal polyps; and (iv) a high frequency of severe asthmatic attacks.

To date, no reliable in-vitro tests are available for the diagnosis of ASA intolerance. The only validated diagnostic tool for ASA sensitivity is provocation. Carefully controlled challenge tests with ASA or other NSAIDs are justified; however, they should only be carried out in specialized clinics fully prepared for cases of anaphylactic reactions. Four types of ASA challenge can be performed depending on the manner of administration: oral, inhalative, nasal and intravenous [3,5,7].

Figure 1 Arachidonic acid metabolism: cyclooxygenase and lipoxygenase pathways

Although the exact mechanisms causing aspirin intolerance, as well as those involved in therapy by ASA desensitization, remain unclear, evidence exists that the pathogenesis of aspirin intolerance is due to abnormal metabolism of arachidonic acid. By inhibiting the cyclooxygenase (COX) pathway, aspirin diverts metabolites to the lipoxygenase pathway. Moreover, patients intolerant to ASA have been shown to have increased leukotriene C₄ (LTC₄) synthase activity in their bronchial mucosa. Together, these mechanisms result in a shift away from the anti-inflammatory prostaglandins, especially prostaglandin E₂ (PGE₂), towards an increase in the synthesis of inflammatory cysteinyl leukotrienes, particularly LTA₄, LTB₄, LTC₄ and LTD₄.



To date, oral and bronchial challenge tests are most common standard and have proven high sensitivity [4]. In the case of predominant nasal symptoms like recurrent polyposis or rhinosinusitis, nasal provocation might be performed as the method of choice because of its reliability and its safety, even in patients with unstable asthma [23].

Management and prevention

The general rules concerning the treatment of AIA do not differ from the published guidelines on the management of asthma with preventative therapies, including inhaled corticosteroids, long acting β -agonists and oral corticosteroids [24]. Nevertheless, important differences in the treatment of AIA should be pointed out: because of potentially life-threatening severe asthma attacks after the ingestion of ASA, ASA-intolerant patients should avoid ASA and all other non-selective COX inhibitors. Therefore it is essential that patients are sufficiently informed about NSAIDs cross-reacting with ASA, for example by receiving a list containing the contraindicated drugs [3] (Table 1). Selective COX-2 inhibitors,

however, might be used safely in the majority of ASA-sensitive patients [25].

Aspirin desensitization

ASA desensitization plays a major role in the management of ASA-sensitive patients, by inducing immunologic tolerance. Zeiss and Lockey [26] were the first authors to describe a 72 h refractory period after oral ASA challenge in ASA-sensitive patients [27].

Various desensitization protocols and routes of administration have been elaborated in the last two decades, as described below.

Endonasal administration

Some studies on ASA desensitization have focused on the endonasal administration of lysine-ASA [28*,29]. This route of administration has mainly shown efficacy in the treatment of nasal polyps in ASA-sensitive patients. In a study by Patriarca *et al.* [29], 43 patients suffering from nasal polyposis underwent intranasal treatment with increasing doses of lysine-ASA corresponding to 20, 200,

Table 1 Non-steroidal anti-inflammatory drugs (NSAIDs) that cross-react with aspirin [3]

Inhibitor pathways	NSAIDs
Predominant COX-1 and COX-2 inhibitors	Piroxicam; indomethacin; sulindac; tolmetin; diclofenac; naproxen; naproxen sodium; ibuprofen; fenoprofen; ketoprofen; flubiprofen; fefenamic acid; meclofenamate; ketorolac; etodolac; diflunisal; oxyphenbutazone; phenylbutazone
Poor COX-1 and COX-2 inhibitors	Acetaminophen; salsalate
Relative inhibitors of COX-2	Nimesulide; meloxicam
Selective COX-2 inhibitors	Celecoxib; rofecoxib

COX, cyclooxygenase.

and 2000 μg of ASA, until a maximum dose of 2000 μg weekly was reached. Recurrence rates of nasal polyps were significantly lower in the therapy group compared with controls in a 5-year follow-up. Recently, the first randomized, double-blind, placebo-controlled, crossover trial of topical desensitization with low-dose (16 mg) intranasal administration in 11 ASA-sensitive patients with nasal polyps was reported [28]. Despite a failure to demonstrate clinical benefit, tissue studies showed a significant improvement at the microscopic level. The lack of a significant clinical effect might have been due to the low number of patients, and a trial with larger numbers of patients along with conventional treatment might reveal a clinical improvement in desensitized patients.

Bronchial administration

This route of administration has been developed on the premise that refractory tolerance could be achieved by repeated provocation with lysine-ASA inhalation [30].

Oral administration

In an early study by Stevenson *et al.* [27], two patients with AIA were described who underwent an initial desensitization with incremental doses of ASA followed by daily therapy. In both cases, nasal obstruction was reduced and loss of olfaction was diminished. Furthermore, improvements of the ASA-sensitive asthma as well as of nasal polyps were revealed. This report marked a new therapeutic option in the management of ASA-sensitive patients: was it possible to treat the inflammatory airway process with exactly the same medication which might be the cause of the disease? If this was found to be the case, it raised the question of what immunological pathomechanisms are involved in the desensitization process.

Only 4 years later, the first randomized, double-blind, placebo-controlled crossover trial of ASA desensitization in 25 patients with ASA-sensitive asthma was carried out [31]. This study revealed a significant improvement in symptoms of rhinosinusitis and a decrease in the daily amount of nasal corticosteroids required while on ASA. No changes in asthma medications, lower respiratory symptoms or FEV₁ (forced expiratory volume in 1 s) were described, however, and the patients' need for systemic corticoids could not be reduced significantly. A possible explanation for these poor results might be the small number of patients investigated and non-homogeneous doses of ASA application.

The therapeutic role of ASA desensitization was investigated in a retrospective trial including 107 patients with diagnosed ASA sensitivity with rhinosinusitis-asthma [32]. The clinical outcome of 65 patients who underwent ASA desensitization was compared with that of a group

of 42 patients who avoided all NSAIDs. Interestingly, the group of patients on ASA demonstrated statistically significant reductions in the numbers of hospitalizations, emergency room visits, outpatient visits, upper airway tract infections and sinus operations, as well as an improvement in olfactory sense, compared with those avoiding NSAIDs. In addition, ASA desensitization concomitantly allowed reduction of systemic corticosteroids. Taken together, these data clearly demonstrate a clinical benefit of ASA desensitization therapy for ASA-sensitive patients. Unfortunately, however, 20% of the 65 patients of the therapy group reported symptoms of gastritis, and almost 50% discontinued the therapy after a few years, which made it impossible to investigate long-term effects.

In a long-term follow-up study of 65 ASA-sensitive patients between 1988 and 1994 who underwent ASA desensitization with a daily peroral dose of 1300 mg, significant decreases in the number of sinus infections and courses of prednisone were reported, along with improvements in smell, nasal, sinus and asthma symptoms, when compared with the period prior to therapy [33]. Interestingly, this study was the first to show evidence that ASA desensitization in fact reduces the aggressive growth and recurrence rate of sinunasal polyps in ASA-sensitive patients over a longer time period. The necessity for sinunasal surgery declined from one operation per 3 years to one operation per 9 years. The numbers of emergency room visits and the need for inhalative corticosteroids remained unchanged in this study, however. The statistical analysis of the subgroups (therapy < 3 years compared with therapy > 3 years) concerning these clinical results revealed no differences [33]; hence this study could clearly demonstrate the long-term effects of ASA desensitization over a period of at least 6 years.

A subsequent study by Berges-Gimeno *et al.* [34] on 172 patients, using a similar study design, revealed that a clinical response to treatment rate of 67% was evident as early as 6 months and persisted for 1–5 years. One major finding of this study was a reduction in the rate of purulent sinusitis from an average of five times per year before therapy to less than half that. It was reported that 9% of patients discontinued the long-term desensitization therapy due to gastritis; however, compared with the study by the same group from 1996 [28], a decrease in the rate of gastritis was observed. This might have been due to the use of misoprostol and proton pump inhibitors, both of which have become available in recent years. In cases of gastritis-related complaints, the authors recommended decreasing the dose of ASA after 6 months of therapy.

Taken together, these trials underline the clinical benefit of ASA desensitization treatment; however, larger

randomized, placebo-controlled trials should be carried out to confirm this effect, in view of the low-grade evidence of the published data.

Mechanisms of aspirin desensitization

Peripheral blood monocytes were taken from ASA-sensitive patients after desensitization therapy with ASA (650 mg twice daily) for 2 weeks or longer [35]. As expected, in a cell culture model ('functional cell testing') the monocytes revealed a significantly reduced production of thromboxane B₂ as a product of COX-1 and COX-2. Interestingly, leukotriene B₄, a product of the monocyte lipoxygenase, was also reduced to the same level as found in normal controls. This effect might be related to a modulation of arachidonic acid metabolism by the therapy.

Other authors [36] reported a 20-fold decrease in bronchial responsiveness to inhaled leukotriene E₄ on the first day of the ASA sensitization therapy. These results could be explained by diminished leukotriene receptors or inactivated intracellular mechanisms inhibiting leukotrienes from inducing an effector event. Additionally, it has been suggested that ASA could have a direct inhibitory effect on mast cells, preventing them from releasing histamine and prostaglandin D₂ [4].

Another possible mechanism of ASA desensitization is direct modulation of the intracellular biochemical pathways of inflammatory cells, such as activation/inactivation of particular transcription factors [37].

Conclusion

In the last few years, a rapid growth of knowledge concerning mechanisms and clinical features of ASA intolerance has occurred. In addition, research has focused on new strategies of ASA desensitization, in particular oral administration using high-dosage protocols. Further studies might be expected to determine the most favourable doses for long-term therapy, as well as alternative routes of administration (such as intravenous application), or potential immune-modulating substances as add-on therapy.

References and recommended reading

Papers of particular interest, published within the annual period of review have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 242–243).

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