

Aspirin Intolerance: Does Desensitization Alter the Course of the Disease?

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KEYWORDS

- Samter triad • Morbus samter • Nasal polyps
- Aspirin sensitive • Aspirin intolerance
- Aspirin desensitization

In 1902, shortly after aspirin (acetylsalicylic acid [ASA]) was invented, cases of severe anaphylactoid reactions after aspirin ingestion were described by Hirschberg.¹ In 1922, Widal and colleagues² were the first to portray the association of aspirin sensitivity, aspirin-induced asthma (AIA), and nasal polyposis. The full clinical picture was subsequently pointed out in studies by Samter and Beers.³ In many cases, nasal polyps reveal as the first symptom of ASA sensitivity.⁴ This might indicate that the upper airways are predominantly involved in the pathogenetic process. Hence, the emphasis of this article is on the upper airways in ASA-intolerant patients.

ACETYLSALICYCLIC ACID INTOLERANCE: EICOSANOIDS AND THE ARACHIDONIC ACID METABOLISM

In the last decade, knowledge concerning the pathophysiologic mechanisms underlying ASA intolerance has been focused on in several studies. Evidence was found that the pathogenesis of aspirin intolerance is not an IgE-mediated reaction, but is related to an abnormal metabolism of arachidonic acid implicating both the lipoygenase (LO) and the cyclooxygenase (COX) pathways.^{4,5} This deviation results in an imbalance of the synthesis of eicosanoids, leukotrienes, and prostaglandins. Anti-inflammatory prostaglandins, especially E₂, decrease; and the synthesis of cysteinyl-leukotrienes, such as leukotrien-A₄, -B₄, -C₄ and -D₄, is increased.^{5,6}

PREVALENCE OF ACETYLSALICYCLIC ACID INTOLERANCE

Aspirin intolerance is thought to be underestimated. In a population of 500 patients with AIA studied in the European Network of Aspirin-Induced Asthma, 18% were

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unaware of aspirin intolerance before having aspirin challenge tests.⁷ More interesting, when patients with AIA also suffered from concomitant rhinosinusitis, 34% were unaware of their disease before testing.^{8,9} Other data reveal incidence rates from 0.6% to 2.5% and, in adult asthmatics, from 4.3% to 11%.⁸

CLINICAL SIGNS

In most cases, sensitivity to ASA reveals a typical pattern: rhinitis often becomes the first clinical sign during the third decade, often after a viral respiratory infection. After some months, concomitant chronic nasal congestion, hyposmia, chronic rhinorrhea, and nasal polyps might appear.^{8,9} Finally, the disease results in AIA. Twenty percent of AIA patients suffer from mild and intermittent asthma, 30% are moderate asthmatics who can be controlled with inhaled steroids, and 50% of the patients have a chronic, severe corticoid-dependent asthma often accompanied by systemic anaphylactoid reactions.⁹

Upper-airways: The Key Area of Acetylsalicylic Acid Intolerance

Rhinosinusitis was found to be a predominating symptom in 500 ASA-intolerant patients in a multicenter survey by Szczeklik and Nizankowska.¹⁰ Nasal symptoms revealed at an average age of 30 years, often as a result of a viral respiratory infection. In these cases, the discharge of the nose was perennial and often watery. Hyposmic sensations were found in 55%. On average, the first asthmatic symptoms appeared two years later.

Nasal Polyps

In 70% of ASA-intolerant patients, nasal polyps can be found; whereas in the general population the overall prevalence of nasal polyps is only about 4%.^{10,11} Typical for the polyps in ASA-intolerant patients is their aggressive growth that involves all paranasal sinuses bilaterally.¹² By means of CT-scans, Pansinus infection could be radiologically proven in almost all cases with AIA.⁹

The exact mechanisms of aspirin intolerance and those of therapy by ASA desensitization remain unclear. Evidence has been worked out that ASA intolerance is not an IgE-mediated reaction, but is related to an abnormal metabolism of arachidonic acid implicating both the LO and the CO pathways. This deviation results in an imbalance of the synthesis of the eicosanoids toward a predominance of the proinflammatory leukotrienes.^{5,6}

The pathogenetic link between ASA intolerance and the origin of nasal polyps remains unclear. Infectious agents like viruses, bacteria, or fungi as potential primary factors might activate nasal epithelial cells and proinflammatory cytokines such as eotaxin and growth factors, thereby promoting the inflammatory process.^{11,13,14} Other possible explanations might be differences in HLA genes,¹⁵ a reduced apoptosis rate of local inflammation cells (eg, eosinophils¹⁶), or a differential role of COX-1 and COX-2 having special regulatory functions in the pathogenesis of nasal polyps.¹⁷

The recurrence rate of nasal polyps after resection in ASA-intolerant patients is tremendously high. In a study by Jantii-Alanco and colleagues,¹⁸ the reoccurrence rate is almost three times higher in AIA than in non-intolerant intrinsic asthmatics.

DIAGNOSIS

Four typical findings in the patient's history might correspond to intolerance to aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs): (1) typical symptoms of respiratory reactions after aspirin challenge, (2) asthma attacks accompanied by

chronic nasal congestion and watery, profuse rhinorrhea, (3) high frequency of severe asthmatic attacks, and (4) high frequency of nasal polyps.⁵⁻⁷

So far, validated and reliable in-vitro tests are not available for the diagnosis of aspirin intolerance. Provocation testing still is the only validated diagnostic tool for aspirin sensitivity. Nevertheless, challenge tests undoubtedly are harmful and should only be performed in specialized clinics well prepared for cases of anaphylactic reactions. Four types of aspirin challenge can be performed depending on the manner of administration: oral, inhalant, nasal, and intravenous.⁷

In cases of predominant nasal symptoms, a nasal challenge test with aspirin might be the method of choice because of its safety and its reliability.¹⁹ In case of a negative test result in nasal challenge testing, but strong suspicions for AIA in the patient's history, bronchial or oral challenge tests should follow.^{5,7}

THERAPY

Prevention of Selective COX-1

General rules concerning the treatment of AIA are related to the published guidelines on the management of asthma. Moreover, asthma attacks in AIA often result in a severe, potentially life-threatening course. This underlines the importance of educating the patients in avoiding ASA and all other cross-reacting, nonselective COX-inhibitors.^{5,6} However, selective COX-2 inhibitors might be used safely in the majority of aspirin-sensitive patients.²⁰

SURGERY

Massive growth of polyps in the nasal and paranasal-sinuses are resected by endoscopic or microscopic techniques. However, the recurrence rate is quite high. In a prospective study of 227 patients operated on for nasal polyposis between 1993 and 2001, a significantly higher rate of recurrences has been revealed in the AIA group compared with patients tolerant to ASA.²¹

ACETYLSALICYLIC ACID DESENSITIZATION (ASPIRIN DESENSITIZATION, ADAPTIVE DESENSITIZATION)

In 1976, Zeiss and Lockey²² described the paradoxical finding that ASA-intolerant patients revealed a 3-day refractory period after oral aspirin challenge. This report marked a new therapeutic option in the management of aspirin sensitive patients. Is it possible to treat the inflammatory airway-process with exactly the same medication which undoubtedly caused the symptoms? Based on these findings, various desensitization protocols and routes of administration have been elaborated on in the last 2 decades: bronchial, endonasal, oral, and (recently published) intravenous.

Bronchial Administration

This route of administration has been developed on the premise that refractory tolerance could be achieved by repeated provocation with lysine-aspirin inhalation.²³

Endonasal Administration

In case of predominating nasal symptoms such as rhino-nasal polyposis, this route of administration has shown efficacy. In a study by Patriarca and colleagues,²⁴ intranasal desensitization was performed on 43 patients suffering from nasal polyposis with increasing doses of lysine acetylsalicylate corresponding to 20, 200, and 2000 micrograms of aspirin until a maximum dose of 2000 micrograms weekly was reached. In

a 5-year follow up, recurrence rates of nasal polyps were significantly lower in the aspirin-treated group compared with the control group. Another randomized, double-blind, placebo-controlled, crossover trial of topical desensitization with a low-dose (16 mg) intranasal administration in 11 aspirin-sensitive, nasal polyp patients has been reported.²⁵ This study revealed only a poor clinical effect by the endonasal desensitization therapy, but significant improvement at the microscopic level.

Oral Administration

Stevenson and colleagues,²⁶ were the first to describe two cases of AIA patients who underwent an initial desensitization with incremental doses of aspirin followed by daily therapy. Interestingly, both patients revealed an improvement of the aspirin-sensitive asthma and a reduction of the nasal polyps. Only 4 years later, the same group published the first randomized, double-blind, placebo-controlled, crossover trial of aspirin desensitization in 25 patients with aspirin-sensitive asthma with a daily dosage between 325 and 1300 mg over a 3 month period.²⁷ This survey could demonstrate both a significant improvement of rhino nasal symptoms and a reduced need for nasal corticosteroids in the ASA-treated group compared with placebo. Nevertheless, only half of the patients experienced an improvement of their asthma symptoms.

One hundred and seven patients with diagnosed aspirin sensitivity with rhinosinusitis symptoms and AIA were involved in a retrospective survey published 6 years later.²⁸ In this study, 65 patients were treated by aspirin desensitization whereas a control group of 42 patients avoided all nonsteroidal antiinflammatory drugs (NSAIDs). Taken together, these data clearly demonstrate the clinical benefit of the desensitization therapy for aspirin-sensitive patients including a reduction in the number of hospitalizations and emergency room visits, upper-airway tract infections, and sinus operations; and an improvement in olfactory sense. Twenty percent of the 65 patients of the therapy group reported gastric complaints. Between 1988 and 1994, a long-term, follow-up study on aspirin desensitization with a daily peroral dose of 1300 mg was inaugurated.²⁹

The importance of this study was the finding that aspirin desensitization reduces the aggressive growth and recurrence rate of sinunasal polyps in aspirin-sensitive patients over a longer period. The necessity for a sinunasal surgery declined from one operation every 3 years to one operation every 9 years. However, the number of emergency room visits and need for inhalable corticosteroids remained unchanged. A subsequent study with a similar design on 172 patients demonstrated a reduction of purulent sinusitis from an average of 5 times per year before therapy to less than half of

Table 1 Adaptive desensitization by IV application on patients with low-grade-intolerance		
Day (Hospitalization)	Daily Dose of Lysine-Aspirin in mg (Given Bid, Morning and Afternoon)	
1	50	50
2	100	100
3	200	200
4	300	400
5	400	500
Maintenance-dose (outpatient)	300 mg aspirin daily, po	

Data from Pfaar O, Spielhaupter M, Wrede H, et al. Aspirin desensitization on patients with aspirin intolerance and nasal polyps. A new therapeutic approach by the intravenous route. *Allergologie* 2006;8:322–31.

Table 2

Adaptive desensitization by IV application on patients with high-grade-intolerance

Day (Hospitalization)	Daily Dose of Lysine-Aspirin in mg (Given Bid, Morning and Afternoon)	
1	25	25
2	50	50
3	100	100
4	200	200
5	300	400
6	400	500
Maintenance-dose (outpatient)	300 mg aspirin daily oral, po	

Data from Pfaar O, Spielhaupter M, Wrede H, et al. Aspirin desensitization on patients with aspirin intolerance and nasal polyps. A new therapeutic approach by the intravenous route. *Allergologie* 2006;8:322–31.

that.³⁰ A clinical response to treatment by 67% of patients was evident as early as 6 months, which indicates an early therapeutic effect of the desensitization therapy. Furthermore, these results persisted for 1 to 5 years. On the other hand, 9% discontinued the long-term therapy because of gastric symptoms, which was lower compared with the data of the same group from 1996.²⁹ The authors related these findings to the use of misoprostol and proton pump inhibitors, which became available in recent years.

Intravenous Administration

Recently, the intravenous (IV) route for ASA desensitization has been introduced into clinical practice.³¹ N = 36 patients with a clear, positive history of ASA-intolerance, recurrent sinonasal polyps, and a positive test result in an oral challenge procedure and in an ex vivo test assay³² were treated by ascending doses of intravenous lysine-aspirin under hospital conditions (Tables 1 and 2). The total amount of systemic reactions observed was n = 27 or 6.6% of all therapeutic doses. Of all systemic reactions, 81% were first-degree reactions and 19% second-degree reactions. Systemic reactions of the third or fourth degree have not been revealed.

Taken together, this survey indicated that the intravenous route for the initial ascending phase of ASA desensitization might be a safe procedure without severe complications comparable to the peroral route. In contrast to the peroral application, the intravenous procedure might have the advantage of interrupting the ASA application by stopping the infusion therapy in case of beginning systemic reactions. Undoubtedly, more studies are necessary to investigate the IV application concerning its safety aspects and comparability to the peroral application in the early phase of therapy.

SUMMARY

ASA desensitization is the only treatment that has shown to interfere with the natural course of ASA-intolerance syndrome (Samter's disease). Today, we have good evidence that desensitization reduces the growth and recurrence rate of nasal polyps in aspirin-sensitive patients over a longer period. The necessity for sinus surgery declined and the need for nasal corticosteroids had been reduced. The effect on symptoms, medication need, and exacerbation rate of bronchial asthma in ASA-intolerant patients is not as consistent as the effect on the upper airways. It was proposed

30 years ago that aspirin-precipitated reactions result from inhibition of COX by aspirin-like drugs in the airways or the skin of hypersensitive patients.³³ This basic COX theory has been restricted recently to COX-1 enzyme. Inhibition of COX-1 diminishes the synthesis of prostaglandin E₂, normally acting as a brake on the production of cysteinyl leukotrienes (cysLTs).⁴ Another distinguishing feature of aspirin hypersensitivity is the upregulation of the 5-lipoxygenase pathway, resulting in cysLT overproduction.^{32,34}

In the beginning of ASA desensitization, a refractory status to aspirin or NSAIDs was thought to be the mechanism of action of this therapeutic approach. Now, however, there is more and more evidence for regulatory effects of ASA desensitization.

Based on recent clinical and laboratory data, the authors hypothesize that ASA desensitization leads to a quantitative or qualitative induction of cyclooxygenases, especially COX-1. These enzymes are quantitatively reduced or inactive in ASA-intolerant patients even without the intake of aspirin or other NSAIDs. Therefore, ASA desensitization does alter the natural course of the disease.

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