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EICOSANOIDS, ASPIRIN-INTOLERANCE AND THE UPPER AIRWAYS - CURRENT STANDARDS AND RECENT IMPROVEMENTS OF THE DESENSITIZATION THERAPY

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In 1922, Widal *et al.* were the first to describe intolerance reactions to acetylsalicylic acid (ASA, *e.g.* in aspirin) and to other nonsteroidal anti-inflammatory drugs (NSAIDs). The full clinical picture reveals a classic triad of symptoms (Samters Triad): aspirin induced bronchial asthma (with severe acute asthma attacks), aspirin-sensitivity and chronic rhinosinusitis with nasal polyps. In many cases, nasal polyps reveal as the first symptom of ASA sensitivity indicating that the upper airways are predominantly involved in the pathogenetic process. Therefore, emphasis of this article mainly focuses on the upper airways in ASA-intolerant patients. In the last decade, clear evidence has been pointed out that ASA-intolerance is related to the abnormal metabolism of arachidonic acid leading towards excessive leukotriene (LTs) production. The resulting dysbalance of the eicosanoids leukotrien and prostaglandine might be the crucial pathophysiologic keypoint of the disease. The incidence of aspirin hypersensitivity in the general population ranges from 0.6 % to 2.5% and in adult asthmatics from 4,3 % to 11%. Besides the patients history, challenge tests with Lysin-aspirin are performed as the diagnostic tool of choice. Apart from surgical or pharmacological therapy, ASA desensitization therapy is the only specific treatment of choice. As first described by Stevensson *et al.* in the early 1984, oral administration by means of an initial desensitization with gradually ascending doses of aspirin is followed by a daily maintenance-dose. In the last years, many publications on various desensitization protocols and routes of administration have been worked out. Recently, the intravenous route for the initial increment desensitization has been described which might offer new therapeutical possibilities in the treatment of ASA-intolerant patients.

Key words: *Samter-triad, nasal-polyps, aspirin-sensitive, aspirin-intolerance, aspirin-desensitization, intravenous-route*

INTRODUCTION

Shortly after aspirin (acetylsalicylic acid: ASA) was elaborated cases of severe anaphylactoid reactions after aspirin-ingestion were described by Hirschberg in 1899 (1). Widal *et al.* were the first to portray the association of aspirin sensitivity, Aspirin-induced Asthma (AIA) and nasal polyposis in 1922 (2). The full clinical picture was subsequently pointed out in studies of 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, emphasis of this article mainly focuses on the upper airways in ASA-intolerant patients.

ASA-intolerance: eicosanoids and the arachidonacid-metabolism

In the last decade, knowledge concerning the pathophysiologic mechanisms underlying ASA-intolerance has been focussed 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 Lipoxygenase (LO) and the cyclooxygenase (CO)-pathways (4, 5). This deviation results in a dysbalance of the synthesis of both eicosanoids, leukotriens and prostaglandins. Anti-inflammatory prostaglandins, especially E₂, decrease and the synthesis of cysteinyl-leukotriens like leukotrien-A⁴, -B⁴, -C⁴ and -D⁴ is increased (5, 6) (*Fig. 1*).

Prevalence of ASA-intolerance

Aspirin intolerance is supposed to be underestimated: in a population of 500 patients with AIA studied in the European Network of Aspirin-Induced Asthma (AIANE), 18% were unaware of aspirin intolerance before having aspirin challenge tests (7). More interesting, when patients with AIA also suffered from concomitant rhinosinusitis even 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 even 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 concomittant chronic nasal congestion, hyposmia, chronic rhinorrhea as well as nasal polyps might reveal (8, 9). Finally, the disease results in AIA: 20% of the AIA-patients suffer from mild and intermittent asthma, 30% are moderate asthmatics who can be controlled with inhaled steroids whereas 50% of the patients have a chronic, severe corticoid-dependent asthma often accompanied by systemic anaphylactoid reactions (9).

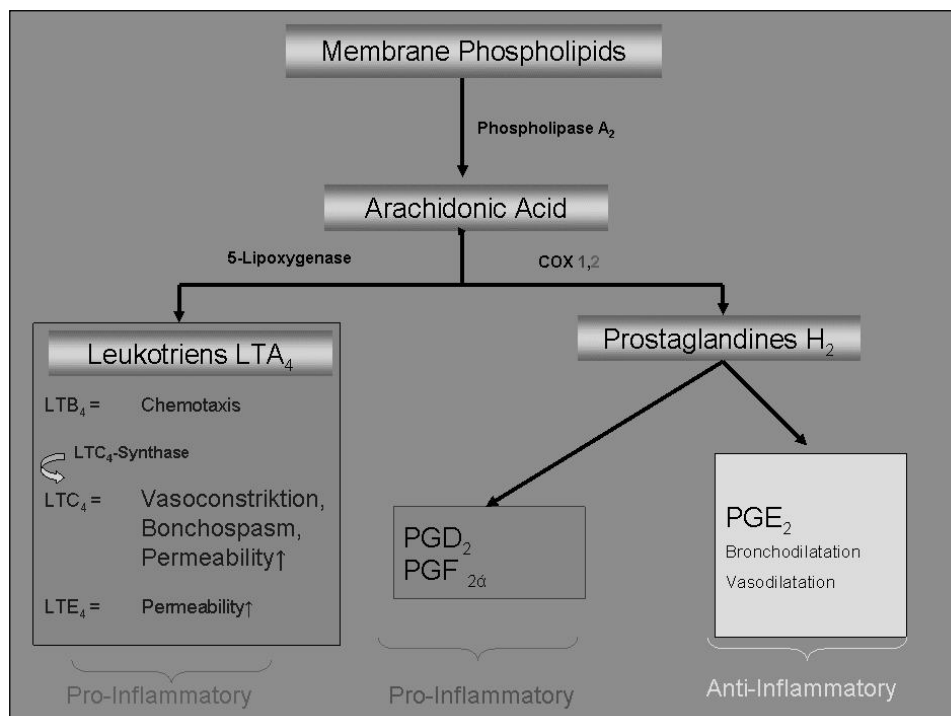


Fig. 1. The exact mechanisms of aspirin intolerance as well as those of therapy by ASA-desensitization still remain unclear. Evidence has been worked out that ASA-intolerance is not an IgE-mediated reaction but is related to an abnormal metabolism of arachidonic acid implicating both the Lipoxygenase (LO) and the Cyclooxygenase (CO)-pathways. This deviation results in a dysbalance of the synthesis of the eicosanoids towards a predominance of the pro-inflammatory leukotriens (5, 6).

Upper-airways: "key-area" of the ASA-intolerance

Rhinosinusitis was found to be a predominating symptom in 500 ASA-intolerant patients in a multicenter survey of Szczeklik and Nizankowska (10). Interestingly, nasal symptoms revealed on 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%. In average the first asthmatic symptoms appeared two years later.

Nasal polyps

In 70 % of ASA-intolerant patients nasal polyps can be found whereas in 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 affection could be radiologically proven in almost all cases with AIA in an American study (9).

The pathogenetic link between ASA-intolerance and the origin of the nasal polyps still remains unclear: infectious agents like viruses, bacteria or fungi as potential primary factors might activate nasal epithelial cells and proinflammatory cytokines like eotaxin and growth factors and, thereby, promote the inflammatory process (11, 13, 14). Further possible explanations might be differences in HLA genes (15), a reduced apoptosis-rate of local inflammation cells *e.g.* eosinophils (16) or a differential role of cyclooxygenase 1 and cyclooxygenase 2 having special regulator functions in the pathogenesis of nasal polyps (17).

Interestingly, the recurrence rate of nasal polyps after resection in ASA-intolerant patients is tremendously high: in a study of Jantii-Alanco *et al.* the recurrency rate is almost three times higher in AIA than in non-intolerant intrinsic asthmatics (18).

Diagnosis

Four typical findings in the patients history might correspond to intolerance to aspirin and other NSAIDs (5 - 7): i) typical symptoms of respiratory reactions after aspirin-challenge; ii) asthma attacks accompanied by chronic nasal congestion and watery, profuse rhinorrhoea; iii) high frequency of severe asthmatic attacks; iv) high frequency of nasal polyps.

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 carried out in specialised clinics fairly prepared for cases of anaphylactic reactions. Four types of aspirin-challenge can be performed depending on the manner of administration: oral, inhalative, nasal and intravenous (7).

In cases of predominant nasal symptoms nasal challenge test with aspirin might be performed as 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 patients' history, bronchial and/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 results in a severe, potentially life-threatening course. This underlines the importance of educating the patients in avoiding ASA and all other cross-

reacting, non-selective COX-inhibitors (5, 6, *Table 1*). However, selective COX-2 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 microscopical techniques. However, the recurrence rate is quite high: in a prospective study of 227 patients operated on nasal polyposis between 1993 and 2001 a significant higher rate of recurrences has been revealed in the AIA-group compared to patients tolerant to ASA (21).

Aspirin desensitization

In 1976, Zeiss and Lockey described the paradoxical finding that ASA-intolerant patients revealed a 3-day refractory period after oral aspirin challenge (22). This report marked a new therapeutic option in the management of aspirin-sensitive patients: Could it be possible to treat the inflammatory airway-process with exactly the same medicament which undoubtedly caused the symptoms? Based on these findings, various desensitization protocols and routes of administration have been elaborated in the last two decades: bronchial, endonasal, oral and, recently published, intravenous route.

Table 1. NSAIDs that cross-react with aspirin (5)

Inhibitor Pathways	NSAIDs
Predominant COX-1 and COX-2 inhibitors	Piroxicam Indomethacin Sulindac Tolmetin Diclofenac Naproxen Naproxen sodium Ibuprofen Fenoprofen Ketoprofen Flubiprofen Mefenamic 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

i) 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).

ii) endonasal administration

In case of predominating nasal-symptoms like rhino-nasal polyps this route of administration has mainly shown efficacy. In a study of Patriarca *et al.* 43 patients suffering from nasal polyposis intranasal desensitization was performed with increasing doses of lysine acetylsalicylate (LAS) corresponding to 20, 200, and 2000 micrograms of aspirin until a maximum dose of 2000 micrograms weekly was reached (24). In a 5-year follow up, recurrence rates of nasal polyps were significantly lower in the aspirin-treated group compared to the control group. Recently, the first randomized, double blind, placebo controlled, cross-over 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.

iii) oral administration

Stevenson *et al.* were the first to describe two cases of AIA-patients who underwent an initial desensitization with incremental doses of aspirin followed by daily therapy (26). Interestingly, both patients revealed an improvement of the aspirin-sensitive asthma as well as a reduction of the nasal polyps. Only four 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 three-month period (27). This survey could demonstrate both a significant improvement of rhino-nasal symptoms as well as a reduced need of nasal corticosteroids of the ASA-treated group compared to placebo. Nevertheless, only half of the patients experienced an improvement of their asthma-symptoms.

107 patients with diagnosed aspirin-sensitivity with both 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 NSAID. Taken together, these data clearly demonstrate the clinical benefit of the desensitization therapy to aspirin-sensitive patients concerning a reduction in the number of hospitalizations and emergency room visits, upper airway tract infections and sinus operations as well as an improvement in olfactory sense. Interestingly, 20% of the 65 patients of the therapy group reported gastritic complaints.

Between 1988 and 1994 a long term follow-up study on aspirin-desensitization with a daily peroral dose of 1300 mg has been inaugurated (29).

The outstanding importance of this study was the finding that aspirin-desensitization in fact reduces the aggressive growth and recurrence rate of sinusal polyps in aspirin-sensitive patients over a longer time period. The necessity for a sinusal surgery declined from one operation per 3 years to one operation per 9 years. However, the number of emergency room visits and need of inhalative corticosteroids remained unchanged in this study.

A subsequent study on 172 patients with a similar study design demonstrated a reduction of purulent-sinusitis rate from an average of 5 times per year before therapy to less than half of that (30). Interestingly, a clinical response to treatment rate of 67% was evident as early as 6 months which indicates a relative 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 due to gastritic symptoms which was lower compared to the data of the same group from 1996 (29). The authors related these findings to the use of misoprostol and proton pump inhibitors, both of which became available in recent years.

iv) i.v. administration

In a recently published study possible side effects by using the intravenous route for ASA desensitization were studied (31). 36 patients with a clear positive-history of ASA-intolerance, (recurrent) sinusal polyps and a positive test-result using peripheral white blood cells (32) were treated by ascending doses of intravenous lysine-aspirin under hospital conditions (*Table 2a* and *Table 2b*). The total amount

Table 2a. Adaptive desensitization by i.v. application on patients with low-grade-intolerance (31)

Day (Hospitality)	daily dose of lysin-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, p.o.	

Table 2b. Adaptive desensitization by i.v. application on patients with high-grade-intolerance (31)

Day (Hospitality)	daily dose of lysin-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, p.o.	

of systemic reactions observed was $n = 27$ or 6.6% of all therapeutic doses. Of all systemic reactions, 81% were 1st degree reactions and 19% 2nd degree reactions. Systemic reactions of the 3rd or 4th 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 intravenous application concerning its safety aspects and comparability to the peroral application in the early phase of therapy.

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