

Role of aspirin desensitization in the management of chronic rhinosinusitis

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Purpose of review

This review is set to revisit the pathogenesis of aspirin-exacerbated respiratory disease (AERD), the diagnostic method used, and finally the real impact of aspirin desensitization on chronic sinusitis with nasal polyposis (CRSwNP) in aspirin intolerant patients.

Recent findings

In AERD, increased baseline production of cysteinyl-leukotriene (Cys-LT) is associated with upregulation of Cys-LT receptors on nasal inflammatory cells. This is further aggravated by inhibition of cyclooxygenase-1 by aspirin and other NSAIDs. New-found genetic markers need further study. Oral aspirin challenge is still the gold standard of diagnosis and can be safely conducted in a specialized outpatient clinic. Oral and endonasal aspirin desensitization show positive impact on CRSwNP course with decreased polyp recurrence, decreased number of hospitalizations, and decreased need for corticosteroids. Modulation of arachidonic acid metabolism and inhibition of intracellular biochemical pathways in key inflammatory cells involving anti-inflammatory cytokines interleukin (IL)-4 and IL-13 explain the clinical outcomes.

Summary

Future studies should focus on establishing the lowest possible dose to maintain disease under check, allowing more widespread use of this underutilized and underrecognized treatment modality.

Keywords

aspirin desensitization, aspirin-exacerbated respiratory disease, chronic rhinosinusitis with nasal polyposis, cysteinyl-leukotrienes

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Introduction

The triad of sinusitis, bronchial asthma, and aspirin intolerance is known as Widal's syndrome, Samter's triad, and aspirin-exacerbated respiratory disease (AERD). The most recent consensus nomenclature describing acetylsalicylic acid (ASA)-induced respiratory reactions is nonallergic hypersensitivity reaction. Patients with chronic rhinosinusitis (CRS) with nasal polyps are more likely to have aspirin hypersensitivity or asthma than the general population. Nasal polyps are reported in up to 70% of aspirin intolerant patients with asthma, whereas their prevalence is only 4% in the general population. In sensitive individuals, even a very small single dose of aspirin or other cyclooxygenase-1 (COX-1) inhibitor can cause rhinorrhea, bronchospasm, and shock [1•].

These patients usually have a more aggressive sinonasal disease with need for multiple endoscopic sinus surgery over the years.

Aspirin desensitization, although unpopular because of the fear of severe reactions, has proven to be a valuable

therapeutic tool in these severe recalcitrant cases. This paper sums up the pathogenesis of AERD, explores the diagnostic methods that can be used, and finally reviews the role of aspirin desensitization specifically in the treatment of upper airway disease with focus on the mechanism of action of this underutilized treatment modality.

Pathogenesis: nonallergic hypersensitivity reaction

In 1971, Vane discovered the effects of ASA and NSAIDs on inhibition of COX enzymes in the metabolic cascade of arachidonic acid metabolism. The COX enzymes exist in at least two isoforms, COX-1 and COX-2. COX-1 is expressed in most mammalian cells. COX-2 is induced during inflammation. COX-3 is expressed in the brain and heart. In 1980, the first report of a second metabolic pathway for arachidonic acid metabolism also involved in inflammation was published. This pathway involves 5-lipoxygenase enzyme induction of leukotriene synthesis. Leukotrienes C, D, and E₄ [(LTC, LTD, and LTE₄)] are potent mediators of chemotaxis of

eosinophils, increased vascular permeability, mucous gland secretion, and bronchoconstriction. Interestingly, as the COX pathway is blocked, there is preferential diversion to the 5-lipoxygenase pathway [2].

Figure 1 summarizes the pathways of arachidonic acid metabolism with the most important effectors [3].

According to a recent classification, AERD is a type I pseudoallergic reaction independent of IgE, related to excessive production of leukotrienes by 5-lipoxygenase, which results in mast-cell degranulation and release of histamines and cytokines, causing respiratory symptoms such as rhinitis and asthma [4].

Prostaglandin E₂ (PGE₂), produced by the COX pathway, is an inhibitor of 5-lipoxygenase and leukotriene production. Aspirin inhibits production of PGE₂, causing a release of inhibition of the 5-lipoxygenase enzyme and an increase in leukotriene production [1^{*}]. Reduced PGE₂ synthesis also results in decreased mast cell stability and increased release of histamine and tryptase [5^{**},6].

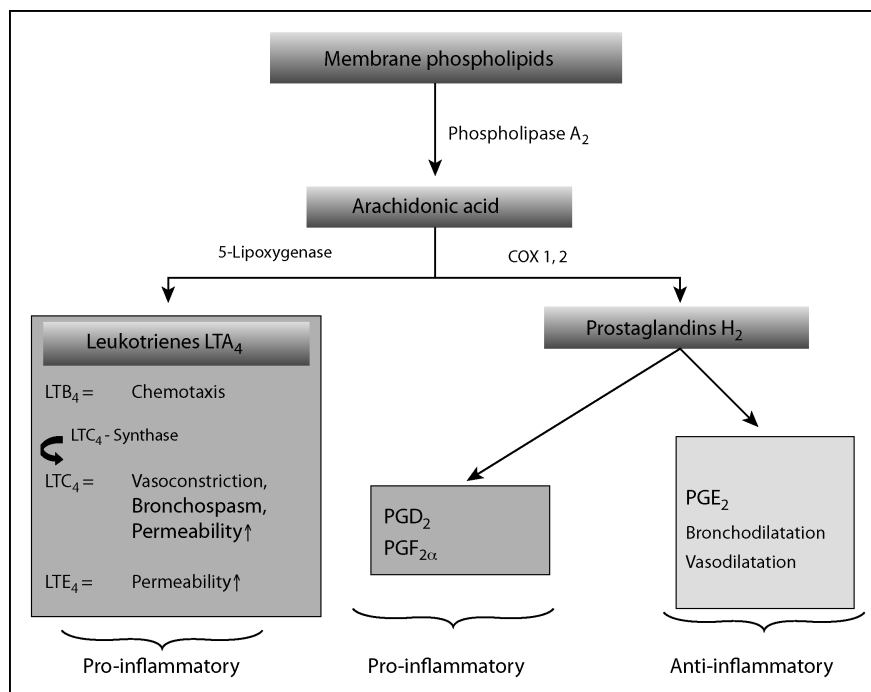
Table 1 summarizes the different NSAIDs with their action on COX. There is now good evidence that selective COX-2 inhibitors such as celecoxib are well tolerated

Key points

- Aspirin-exacerbated respiratory disease (AERD) is a type I pseudoallergic nonIgE-mediated hypersensitivity reaction to aspirin and other cyclooxygenase-1 (COX-1) inhibitors, due to modulation of arachidonic acid metabolism.
- AERD patients have high baseline leukotriene production and leukotriene receptors on nasal and bronchial inflammatory cells.
- Underdiagnosed entity: oral aspirin challenges are the gold standard and can be performed in an outpatient clinic.
- Aspirin desensitization has proven effective in inducing tolerance, and, with chronic treatment, modification of natural disease course occurs, with decrease in polyposis recurrence, decrease in need for endoscopic sinus surgery, decrease in need for systemic corticosteroids, and return of sense of smell.
- Further studies are needed to understand fully the mechanism of action of aspirin desensitization.

by AERD patients. There are even some reports of AERD patients noting improvement of symptoms when using celecoxib [1^{*},5^{**}]. In a double-blind, controlled study of patients with AERD, rofecoxib, unlike ASA, neither precipitated respiratory reactions nor stimulated

Figure 1 Arachidonic acid metabolism: cyclooxygenase and lipoxygenase pathways



Aspirin inhibits cyclooxygenase, diverting the metabolism toward production of leukotrienes. Patients with aspirin-exacerbated respiratory disease (AERD) already have a higher LTC₄ synthase activity in their bronchial mucosa, which imbalances the metabolism away from anti-inflammatory prostaglandins, notably PGE₂. Cyclooxygenase-2 (COX-2) has a smaller role in PGE₂ production. Modified with permission from Pfaar and Klimek [3].

Table 1 NSAID differences in cyclooxygenase-1 and cyclooxygenase-2 inhibition

Inhibitor pathways	NSAIDs
Predominant COX-1 and COX-2 inhibitors	Piroxicam; indomethacin; sulindac; tolmetin; diclofenac; naproxen; naproxen sodium; ibuprofen; fenoprofen; ketoprofen; flurbiprofen; 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 3 inhibitors	Acetaminophen, phenacetin, dipyrrone

COX, cyclooxygenase.

biosynthesis of cysteinyl-leukotrienes (Cys-LTs) [7]. Even though acetaminophen and paracetamol are low COX-1 and COX-2 inhibitors, 1% of patients are sensitive. Paracetamol-induced bronchospastic reactions occur at doses of paracetamol higher than 1000 mg in patients sensitive to low provoking doses of ASA [7–10]. This means that the only safe NSAIDs in ASA patients are COX-2 inhibitors.

Aspirin-sensitive patients seem to be particularly dependent on tonic inhibition of Cys-LTs generation by the action of PGE₂ on target cellular receptors due to relative deficiency of production and/or abnormality of receptor expression and/or signaling. As COX-1 expression is not deficient in bronchial mucosal inflammatory leukocytes in these patients, this imbalance can be related to PGE₂ receptor deficiency on effector cells [11,12].

Moreover, a fundamental feature of aspirin sensitivity is excessive production of Cys-LTs in the steady state, which is further elevated after aspirin exposure [5**]. Sousa *et al.* [13] demonstrated that in AERD-tolerant, and not in ASA-tolerant, asthmatic patients nasal inflammatory cells expressed more Cys-LT₁ receptors. Recent advances in molecular biology showed a Cys-LT₁ receptor polymorphism associated with increased receptor expression in patients with AERD [14]. Thus, more receptors are available to receive leukotrienes. It has also been demonstrated that patients with AERD have reduced biosynthesis of lipoxins through an unknown mechanism; the natural anti-inflammatory system based on lipoxins is impaired [6,8].

The effector cells of this hypersensitivity reaction are first the eosinophils that are colocalized with leukotriene C₄ synthase expression, the key enzyme in the Cys-LT

pathway. Mast cells also participate in this reaction via an IgE-independent mechanism. Microenvironmental conditions created by the presence of fibroblasts and/or eosinophils enable mast cells to release their products (PGD₂ notably) upon activation with stimuli operating on G-protein-coupled receptors [8].

Some authors have suggested that AERD is the result of a chronic or latent viral infection of the respiratory tract with activation of T lymphocytes and secretion of cytokines, followed by recruitment, activation, and stimulation of inflammatory cells [2,5**].

Finally, recent studies [15] have implicated interleukin (IL)-10 and tumor growth factor-β₁ (TGF-β₁) polymorphism in AERD and rhinosinusitis through gene-gene interaction.

Recognizing aspirin-exacerbated respiratory disease: diagnostic methods

AERD usually has a typical pattern of presentation: first rhinitis 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. Finally, the disease results in aspirin-intolerant asthma (an average of 2 years separates rhinitis from asthma). Fifty percent of the patients have a chronic, severe, corticoid-dependent asthma, often accompanied by systemic anaphylactoid reactions [6,16**]. Once developed, aspirin intolerance remains throughout life, although sporadic disappearance of intolerance has been reported.

Despite this typical clinical presentation, this condition is underdiagnosed. In one European survey, 15% of asthmatic patients were unaware of their aspirin sensitivity before undergoing positive aspirin provocation tests. In a meta-analysis of 15 studies that used oral aspirin challenges to detect AERD in adult asthmatic patients, the average prevalence was 21%. In patients with rhinosinusitis and nasal polyposis, the prevalence of aspirin hypersensitivity is even higher, reaching 30–40% [6,17].

Atopy is present in one-third of AERD patients, whereas some report 66% of positive skin tests to common aero-allergens in these patients. It was also observed that aspirin-sensitive rhinitis and asthma develop significantly earlier in patients with positive rather than with negative skin tests [6,8].

There are to date no in-vitro diagnostic tests. Those based on the release of Cys-LTs by peripheral blood leukocytes proved to be nonspecific. Potential genetic biomarkers have been identified and further studies are needed to determine their diagnostic value [18].

Table 2 Oral aspirin challenges in patients with suspected aspirin-exacerbated respiratory disease

Time	Day 1 ^a	Day 2 (or 1)	Day 3 (or 2)
8:00 a.m.	Placebo	20–40 mg ^b	100–160 mg
11:00 a.m.	Placebo	40–60 mg	160–325 mg
2:00 p.m.	Placebo	60–100 mg	325 mg ^c
Measure FEV ₁ every hour and wait 3 h between doses			
FEV ₁ should be at least 1.5 l to proceed but <70% of predicted is preferred			
Reactions can be as follows:			
Naso-ocular alone			
Naso-ocular and a more than 15% decline in FEV ₁ (classic reaction)			
Lower respiratory reaction only (FEV ₁ declines >20%)			
Laryngospasm with or without a,b,c (flat or notched inspiratory curve)			
Systemic reactions: hives, flushing, gastric pain, hypotension			
Aspirin desensitization			
After a reaction has been treated and FEV ₁ values have returned to baseline			
Repeat the aspirin-provoking dose			
If no reaction, continue to escalate the doses as above			
At 325 mg, desensitization is always completed			
Give 650 mg as first dose, and then treat with 650 mg twice daily			

Modified with permission from Stevenson [5^{••}]. FEV₁, forced expiratory volume in 1 s.

^aA placebo challenge can be conducted the week before. If the patient's baseline FEV₁ is the same as the previous best value and if he or she has not used an albuterol rescue inhaler in the past week, you can skip the first day of placebo challenge.

^bUsing a pill cutter, a 81-mg aspirin tablet can be cut in half or into quarters.

^cIf the patient has not reacted to 325 mg, he/she will not react to 650 mg and we call it a negative challenge.

On the other hand, new noninvasive methods, such as the assessment of eicosanoid levels in exhaled air condensate or induced sputum, might be developed in the future as interesting diagnostic tools [8].

The gold standard for the diagnosis of AERD is an oral provocation test under close supervision [1[•]]. There are various protocols: nasal, bronchial, oral, and intravenous [16^{••}]. In case of predominant nasal symptoms, a nasal challenge test is done. If it is negative and the clinical picture is compatible with AERD, bronchial or oral provocation tests are then used [16^{••}]. Oral and bronchial tests have similar specificities, but oral challenge has a higher sensitivity. Nasal tests have lower sensitivity than both oral and bronchial modalities [7]. An example of an aspirin challenge protocol used in the Scripps clinic is illustrated in Table 2 [5^{••}]. Previous studies have shown that severe reactions requiring intubation and ventilation are rare. Authors at the Scripps clinic use an outpatient setting with a qualified team to conduct these aspirin challenges, which makes the diagnostic test more available without compromising patient safety [5^{••}]. If there is any concern about safety, pretreatment with leukotriene antagonists and low provoking dose can be adopted in the protocol [19,20[•]].

Aspirin desensitization: is there any evidence?

One major goal in controlling AERD disease is to reduce inflammation of affected mucosa, with the following corollaries: prevention of nasal polyp formation, and controlling of sinusitis and asthma [2]. Zeiss and Lockey were the first authors to describe a 72-h refractory period after oral ASA challenge in ASA-sensitive patients in 1976 [3].

In 1980, Stevenson *et al.* [21] reported two ASA-sensitive asthmatic patients who became refractory to ASA after single-blind oral challenges with ASA. Both patients, after desensitization, experienced improvement in respiratory disease; nasal obstruction was reduced and loss of olfaction was diminished. 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. Although this study showed significant improvement in symptoms of rhinosinusitis and a decrease in the daily amount of nasal corticosteroids required while on ASA, it was underpowered and no changes in asthma medications, lower respiratory symptoms, or FEV₁ (forced expiratory volume in 1 s) were noted.

A retrospective trial including 107 patients with diagnosed ASA sensitivity with rhinosinusitis–asthma compared the clinical outcome of 65 patients who underwent ASA desensitization with 42 patients who solely avoided all NSAIDs. Significant reductions in the number of hospitalizations, emergency room visits, outpatient visits, upper airway tract infections, and sinus operations were noted in the intervention group. In addition, ASA desensitization concomitantly allowed reduction in systemic corticosteroid needs [22].

In a long-term follow-up study of 65 ASA-sensitive patients at the Scripps clinic 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 [3,16^{••}]. This study was the first to show

evidence that ASA desensitization in fact reduces the aggressive growth and recurrence rate of sinonasal polyps in ASA-sensitive patients over a longer time period. The necessity for sinonasal surgery declined from one operation per 3 years to one operation per 9 years [23]. This treatment modality does not, however, cause regression of preexisting polyps [1•].

In a recent study at the Scripps clinic, 172 patients were desensitized to ASA between 1995 and 2000, treated with 1300 mg of ASA each day and then followed for 1–5 years. Objective measurements of clinical outcomes were obtained at baseline, at 6 months of treatment, and at the end of the last year of follow-up. Improvement in clinical courses, reduction in doses of corticosteroids, and improvement in global assessments were documented at 6 months and did not decline during the remaining 1–5 years of the study [7]. The same results were observed after 1–6 years of daily maintenance therapy of 325–650 mg twice daily (b.i.d.) [2,24].

The positive effect of desensitization on AERD patients' mucosal disease with resultant decrease in need for further revision endoscopic sinus surgery has been further supported by recent studies [23,25,26,27], including one randomized controlled trial [28].

All of these results were observed as early as 4 weeks after the initiation of the desensitization protocol [29].

Various aspirin doses (100–1300 mg) and routes of administration (oral, intranasal, bronchial, and intravenous) are reported. Other NSAIDs such as ibuprofen, which can provoke the symptoms, are not effective in desensitization. To date, desensitization can only be accomplished with aspirin or lysine-aspirin [9]. The recent efficacy of nasal challenge using ketorolac might open the way to alternative products for desensitization [5•,30•]. Threshold doses evoke positive reactions after the ingestion of 30–150 mg ASA (average, 60–75 mg) [7]. Starting doses and final doses vary among studies [31]. Practitioners at the Scripps clinic who pioneered the aspirin desensitization in the treatment of AERD suggest a protocol for an outpatient-based procedure, which is as follows [32]:

(1) Rationale

- (a) Aspirin-induced reactions are dose dependent. Aspirin given in small enough doses will usually induce smaller reactions than the historical reaction (650 mg of aspirin).
- (b) For many patients, historical aspirin reactions occurred before the use of controller therapies: inhaled corticosteroids (ICSs), long-acting bronchodilators (LABs), leukotriene modifier drugs

(LTMDs), and systemic corticosteroids (SCSs). Pretreatment with these medications usually provides stability to the lower airways during aspirin challenge.

(2) Patient selection:

- (a) Suspected AERD with mild-to-moderate prior historical reactions.
- (b) Unresponsive to ICSs, LABs, and LTMDs.
- (c) Aggressive nasal polyp formers.
- (d) Unable to discontinue SCSs or many bursts of SCSs.
- (e) In need of daily aspirin because of coronary artery disease.

(3) Protocol:

- (a) One to 7 days before challenge, determine airway stability.
 - (i) $FEV_1 > 60\%$ of predicted value (> 1.5 l absolute).
 - (ii) FEV_1 every hour $\times 3$ h – $< 10\%$ variability.
 - (iii) Start or continue montelukast, 10 mg every day.
 - (iv) Start or continue ICSs/LABs.
 - (v) Start SCS burst for low FEV_1 or any bronchial instability.
- (vi) Discontinue antihistamines 48 h before challenge.
- (b) Oral aspirin challenge.
 - (i) Day 1: start intravenous line at 7–8 a.m. with heparin lock (keep in for 3 days).
 - (ii) At Scripps, we use gelatin capsules with 30, 45, 60, 100, 150, or 325 mg of aspirin powder. You can use a pill cutter and 81-mg aspirin tablets. Use a first dose of 20.25 or 40.5 mg of aspirin followed by 60.75, 81, and 101.25 mg; then half a 325-mg aspirin tablet; and then a full 325-mg aspirin tablet. Increase every 3 h.
 - (iii) FEV_1 and clinical assessment every hour or with any symptoms.
 - (iv) Reaction will likely occur with doses between 20 and 101 mg. When it occurs, treat with the medications described below. This is called the provoking dose.
 - (v) After the patient is completely stabilized, the provoking dose can be repeated on day 1 (assuming another 3 h before 5 or 6 p.m.). Otherwise, symptoms should be treated, the patient should be sent home, and the provoking dose should be repeated the next morning. Day 2: start with repeating provoking dose (if not given on day 1). Otherwise, physician can begin increasing the dose every 3 h (101.25, 162, 325, and 650 mg).
 - (vi) If nasal, gastrointestinal, or cutaneous reactions occur on day 1, pretreat with H_1 and H_2 blocker for the remainder of the challenge sequence.
 - (vii) Chance of reaction to repeated threshold dose is small, but, if it occurs, repeat that dose until reactions cease and then proceed to the next highest dose of aspirin.
- (4) Treatment of the aspirin-induced reactions
 - (a) Ocular: topical antihistamine.

- (b) Nasal: antihistamine (oral) or diphenhydramine, 50 mg administered intravenously, topical decongestant.
- (c) Laryngeal: racemic epinephrine nebulization (2.5 mg/2 ml), five inhalations and pause.
- (d) Bronchial: five inhalations of β -agonist every 5 min until comfortable.
- (e) Gastrointestinal cramping: intravenous ranitidine, 50 mg.
- (f) Urticaria/angioedema: intravenous diphenhydramine, 50 mg.
- (g) Hypotension: epinephrine 1:1000 0.3 ml administered intramuscularly (occurred in one in 300 of our patients).

The effects of desensitization are temporary because it is not an immunotherapy; if the drug is interrupted for more than 72 h, the patient recovers his/her previous sensitivity within a few days [4]. Furthermore, it permits cross-desensitization to all other NSAIDs.

The need for a chronic intake of aspirin leads to several side-effects that make it impossible for some people to be compliant. In older studies, around 30% of patients had to discontinue aspirin due to gastric irritation. In recent studies, this number is around 9%, due maybe to widespread availability of proton-pump inhibitors and misoprostol [16^{••}]. This has incited some authors to look for the lowest dose possible to achieve respiratory disease control, which led to contradictory results. Indeed, although a dose as low as 81 mg/day can induce tolerance, it has no effect on disease course [33^{••}]. A maintenance dose of 100 mg was then explored: recent prospective studies showed promising results with this low dose [25,34,35,36^{••}], whereas another one noted that 100 mg is inefficient in preventing polyp recurrence and asthma control [37].

Until further evidence is obtained, the classical maintenance dose is still 325–650 mg.

Most older studies use oral protocols. Recently, more studies have been undertaken using endonasal administration as it has lower risk of severe reactions. It has mainly shown good results in treatment of nasal polyps. In a study by Patriarca *et al.* [38], 43 patients suffering from nasal polyposis underwent intranasal treatment with increasing doses of lysine-ASA corresponding to 20, 200, and 2000 mg of ASA, until a maximum dose of 2000 mg weekly was reached. Recurrence rates of nasal polyps were significantly lower in the therapy group compared with controls in a 5-year follow-up. In 2005, 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 [39]. Despite a failure

to demonstrate clinical benefit, tissue studies showed a reduction in the number of inflammatory cells in nasal mucosa expressing Cys-LT receptor. The lack of a significant clinical effect may have been due to the low number of patients.

Bronchial administration protocol consists of inhalation of aerosolized L-lysine aspirin. The test can be completed in 4 h, and reactions are generally mild bronchospasm, easily reversed with β -agonists and usually restricted to the lower respiratory tract [7]. This route of administration has been developed on the premise that refractory tolerance could be achieved by repeated provocation with lysine-ASA inhalation [3,16^{••}].

Finally, the intravenous protocol has recently been introduced to clinical practice using intravenous lysine-aspirin in a controlled setting. Initial surveys [16^{••}] show it to be a relatively safe procedure with no more severe systemic reactions than the peroral route of administration, with the advantage of being able to stop the infusion in case a severe reaction occurs. More studies are needed to investigate the safety profile and the comparability to peroral results [16^{••},40].

Regardless of the protocol used, the exact mechanism of action of aspirin desensitization in AERD disease course is still undefined. However, recent studies shed light on several putative mechanisms.

Modulation of arachidonic acid metabolism

As cited previously, one of the pathomechanisms of AERD is an increased expression of Cys-LTR1 on inflammatory cells from nasal and bronchial mucosae. In patients with aspirin-induced asthma who had rhinosinusitis, the increased absolute number of nasal inflammatory cells expressing Cys-LT₁ receptors after 5 months of treatment with nasal ASA-lysine declined to a level found in non-ASA-sensitive control asthmatic individuals [3,8,9,13].

Significantly reduced production of thromboxane B₂ as a product of COX-1 and COX-2 in monocytes taken from ASA-sensitive patients undergoing chronic desensitization therapy (650 mg b.i.d.) has also been seen. LTB₄ synthesis in peripheral monocytes declined to the same level as found in normal controls. Chronic ASA desensitization depressed urine LTE₄ levels, but not to the levels found in normal controls [3].

Modulation of other biochemical pathways

Current evidence supports the concept that treatment success is not mediated through acetylation of COX-1 enzyme by aspirin. ASA might have direct effects on the

internal biochemical pathways of key inflammatory cells. For example, in a variety of cells, ASA and sodium salicylate have been reported to inhibit activation of the transcription factor nuclear factor- κ B (NF- κ B) and to inhibit IL-4-induced and IL-13-induced activation of STAT6. These studies raise the possibility that, after ASA desensitization is completed, the intracellular inhibitory effects of ASA lead to blunting of the inflammatory response [7,41,42*,43*]. These studies also give insight into finding candidate drugs that can act on IL-4 via a COX-independent mechanism, allowing us to use agents to desensitize patients without the concern for an adverse hypersensitivity reaction. The possibility of a new, nonaspirin, salicylate-based treatment for AERD is worthy of further study [33**].

Conclusion

Although unpopular, aspirin desensitization has proven to have a positive impact on the disease course of AERD patients with chronic sinusitis with nasal polyposis (CRSwNP). Recently, it has been regarded as a beneficial treatment (class A recommendation) that should be considered in all patients with AERD and refractory CRS with nasal polyposis requiring high-dose systemic corticosteroids or repeated endoscopic sinus surgeries, or in patients requiring ASA/NSAIDs for other diseases such as thromboembolism and arthritis [5**,44,45]. Contra-indications include patients with unstable asthma, asthma nonresponsive to corticosteroid therapy, patients on β -blockers, and patients with potential compliance problems [25,32].

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 (p. 232).

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