Individual Monitoring of Aspirin Desensitization

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Background: Patients with aspirin-sensitive rhinosinusitis, which is frequently associated with intrinsic bronchial asthma, can be desensitized by long-term treatment with oral aspirin. The exact mechanisms of this desensitization remain obscure, but modulations of the eicosanoid pathway occur and can be monitored with the help of a practicable in vitro assay on mixed leukocyte cultures.

Objective: To monitor the effect of low-dose aspirin desensitization therapy, 100 mg/d, objectively by an in vitro assay.

Design: In a prospective study, 30 patients with aspirin intolerance, who were treated following a desensitization protocol with a dose of oral aspirin of only 100 mg/d were followed up for 1 year and reassessed every 3 months clinically and in vitro.

Results: Twenty-five patients showed a normalization of in vitro eicosanoid levels during this period, 4 showed some improvement, and 1 showed no therapeutic effect on eicosanoid release. Clinical follow-up revealed a low recurrence rate of nasal polyposis, with recurrent disease only in 4 individuals who also showed no normalization of eicosanoid release levels. Furthermore, a reduction of the average incidence of purulent episodes of sinusitis was seen after 1 year. Of 12 patients with asthma, 9 experienced marked improvement in pulmonary function. Of 16 individuals with a marked impairment of nasal breathing, 14 felt an increase of nasal patency, and 7 of 11 patients with pretreatment hyposmia had an improved sense of smell after 1 year.

Conclusions: Desensitization therapy in patients with aspirin-sensitive rhinosinusitis can be successfully performed with low oral doses of aspirin, and the individual course throughout the desensitization can be monitored with the help of an in vitro analysis of eicosanoid release from mixed leukocyte cultures.


ASPIRIN INTOLERANCE (AI) in patients with chronic rhinosinusitis has been recognized as one possible reason for recurrent nasal polyps and certainly should be considered as a pathogenic mechanism in patients in whom nasal polyposis is combined with intrinsic bronchial asthma.1,2 Since the onset of the different clinical symptoms in the development of AI is variable, sometimes by a number of years, the diagnosis of AI is not always associated with the full clinical picture of the aspirin triad, which consists of (1) nasal polyposis; (2) intrinsic bronchial asthma; and (3) aspirin-induced worsening of asthmatic symptoms, often associated with naso-ocular symptoms.3,4 However, in sensitive individuals, even small, single doses of aspirin may cause rhinorrhea, bronchiolar constriction, and shock symptoms related to a non–IgE-mediated pharmacological hypersensitivity reaction.5 After recently published data pointed out an imbalance of prostaglandin E2 (PGE2) and peptidoleukotrienes (pLTs) in aspirin-intolerant individuals with asthma,6 2 further studies7,8 were initiated. The results of these studies supported the hypothesis that this assay can be used as an alternative method to establish the diagnosis of AI as opposed to the use of oral, nasal, or bronchial aspirin challenge tests. It is known that not only aspirin but most other nonsteroidal anti-inflammatory drugs interact with the arachidonic acid pathway. They are known to cause inhibition of the cyclooxygenases (mainly isoenzyme cyclooxygenase 1), which metabolize arachidonic acid to prostaglandins. This inhibition leads to an up-regulation of the alternative pathway, with lipoxygenases metabolizing arachidonic acid to leukotrienes. However, this cannot be the sole
PATIENTS AND METHODS

In a prospective study, 30 patients (16 men and 14 women; average age, 47.9 years; age range, 28-63 years) underwent aspirin desensitization therapy and were followed up for 1 year. Twenty were local residents and available for close monitoring at our institution at 3-month intervals (group 1), while 10 from other parts of the country were only reassessed after completion of 9 months of desensitization and at 12 months after the initiation of treatment (group 2). Patients who experienced multiple recurrences of nasal polyposis or presented with at least 2 of the 3 criteria of the AI triad were included in this study. On their first visit to our institution, only 6 patients were aware of their aspirin hypersensitivity, as either they had experienced clinical reactions like severe asthmatic symptoms after taking aspirin or their referring physician had made them aware of this condition due to the constellation of symptoms observed. All 30 individuals had experienced nasal polyposis for a prolonged period and had undergone one or more endonasal sinus surgical procedures. Before starting the desensitization, patients were assessed clinically for recurrent polypoid disease, number of episodes of purulent rhinosinusitis in the previous year, nasal patency, the presence and severity of asthmatic symptoms, and their sense of smell, using the “sniffing sticks” (Smiffin Sticks; Burghardt, Wedel, Germany). This olfactory screening test contains 8 sticks, each of which represents a characteristic smell. The degree of hyposmia is determined separately for each side of the nose by the number of correctly identified sticks. Of the 30 patients, 12 were using a topical nasal corticosteroid spray, 9 were using corticosteroid sprays as needed for control of asthmatic symptoms, and 2 were taking systemic corticosteroids for asthma control.

Screening for inhalant allergies, using skin testing, a radioallergosorbent test, and nasal provocation tests, was performed. Three patients with seasonal symptoms due to their sensitization to grain and trees, who had not been treated with immunotherapy, were scheduled for antiallergic hyposensitization, which was performed simultaneously to the aspirin desensitization protocol.

All 30 individuals had a positive test result for AI using a functional in vitro assay following a recently published protocol: blood was drawn from all patients, and a mixed leukocyte culture was prepared using dextran sedimentation. Thereafter, the eicosanoid release of pLTs and PGE2 was analyzed using competitive enzyme immunoassays. The release of pLTs and PGE2 was assayed simultaneously and in duplicate for each sample. The antibody directed against pLTs recognized leukotriene C4 and the metabolites leukotriene D4 and leukotriene E4 with equal sensitivity. The detection limit was 3 pg per well for pLTs and PGE2. The changes in eicosanoid release determined a positive or negative test result. A positive test result was defined as elevated pLT release and lowered PGE2 release, while a negative test result was defined by normal pLT and PGE2 release when compared with the release levels in a healthy control group. The eicosanoid levels of this healthy control group, consisting of 50 individuals who showed no clinical evidence of any symptoms consistent with AI, were assessed by the same assay mentioned previously, in the same laboratory, when the protocol of the assay first had been established.

To initiate the desensitization therapy, oral aspirin was given in increasing dosages for 2 days (day 1, 100 mg [2 doses of 50 mg]; and day 2, 300 mg), and patients were hospitalized for this therapy. Airway resistance and forced expiratory volume in 1 second were closely monitored during this induction period. On the first day after an initial lung function test, 50 mg was given in the morning, and only after a repeated check of airway resistance and forced expiratory volume in 1 second was the second 50 mg administered orally, usually 8 hours after the initial dose. On the second day, 500 mg was given orally if repeated lung function testing had not revealed a decrease in forced expiratory volume in 1 second of 25% or greater. On the third day, aspirin was reduced to the maintenance dose of 100 mg/d, to be given for at least 9 months to minimize the incidence of the known adverse effects of aspirin if given in higher doses for a longer period. We did not encounter any mild or moderate problems, such as acute asthmatic attacks or shock symptoms, gastric pain, or ulcers, following this regimen. However, if on day 2 the patient had a decrease of forced expiratory volume in 1 second of greater than 25%, we assumed that the 100 mg of aspirin that was administered on day 1 was already above the individual threshold of aspirin-related asthmatic symptoms. Therefore, in these patients we did not increase the daily dose further, but treated them with the maintenance dose of 100 mg immediately on day 2, skipping the further increase to 500 mg.

Clinical reassessment and the functional in vitro assay were repeated at each follow-up visit of every patient in an attempt to identify changes in the release of eicosanoids over time and to correlate these with the clinical course.

For the statistical analysis of the data obtained, a Wilcoxon signed rank test was used and results were statistically significant if P<.05 and highly significant if P<.01.

cause of AI, since this effect of nonsteroidal anti-inflammatory drugs occurs in healthy individuals as well. Several additional factors have been discussed, like alterations in cyclooxygenase inhibition and in the kinetics of enzymes like leukotriene synthase or an increased sensitivity of respiratory mucosal tissue to leukotrienes in sensitive individuals. While the exact causative mechanisms have to be further elucidated, the individual chronologic sequence of symptoms is known to be considerably variable. First symptoms usually occur within the fourth decade of life, with recurrent rhinitis followed by nasal polyposis. Intrinsic bronchial asthma can develop some years later and often it takes years again for the clinical sensitivity to nonsteroidal anti-inflammatory drugs to occur. This is the reason why an in vitro assay, like the one applied in this study, can be valuable in establishing the diagnosis of AI. The alteration of arachidonic acid metabolism and eicosanoid release can be detected in patients with an incomplete manifestation, in whom the clinical picture of the aspirin triad has not yet fully developed as in patients with the full triad.

Different researchers described the possibility of a desensitization therapy by oral administration of aspirin for a longer period. The present study was designed
to investigate the effects of an aspirin desensitization therapy with a low oral dose of 100 mg/d, and the role of the in vitro assay in verifying and monitoring the effect of this therapy over time based on the eicosanoid release of isolated blood cells. The focus of this investigation is (1) to monitor the clinical course and especially the recurrence rate of nasal polyps under oral aspirin desensitization and (2) to correlate the clinical course to the development seen in the eicosanoid release of isolated blood cells.

RESULTS

A functional in vitro test for AI before starting the desensitization therapy using mixed leukocyte cultures revealed a positive result in all 30 patients, implying that basal release of pLTs was elevated and basal release of PGE₂ was reduced, which was one of the inclusion criteria for this study.

GROUP 1

Findings Before AI Desensitization

Before initializing the desensitization, 8 of the 20 individuals in group 1 were free of nasal polyps. Twelve showed recurrent polyps, of which 9 had minor findings in the ethmoid region, 2 had more severe findings, and 1 had massive panpolyposis. All of these 12 patients had undergone more than 1 previous surgical intervention, with the last operation having been more than 3 months before the beginning of the desensitization. All patients with recurrent polyps complained about a significant impairment of nasal breathing and a reduction of their sense of smell. Olfactory screening using the sniffing sticks revealed various degrees of hyposmia in 8 patients and total anosmia in those 3 with severe polyposis. Eight individuals had intrinsic asthma of variable severity, but all achieved good symptom control with the use of a topical inhalant or systemic corticosteroids.

Screening for inhalant allergies revealed a positive test result in 11 patients: 6 were allergic to grain and trees, 3 to mite, and 2 to animal hair. Three of these patients had undergone immunotherapy for a minimum of 3 years, and 3 patients with seasonal symptoms due to their sensitization to grain and trees were scheduled for allergenic hyposensitization simultaneously to the aspirin desensitization therapy.

Clinical Follow-up (at 3, 6, 9, and 12 Months)

The 8 individuals who had been free of polyps after revision surgery before starting the desensitization all remained disease free for 12 months. Of those 9 with minor findings of recurrent polyps at the beginning of the treatment, 7 also showed no evidence of disease after 12 months of desensitization, indicating a marked clinical improvement (2 of these 7 underwent immunotherapy for antiallergic hyposensitization); and the other 2 remained at a steady state without worsening of their symptoms. Two patients with more severe forms of recurrent polyposis showed a reduction of polyps over time as their eicosanoid release levels improved simultaneously (1 of these 2 underwent immunotherapy for antiallergic hyposensitization). The patient who had started out with recurrent polypoid disease even experienced some worsening during the 12 months of follow-up and continued to be anosmic, with highly impaired nasal breathing. This patient also experienced further worsening of asthmatic symptoms, which had been progressing during the last 3 years.

Of the 8 asthmatic patients, 5 reported a reduction of clinical symptoms and a decreased frequency of their need to use inhalant corticosteroids. In those 12 individuals who had complained about an impairment of nasal breathing due to recurrent polyps, 11 reported noticeable improvement after 1 year. Of the 8 patients who had shown marked hyposmia, 4 experienced a marked improvement in their sense of smell, which went along with a strong improvement in subjective quality of life. With the exception of the individual previously mentioned, the other 2 anosmic patients regained some sense of smell, both reporting this subjective change at the 9-month and the 1-year visits.

In Vitro Follow-up (at 3, 6, and 9 Months)

In vitro variables correlated well with the clinical findings. During the first 3 months of desensitization, the levels of PGE₂ decreased and those of pLTs increased in some patients, resulting in an even more pathologic ratio of PGE₂ and pLT (PGE₂/pLT index). However, this tendency was reversed after 3 months. Of the 20 patients in group 1, 9 underwent an in vitro test at 6 months. They all showed a tendency toward normalization of eicosanoid levels. Basal PGE₂ release was higher and basal pLT release lower than before the beginning of the desensitization therapy. However, these eicosanoid levels were not normal when compared with those of a healthy control group. At this point, eicosanoid levels of only 3 individuals had reached levels comparable to those of healthy controls. At 9 months, all 20 patients were tested again, and 19 showed an improvement in the basal release levels of pLTs and PGE₂. 17 had levels comparable to those of healthy controls, and 2 still showed “shifting” toward higher levels of pLTs (these were the 2 individuals who remained at a steady state clinically). In the one patient with progression of polyps clinically, eicosanoid levels remained unchanged throughout the observation period (Figure 1A-C).

GROUP 2

Findings Before AI Desensitization

Evaluation of these 10 patients showed similar results. Clinically, while the remaining 6 were free of polyps, 4 individuals had minor recurrence of nasal polyps before initiating the desensitization. Nasal breathing was impaired in patients with recurrent polyps, and 3 of these 4 presented with hyposmia. Inhalant allergies were found in 3 of these 10 individuals: 2 were allergic to animal hair and 1 to grain and trees. None of these patients underwent immunotherapy for antiallergic hyposensitization.
throughout the observation period. Four patients had a history of intrinsic bronchial asthma and were taking topical corticosteroids.

Clinical Follow-up (at 9 and 12 Months)

After 1 year of follow-up, none of the 4 individuals previously mentioned showed any progression of the recurrent polyposis, 3 showing improvement in nasal obstruction secondary to polyps on nasal endoscopy. Also, the 6 individuals without polyposis remained free of disease. Nasal patency improved in 3 of those 4 individuals in whom it had been impaired, and the 3 hyposmic individuals reported an ameliorated sense of smell, which could be verified using the sniffing sticks. The 4 asthmatic patients all reported a decreased need for inhalant corticosteroids for symptom control.

In Vitro Follow-up (at 9 Months)

In vitro variables also correlated well with the clinical course and showed a normalization of the eicosanoid release levels in 8 patients and some residual pathologic shifting in 2 patients after 9 months.

GROUPS 1 AND 2

Looking at all 30 patients, the mean number of sinus infections per year was reduced from 4 to 2 after the initiation of therapy, while the number of patients with more than 3 episodes of purulent sinusitis per year decreased from 11 to 2. After 9 months of aspirin desensitization, the eicosanoid levels were normal in 25 patients, there was residual pathologic shifting in 4, and the levels were unchanged in 1. The development of the clinical and in vitro variables for all 30 patients in groups 1 and 2 is summarized in Tables 1, 2, and 3 and in Figure 2A-C. Statistical significance was evaluated using the Wilcoxon signed rank test.

Table 1. Clinical Assessment of All 30 Patients Before the Initiation of Aspirin Desensitization

<table>
<thead>
<tr>
<th>Clinical Finding</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free of nasal polyps</td>
<td>14</td>
</tr>
<tr>
<td>Recurrent polyps after previous surgery</td>
<td>13</td>
</tr>
<tr>
<td>Minor finding</td>
<td>3</td>
</tr>
<tr>
<td>Major finding</td>
<td>3</td>
</tr>
<tr>
<td>Bronchial asthma</td>
<td>12</td>
</tr>
<tr>
<td>Inhalant allergies</td>
<td>14</td>
</tr>
<tr>
<td>Impaired nasal breathing</td>
<td>16</td>
</tr>
<tr>
<td>Hyposmia</td>
<td>12</td>
</tr>
<tr>
<td>Anosmia</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 2. Endoscopic Assessment of Nasal Polyposis of the 30 Patients After 12 Months*

<table>
<thead>
<tr>
<th>Result</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No recurrence†</td>
<td>14</td>
</tr>
<tr>
<td>Marked improvement</td>
<td></td>
</tr>
<tr>
<td>Minor disease before desensitization‡</td>
<td>10†</td>
</tr>
<tr>
<td>Major disease before desensitization‡</td>
<td>2§</td>
</tr>
<tr>
<td>Steady state (minor disease before desensitization)</td>
<td>3</td>
</tr>
<tr>
<td>Progressive disease (major disease before desensitization)</td>
<td>1</td>
</tr>
</tbody>
</table>

*There was no progression of nasal polyps in 26 of the 30 patients.
†Free of polyps throughout desensitization.
‡Including 2 patients who underwent simultaneous antiallergic hyposensitization.
§Including 1 patient who underwent simultaneous antiallergic hyposensitization.

Aspirin intolerance, since it was first described in the beginning of the century,1,13 has been studied by many researchers,1-29 yet the exact causative mechanisms still remain obscure. Clinically, aspirin-sensitive rhinosinusitis...
is often associated with recurrent polypoid disease. However, not all patients present with the classic clinical triad of nasal polyposis, intrinsic bronchial asthma, and worsening of asthmatic and/or nasal symptoms after ingestion of aspirin. Several researchers have demonstrated the possibility of successfully desensitizing individuals to aspirin. The underlying mechanisms explaining this desensitization still require further elucidation. Changes in the metabolism of arachidonic acid and the eicosanoid pathway during desensitization have been detailed, mainly by analyzing urinary leukotrienes but also by measuring leukotriene release from peripheral blood monocytes or mixed leukocytes. Following a recently published protocol, we were able to show that analyzing eicosanoid release in mixed leukocyte cultures offers an alternative to oral, bronchial, or nasal challenge tests. In a recent investigation, we found this in vitro analysis reliable in establishing the diagnosis of aspirin sensitivity, especially if patients did not present with a clear clinical picture of the aspirin triad. This is of particular interest, since the onset of clinical symptoms and the development of AI is known to be quite variable. Often, nasal polyps occur years before the development of intrinsic asthma, which is then followed by clinical intolerance to aspirin. Early diagnosis and treatment before the manifestation of the complete triad may be crucial for therapeutic success.

The results of the present study suggest that this functional in vitro test is suitable for monitoring the effectiveness of a long-term aspirin desensitization protocol and for giving a correlation for clinical improvement or stagnation. Using a dose of as little as 100 mg/d, maintained after the induction period of 2 days, we found effects on the eicosanoid release comparable to data we had gathered earlier with higher doses of 300 and 500 mg/d (J.G., D.S., and W.J.M., unpublished data, 1998). After having correlated the clinical effectiveness of this low dose of 100 mg with the positive development of the in vitro variables and thus proving the effectiveness of this protocol, we think that in the future it could be reduced to just monitoring the clinical course and, therefore, be applied in institutions that would not have in vitro testing available. However, the main value of the in vitro assay will remain in establishing the diagnosis in patients without a typical triad of symptoms and furthermore in relating individual clinical courses and possible failures of treatment to the individual eicosanoid levels. The question of which dose of oral aspirin should be administered to induce tolerance to aspirin is controversially discussed throughout the literature. Most researchers suggest daily doses to be maintained at considerably high levels, between 500 and 1000 mg; in some studies, dosages of even more than 2000 mg/d were used. The 9-month course of the 30 patients described in this study, who received a dose of 100 mg/d, shows clear positive effects on the recurrence rate for nasal polyps, the number of episodes of purulent sinusitis, nasal patency, and the sense of smell. These effects are positively correlated with the results of the repeated measurements of eicosanoid release in vitro. All patients with such positive effects on their clinical course also showed a clear tendency toward normalization of basal release levels of

Table 3. Effects of the Desensitization Therapy on Clinical Symptoms, Other Than Polyposis, That Are Associated With Aspirin Sensitivity

<table>
<thead>
<tr>
<th>Variable</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average incidence of purulent</td>
<td>Reduced from 4 to 2 per year</td>
</tr>
<tr>
<td>episodes of sinusitis</td>
<td></td>
</tr>
<tr>
<td>Patients with &gt;3 episodes of</td>
<td>Reduced from 16 to 2</td>
</tr>
<tr>
<td>sinusitis</td>
<td></td>
</tr>
<tr>
<td>Need for less asthma medication</td>
<td>9 of 12 asthmatic patients</td>
</tr>
<tr>
<td>Improvement of nasal airflow</td>
<td>14 of 16 patients</td>
</tr>
<tr>
<td>Improvement of sense of smell</td>
<td>7 of 11 hypoxic patients</td>
</tr>
<tr>
<td>Regained sense of smell</td>
<td>2 of 3 anosmic patients</td>
</tr>
</tbody>
</table>

* There was a marked improvement of these variables over time.

Figure 2. Data are shown before and 9 months after initiating the desensitization therapy in groups 1 and 2 (n=30). Lines show the individual courses of the 30 patients, and the large shaded boxes indicate mean values. A, Peptidoleukotriene (pLT) release. Significant changes (P<.05) are marked with an asterisk. B, Prostaglandin E2 (PGE2) release. Significant changes (P<.05) are marked with an asterisk. C, The PGE2/pLT index. Highly significant changes (P<.01) are marked with a dagger.
plTs and PGE₂. On the other hand, the only individual who did not benefit from desensitization clinically and had to be scheduled for revision surgery due to massive recurrence of polyps still showed pathologic eicosanoid release levels after 9 months that were virtually unchanged when compared with the first measurement at the beginning of therapy.

We are aware that in those 3 individuals who underwent aspirin desensitization and antiallergic hypo-sensitization simultaneously throughout the observation period, the observed clinical improvement could in part be contributed to the antiallergic treatment because of IgE-related mechanisms that are being discussed in the pathogenesis of nasal polyps and asthma.³⁰,³¹ However, the in vitro variables used in this study did not show any marked differences between these 3 individuals and those who improved clinically but did not undergo antiallergic hyposensitization.

The in vitro follow-up revealed an initial tendency to even more pathologic eicosanoid release levels within the first 3 months of aspirin desensitization, which was not accompanied by a worsening of clinical symptoms. But only after the in vitro variables started to improve (6- and 9-month visits) did the clinical improvement become obvious. This lack of correlation within the first 3 months cannot be fully explained by the data gathered in this investigation, but suggests the existence of compensating mechanisms in case of a further deterioration of already pathologic eicosanoid levels.

The use of topical corticosteroid sprays has been shown to have no impact on the eicosanoid levels measured by immunoaassay. Building on this knowledge, the use of systemic corticosteroids for asthma control, as after 9 months they showed reduced plTs levels but still had reduced PGE₂ levels. This does not indicate ineffectiveness or failure of the desensitization in these individuals. Rather, the achieved improvement of asthmatic symptoms in both individuals, with a cessation or reduction of corticosteroid use, may lead to a normalization of PGE₂ levels as well.

In conclusion, we believe that the results presented in this study support the use of a low dose of aspirin (100 mg/d) in an effort to induce tolerance in aspirin-sensitive patients. The in vitro analysis of eicosanoid release from mixed leukocyte cultures using a functional in vitro assay offers a new tool not only to help establish the diagnosis of AI but also to individually monitor the effect and objectively verify the success of a desensitization therapy over time.

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