

Intranasal treatment with lysine acetylsalicylate in patients with nasal polyposis

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Forty-three patients suffering from nasal polyposis underwent intranasal treatment with increasing doses of lysine acetylsalicylate (LAS) corresponding to 20, 200, and 2000 µg of aspirin (ASA), until a maximal dose of 2000 µg weekly was reached. The patients were divided in two groups: a group of 28 patients with ASA intolerance, including 20 with ASA triad, and a group of 15 patients without ASA intolerance. The local treatment was usually started 1 month after polypectomy and was well tolerated without side effects. A control group included 191 subjects with nasal polyposis, 130 of whom had ASA intolerance. After polypectomy the controls received no further medical treatment. Patients were examined every 3 months and radiographs of the paranasal sinuses were obtained every 6 months. After 24 months 34 of 43 patients (79.1%) treated with topical LAS had suffered no relapse of polyposis. Only 45 of 191 control patients (23.6%) failed to relapse after 24 months ($P < .0001$). Nine of 28 (32.1%) ASA-intolerant patients treated with LAS and 105 of the 130 (80.77%) control subjects relapsed ($P < .0001$). None of the 15 ASA-tolerant patients treated with LAS relapsed, but 41 of the 61 (67.21%) nontreated control subjects relapsed ($P < .00001$). These data indicate topical LAS is effective in preventing recurrence of nasal polyps after polypectomy.

INTRODUCTION

Nasal polyposis is a disease that occurs frequently in both atopic and nonatopic subjects. The etiology is uncertain.

Nasal polyps are composed of edematous hyperplastic mucosa, occurring bilaterally in clusters and involve the ethmoid sinuses. The cells most frequently observed are lymphocytes, eosinophiles, neutrophils, and plasma cells; immunoglobulins, including IgE, have often been identified in the stroma by means of immunofluorescence.¹

Aspirin (ASA) intolerance, mainly expressed as respiratory disease (rhinitis and/or asthma), is often associated with nasal polyposis. Approximately one-fourth of patients with nasal polyps (21% according to our studies²) suffer from mostly intrinsic bronchial asthma and the administration of ASA or other nonsteroidal antiinflammato-

tory drugs (NSAIDs) can worsen the bronchospasm.³

This triad of symptoms (ASA intolerance, nasal polyposis, and bronchial asthma) characterizes the "ASA disease" or ASA triad. The chronologic sequence of these symptoms varies from patient to patient (Fig. 1).

Oral, bronchial and nasal provocation tests used for diagnostic and therapeutic purposes, have helped to explain ASA intolerance. In 1976 Zeiss and Lockey⁴ observed that after a positive oral provocation test (OPT) with ASA in aspirin-sensitive patients (in whom asthma occurred after ASA administration), a 1- to 10-day "refractory period" or "desensitization period" occurred; no episode of asthma was reported when administering further quantities of ASA in this period. Successful oral ASA desensitization attempts followed, but no important beneficial effect on asthma was observed⁵ while nasal and sinus symptoms (when present) improved.^{6,7} Other authors⁸ reported occasional inhibition of polyp relapse after oral ASA desensitization.

In 1977⁹ a bronchial provocation

test (BPT) with ASA (more precisely LAS: lysine acetylsalicylate) in aspirin-sensitive asthmatic patients elicited a refractory period. Consequently we suggested^{10,11} a nasal provocation test (NPT) with LAS in aspirin-sensitive patients. We observed a strongly positive NPT in patients with nasal polyposis. This suggested a relationship between ASA intolerance and nasal polyposis. Furthermore, the positive test was followed by a "refractory period" of 1-day to more than 15 days (Fig. 2).

Because of complete nasal obstruction and worsening of asthma, when present, it is often necessary to remove polyps surgically. Unfortunately polypectomy is not definitive, since polyps frequently relapse. Polyps may relapse in 42%¹² to 87% of cases¹³ within 1 year; or in 53%¹⁴ to 59% of cases¹⁵ within 4 years. As early as 4 months after surgery polyps relapse in 18% of cases.¹⁶ Others¹⁷ have reported relapse in 15.5% to 16.8% of cases, within 6 months to 8 years (mean 31 months) depending on the kind of surgery performed. Because of these observations we decided to investi-

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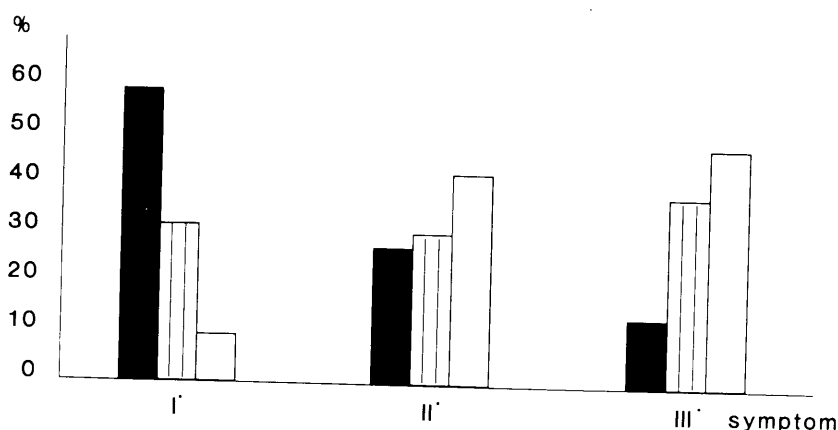


Figure 1. Percentage frequency with which each symptom of the ASA-triad (bronchial asthma, nasal polyposis, and ASA intolerance) appears as the first symptom, second, or third in 139 patients ■ asthma, ▨ polyposis, and □ ASA-intolerance.

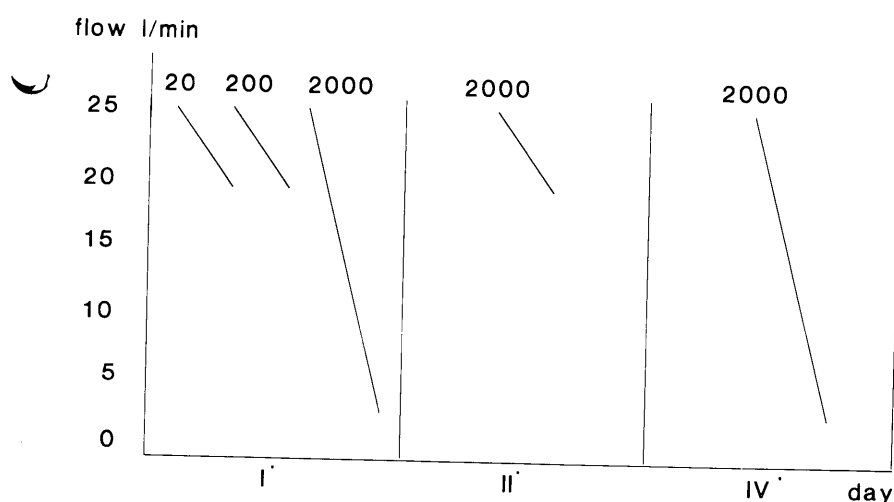


Figure 2. Nasal provocation test (anterior rhinomanometry) with LAS (20, 200, and 2000 µg of ASA) (refractory period <2 days).

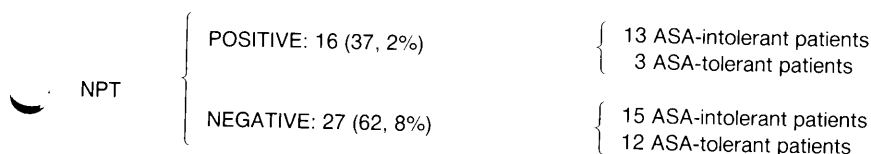


Figure 3. Nasal provocation test with LAS in 43 patients suffering from nasal polyposis.

gate the effect of local intranasal treatment with LAS on prevention of relapse of polyposis.

MATERIALS AND METHODS

We studied 43 patients, 21 men and 22 women, 19 to 70 years of age all suffering from nasal polyposis. We divided the patients into two groups, a first group of 28 ASA intolerant patients, 20 of whom had the ASA

triad, and a second group of 15 ASA tolerant patients. A detailed medical history and physical examination was completed for each. Patients underwent conventional allergy testing: skin prick tests with inhalant allergens, specific and total IgE-RIA; examination of the ears, nose, and throat, including fiberoptic rhinoscopy; and skull radiographs. Only patients with diagnoses of sim-

ple nasal polyposis were admitted in the study. We excluded all nasal cavity malignancies, turbinate hyperplasias and trophic decompensations and inflammatory diseases. Each patient underwent an oral provocation test (OPT) with ASA. Every hour increasing doses of ASA were administered orally: 1, 10, 50, 100, 500 mg. The test was considered positive if the following occurred: wheal and flare reaction, angioedema, rhinitis with at least a 40% decrease of nasal air flow (anterior rhinomanometry) or bronchospasm with a FEV₁ decrease of at least 20%. A positive OPT with ASA was the main requirement for classification as ASA intolerant for our study. A negative OPT with ASA, defined patients as ASA tolerant.

Each patient also underwent a nasal provocation test (NPT) with LAS: LAS was diluted in isotonic saline solution (NaCl 0.9%) and administered in increasing doses (corresponding to 20 to 200 µg of ASA), until a maximal dose of 2000 µg was obtained. The intranasal insufflation of LAS was carried out using a dosimeter (Mephaphar). This instrument was calibrated (1.5 kg/cm²-0.4 sec) and connected to an ampulla with olive-shaped nasal adapters. The nasal flow rates (anterior rhinomanometry) were recorded before the drug administration and 10 and 20 minutes after the drug had been given, using a digital rhinomanometer (Allergopharma A440), provided with a mask and con-

Table 1. Periods Elapsing Between Surgery and the Nine Polyposis Relapses in Treated Patients*

Period	Number of Patients
7 months	1
9 months	1
12 months	1
18 months	2
19 months	1
22 months	2
23 months	1

* All aspirin intolerant.

nected to a graphic recorder (Philips PM 8040/S). The value of nasal air flow per cycle (inspiration and expiration) was digitally recorded as $P = 1.5$ mbar (P being the difference in mbar between the nostril outer atmospheric pressure and the choana inspiratory and expiratory pressure). The instrument connected to the recorder is able to draw a parabolic resistance curve of the nasal breathing, using the square of the flow and a pressure of 1.5 mbar. If the flow is proportional to the conductance, the pressure being a constant value ($C = \frac{F}{P}$), the percentage of conductance decrease is equal to the percentage of flow decrease. Therefore, we consider the nasal flow as a reference parameter in the evaluation of the nasal provocation test with anterior rhinomanometry. Before starting the test, a challenge with a placebo (isotonic saline solution, (NaCl 0.9%) in the nostrils) to exclude nonspecific hyperreactivity of the nasal mucosa (evaluation of nasal air flow) was carried out. The test was considered positive when a 40% flow decrease occurred.^{10,11}

Computed axial tomography of the skull with details of the paranasal cavities was carried out in all patients, who then underwent surgery according to the radiologic findings. In case of chronic ethmoid sinusitis without maxillary cavity involvement, intranasal polypectomy by microscopy and ethmoid cell opening with subtotal exeresis were performed. In case of important maxillary cavity involvement, surgery was performed following the maxillary pathway according to the Pietrantoni De Lima¹⁸ technique. The mainly damaged maxillary cavity was opened and cleaned through the gingival fornix; the ethmoid was opened medially. If necessary, drainage of the sphenoid sinus and frontal sinuses through the same maxillary pathway was carried out also.

One month after polypectomy, intranasal treatment with LAS was started. Increasing doses of LAS (the equivalent of 20, 200, 2000 μ g of ASA) were administered until a weekly maintenance dose of 2000 μ g was reached. Patients underwent examination every 3 months and radiographs of the paranasal sinuses were obtained every 6 months.

Both treated and control patients were followed for 24 months. The controls included 191 subjects with nasal polyposis (101 men and 90 women, aged 16 to 70 years), 61 of whom were ASA tolerant and 130 of whom were ASA intolerant with histories of two to three episodes of rhinitis and/or asthma after ASA

administration. The control group also underwent polypectomy but received no intranasal LAS; every three months they were examined and every 6 months radiographs of the paranasal sinuses were obtained. Comparisons of nasal polyposis relapse rates were carried out by means of the life-table method and Cograk chi-squared test.¹⁹ All patients provided informed consent. The protocol was approved by the Ethical Committee of our University.

RESULTS

According to the family history, atopy was evident in 4.6% of the patients and nasal polyposis in

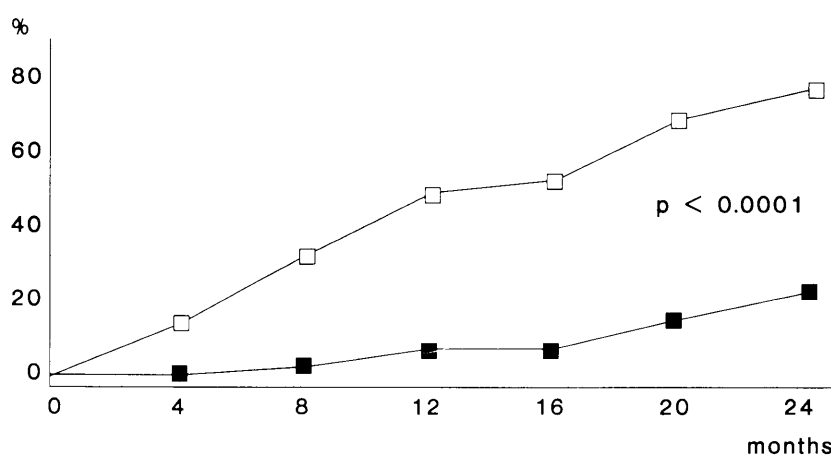


Figure 4. Relapse of nasal polyposis in treated and untreated patients: ■ treated 43 and □ untreated 191.

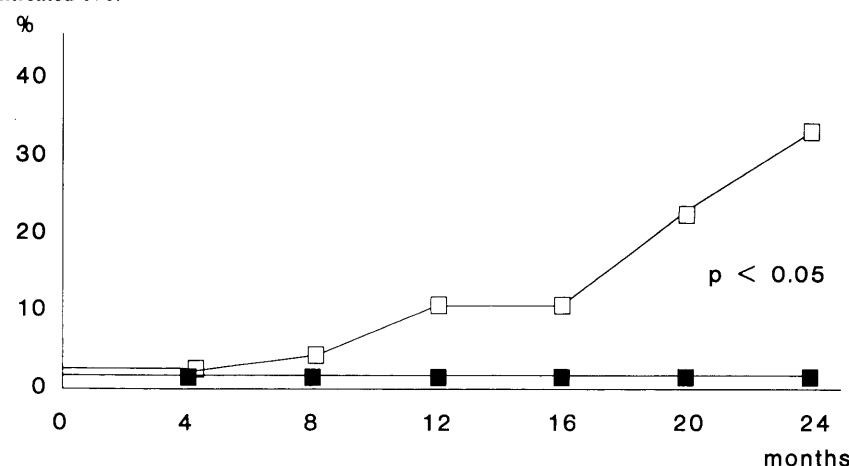


Figure 5. Relapse of nasal polyposis in ASA tolerant and ASA-intolerant treated patients: ■ ASA tolerant 15 and □ ASA intolerant 28.

11.6%. Patients were mainly aged between 30 and 50, with an average age of 43 years (range: 19 to 70 years).

Allergy testing using common inhalant allergens was positive in three of 43 patients (6.9%). Nasal provocation test was positive in 16 of 43 patients (37.2%), 13 of whom were ASA intolerant (Fig 3).

In 16 of the 20 patients suffering from the ASA triad (80%), asthma was more or less stable during the treatment. In the other four (20%), improvement was observed (smaller quantity of drugs used, asthma decreased). However, this therapy was always well tolerated and no side effect occurred.

Nine (20.9%) of 43 patients treated with topical intranasal LAS had recurrence of polyposis within 24-months. Three of these nine patients (6.9%) relapsed within the first year, (after 7 to 9 and 12 months of treatment) while the six others relapsed during the second year (after 18, 18, 19, 22, 22, 23 months) (Table 1). Recurrence of polyposis was significantly less frequent among the treated patients than control subjects ($P < .0001$, Fig. 4); while the rate of relapse in the treated group was 20.9% (nine relapses out of 43 patients) within 24-months that in the control group was 76.4% (146 relapses out of 191 patients). The relapse rate in the untreated control group within 12 months (94 of 191 patients, 49.2%), was also significantly higher ($P < .0001$) than among treated patients [three of 43 (6.9%)].

Relapses were more frequent in ASA-intolerant patients (Fig 5) compared with patients with simple polyposis ($P < .05$). ASA intolerance in treated patients with nasal polyposis apparently increases the relapse risk. Others¹⁵ have asserted that polyposis relapses more frequently in ASA-intolerant subjects after surgery than in ASA-tolerant patients, and our observations agree with this. One year after polypectomy, 50% of the patients we stud-

ied had relapsed, and 24 months after surgery, polyp relapse had occurred in 67.2% of ASA-tolerant patients and in 80.7% of ASA-intolerant patients. The difference between the two groups is not statistically significant. We separately compared the two groups of patients (ASA tolerant and ASA-intolerant) with their respective control groups. In both groups of treated patients, the risk of polyp relapse was lower ($P < .0001$) compared to untreated patients (Figs 6 and 7). No ASA-tolerant treated patient experienced relapse, while up to 67.2% of the untreated ones relapsed.

We also evaluated the influence

of a positive NPT with LAS on polyp relapse. No statistically significant difference between patients with a positive test and patients with a negative test was detected.

CONCLUSIONS

The great majority of these patients (34 of 43, 79.1%) treated with topical intranasal LAS did not relapse after a 24-month follow-up, while only 45 subjects of 191 (19.23%) untreated control subjects failed to relapse. The difference between the rates of relapse of treated and untreated polypotic patients was highly significant. The difference is statistically significant both among ASA-intolerant patients and ASA-

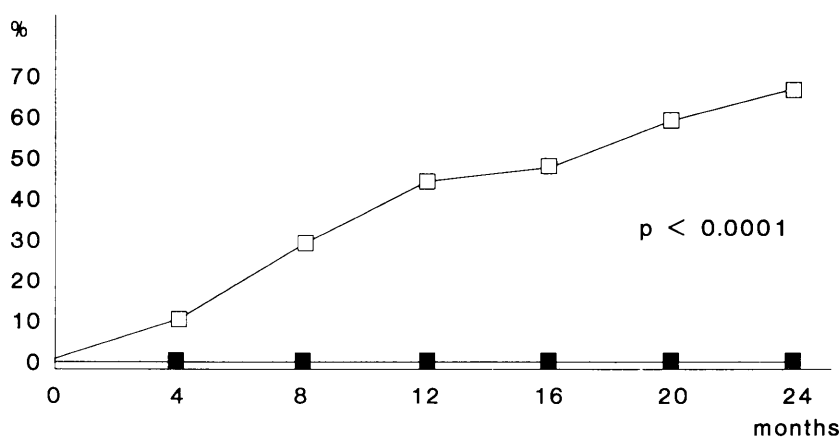


Figure 6. Relapse of nasal polyposis in ASA tolerant treated and untreated patients: ■ treated 15 and □ untreated 61.

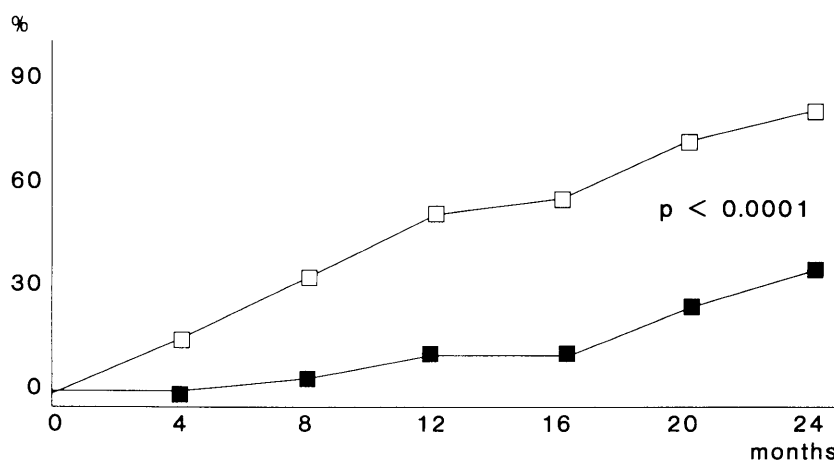


Figure 7. Relapse of nasal polyposis in ASA-intolerant treated and untreated patients: ■ treated 28 and □ untreated 130.

tolerant ones. Nine of 28 (32.1%) ASA-intolerant subjects and 105 of 130 (80.77%) control subjects relapsed. None of the 15 polypotic ASA-tolerant patients relapsed after topical intranasal treatment with LAS, whereas, 41 of the 61 control subjects (67.2%) relapsed. Therefore, the ASA-tolerant subjects must be considered the ideal patients for this kind of treatment.

Nasal provocation test with LAS, a relatively simple technique^{10,11} and subsequent local intranasal treatment can be implemented easily with favorable results and no side-effects. The benefit of LAS treatment in ASA-tolerant subjects is due to the antiinflammatory effect of the drug more than to "desensitization." We are planning a double-blind study with a larger number of patients to evaluate further effects of this treatment on delaying or preventing polyp relapses.

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