

# Nasal provocation test with lysine-aspirin for diagnosis of aspirin-sensitive asthma

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Nasal provocation tests (NPTs) with lysine-aspirin (L-ASA) have been recently introduced for assessment of aspirin-induced asthma (AIA). They differ in dose and means of aspirin instillation, duration of observation period, and criteria for positivity. Thus far they have not become a routine part of clinical diagnosis. Fifty-one patients with AIA, confirmed by oral challenge test, were recruited to undergo diagnostic NPTs with L-ASA. In 10 of these patients (19.6%), NPTs could not be performed because of total obstruction of at least one nostril or marked fluctuations in nasal flows, leaving 41 patients with AIA for the study. Control groups consisted of 13 aspirin-tolerant asthmatic patients and 10 healthy subjects. L-ASA at a total dose of 16 mg of acetylsalicylic acid applied bilaterally into the inferior nasal conchae caused significant fall in inspiratory nasal flow in at least one nostril (>40%), which was measured by anterior rhinomanometry, and clinical symptoms of watery discharge and nasal blockage in 35 of 41 patients with AIA, one of 10 healthy subjects, and none of 13 aspirin-tolerant asthmatic patients. No relationship was found between the baseline nasal flow values and the intensity of response to L-ASA. No systemic reactions, including bronchospasm, were noticed, even in patients whose initial FEV<sub>1</sub> was lower than 70% of predicted value. This test is highly specific (95.7%) and sensitive (86.7%), but negative results do not exclude possible intolerance to aspirin (predictive value of a negative result 78.6%). In conclusion, the NPT described is a simple, safe, and quick test for diagnosis of AIA. It can be used in patients with unstable asthma. It may be a method of choice to confirm hypersensitivity to aspirin manifested only by symptoms from the upper respiratory tract. Patients suspected of aspirin intolerance who have negative NPT results should undergo bronchial or oral challenge tests with aspirin. (*J Allergy Clin Immunol* 1998;101:581-6.)

**Key words:** Aspirin-sensitive asthma, bronchial asthma, nasal provocation test, rhinitis

Aspirin-induced asthma (AIA) is a clear-cut clinical syndrome characterized by acute airway reactions to aspirin and other nonsteroidal antiinflammatory drugs. It has a distinct clinical picture and affects about 10% of adults with asthma.<sup>1-4</sup>

Aspirin-precipitated bronchoconstriction is usually accompanied by nasal congestion and profuse rhinorrhoea.

## Abbreviations used

|        |                        |
|--------|------------------------|
| AIA:   | Aspirin-induced asthma |
| L-ASA: | Lysine-aspirin         |
| NPT:   | Nasal provocation test |

In sporadic patients only nasal symptoms are elicited by aspirin (i.e., aspirin-induced rhinosinusitis).<sup>5-7</sup> Chronic nasal congestion is the major clinical manifestation of AIA. Watery rhinorrhea and nasal obstruction, leading to frequent development of nasal polyps, precede the appearance of asthma and aspirin intolerance for months or years. Chronic hyperplastic rhinosinusitis with or without nasal polyps accompanies asthma once it becomes established.

There is no in vitro test for identification of aspirin intolerance. The diagnosis is made by oral<sup>5, 8-10</sup> or inhalation<sup>8, 11-14</sup> aspirin provocation tests. Oral tests can sometimes precipitate a severe asthmatic reaction, necessitating intensive care treatment<sup>15</sup>; they should be performed in specialized centers close to an intensive care unit. Inhalation of increasing concentrations of lysine-aspirin (L-ASA) solution has proved safer and quicker to perform than an oral challenge test. It is, however, unsuitable for patients whose asthma is not in clinical remission and whose FEV<sub>1</sub> is lower than 70% of predicted value.

It is therefore desirable to have an alternative diagnostic test for aspirin-sensitive asthma. This study was carried out to investigate the diagnostic value of the nasal lysine-aspirin challenge test and to evaluate its effect on nasal and lung function in aspirin-intolerant asthmatic subjects.

## METHODS

### Subjects studied

Fifty-one patients with AIA, confirmed by oral challenge test, were recruited to undergo diagnostic nasal provocation tests (NPTs) with L-ASA. In 10 of these patients (19.6%), the test could not be performed because of either total obstruction of at least one nostril or marked fluctuations in nasal flows (>40%) measured rhinomanometrically before the test with L-ASA. NPTs with L-ASA were thus carried out on 41 patients with AIA, nonsmokers who all experienced at least mild chronic nasal symptoms for about 3 years preceding the study (Table I).

The control groups consisted of 13 aspirin-tolerant asthmatic patients who had negative oral aspirin challenge test results and 10 healthy nonsmoking subjects. Eight of the asthmatic patients received a diagnosis of chronic rhinitis and sinusitis. The

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TABLE I. Characteristics of the subjects studied

|                                      | Aspirin-sensitive<br>asthmatic subjects | Aspirin-tolerant groups |                              |
|--------------------------------------|-----------------------------------------|-------------------------|------------------------------|
|                                      | AIA (n = 41)                            | ATA (n = 13)            | Healthy subjects<br>(n = 10) |
| Age (yrs)/range                      | 44.4/24-64                              | 42.1/28-62              | 36.5/20-59                   |
| M/F                                  | 8/33                                    | 4/9                     | 3/7                          |
| Pre-NPT FEV <sub>1</sub> (ml)/range  | 2766/1080-3800                          | 3227/2290-5560          | 3432/2480-5080               |
| FEV <sub>1</sub> (% predicted)/range | 88.3/48-130                             | 92.1/69-131             | 108/102-129                  |
| Post-NPT FEV <sub>1</sub> (ml)/range | 2531/1070-3600                          | 3384/2320-5600          | 3496/2560-5080               |
| FEV <sub>1</sub> (% predicted)/range | 85.2/47-124                             | 93.7/71-132             | 108.8/106-129                |
| Current therapy                      |                                         |                         |                              |
| Long-term $\beta$ -agonist           | 5                                       | 1                       |                              |
| Oral theophylline                    | 9                                       | 12                      |                              |
| Inhaled steroids                     |                                         |                         |                              |
| No. of patients                      | 39                                      | 11                      |                              |
| Dose ( $\mu$ g/day)/range            | 850/600-1400                            | 750 (400-1200)          |                              |
| Nasal steroids                       |                                         |                         |                              |
| No. of patients                      | 12                                      | 5                       |                              |
| Dose ( $\mu$ g/day)/range            | 560/400-800                             | 400/400                 |                              |
| Oral prednisone                      |                                         |                         |                              |
| No. of patients                      | 26                                      | 8                       |                              |
| Dose (mg/day)/range                  | 8.9/5-15                                | 8.2/5-12.5              |                              |
| Polypectomy                          |                                         |                         |                              |
| No. of patients                      | 9                                       | 2                       |                              |
| No. of polypectomies                 | 1-10                                    | 1-2                     |                              |

ATA, Aspirin-tolerant asthmatic subjects.

healthy control subjects had no history of aspirin sensitivity in the past. All of them took aspirin or other nonsteroidal antiinflammatory drugs during the previous year without any clinical symptoms. Healthy subjects were not taking any medication during the study (Table I).

In both groups of asthmatic subjects, patients with large nasal polyps were excluded because in most cases polyps significantly reduced the nasal flow values.

Before nasal challenge, the patients stopped their medications, according to the following scheme: oral antihistamines for 48 hours (hydroxyzine and loratadine for 7 days and astemizole for 1.5 months), nasal cromolyn sodium for 1 week, and nasal inhaled adrenergic or antihistaminic agents for at least 48 hours before the tests. The doses of oral, bronchial, and nasal corticosteroids were kept as small as possible and were not changed for at least 2 weeks before the study and throughout it.

### Aspirin NPT

The aim of the test was to assess the response to instillation of L-ASA in the nostrils of the subjects studied. The response was evaluated by measurement of nasal flows with active anterior rhinomanometry and by scoring the subjective nasal and extranasal symptoms of aspirin intolerance. The clinical symptoms scored included rhinorrhea; nasal congestion (blockade); itching or burning of the nose, ear, palate, or throat; and sneezing and lacrimation (watery or red eyes). The intensity of these symptoms were expressed with the following scale: 0, none; 1, mild; 2, moderate; and 3, severe. The total nasal score at each time interval was calculated as a sum of the above individual scores (maximal score, 15 points).

After the adaptation period of 30 to 45 minutes, baseline inspiratory and expiratory flows in both nostrils were measured while the subjects were in a sitting position by using active anterior rhinomanometry (Homoth 2000) every 10 minutes over half an hour. Nasal inspiratory flow had to be at least 250

ml/sec in each nostril. Then 80  $\mu$ l of 0.9% sodium chloride was instilled locally as droplets from a micropipette to a fixed site on the inferior nasal concha in both nostrils. Anterior rhinomanometry measurements were performed again every 10 minutes for another 30-minute period. If saline did not produce a decrease in nasal flow greater than 20% in either challenged nostril, 80  $\mu$ l of L-ASA solution (180 mg/ml L-ASA, equivalent to 100 mg/ml acetylsalicylic acid) was applied locally through nose droplets on the inferior nasal concha in both nostrils. The total deposited dose of L-ASA was equivalent to 16 mg of acetylsalicylic acid. Rhinomanometry was then performed bilaterally every 10 minutes for the next 2 hours (in some cases 3 hours, see below).

L-ASA was prepared freshly each day by dissolving crystalline L-ASA (Aspegic, Kramer Synthelab SA) in 0.9% sodium chloride to produce a solution containing 180 mg/ml.

The NPT results were regarded as positive if (1) nasal flow decreased more than 40% in at least one nostril as compared with the postsaline baseline value (the mean of three measurements following saline administration was regarded as baseline value), and (2) this decrease in nasal flow was sustained for at least two consecutive rhinomanometric measurements (i.e., it lasted at least 10 minutes) and was accompanied by clinical symptoms persisting at least 30 minutes (the minimal score amounting to 3 or more).

If depression in nasal flow and clinical symptoms appeared only by the end of the 2-hour observation period or the symptoms were absent, the rhinomanometric measurements and clinical observation were prolonged for another hour. The dose of aspirin used by us, duration of the observation period, and criteria for the positivity of the test results were established on the basis of previous experiments<sup>16</sup> in which a range of doses of aspirin from 1.25 to 16 mg had been tested, and observation times varied from 60 to 180 minutes.

Both before and after the nasal challenge with L-ASA,

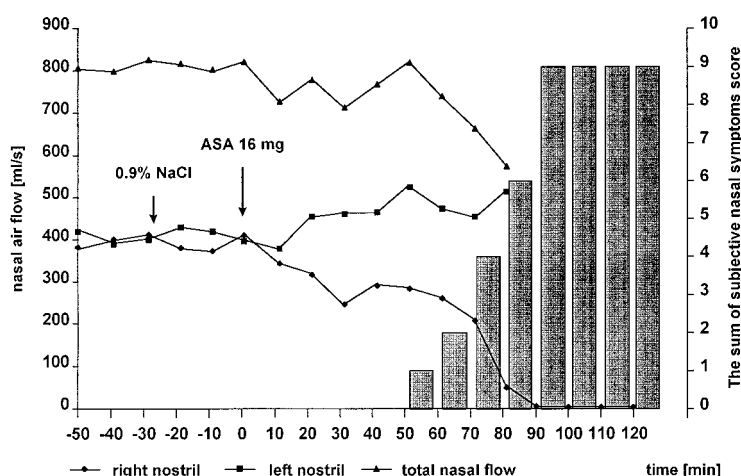


FIG. 1. Example of NPT in patient with AIA (patient age, 52 years). ASA, Aspirin.

asthmatic subjects' symptoms (i.e., dyspnea, wheezing, and chest tightness) were recorded. Simultaneously, pulmonary function parameters (e.g., forced vital capacity, FEV<sub>1</sub>, and mean maximal expiratory flow) were measured by using computerized pneumotachograph (Masterlab, Jaeger), and peak expiratory flow rates were measured by using Mini Wright Peak Flow Meters (Clement Clarke Int. Ltd.).

### Statistical analysis

Data were analyzed by means of the chi-square test with Yates correction. The reliability of NPTs as markers of the presence of intolerance was evaluated by classifying the patients as positive or negative by using the reference technique (oral provocation test). The number of results of NPTs (positive and negative) in concordance with these classifications (TP = true positive and TN = true negative) and discordant results (FP = false positive and FN = false negative) were also evaluated. The reliability of NPTs did not take into account the 10 patients who at entry into the study were disqualified from aspirin nasal challenges because of very low nasal flows at baseline.

Starting from these classified data we calculated the percentages of total accuracy (meaning percentage of concordance [TN+TP/overall cases], sensitivity [TP/TP+FN], specificity [TN/TN+FP], predictive value of a positive result [PVP = TP/TP+FP], and predictive value of a negative result [PVN = TN/TN+FN]).

## RESULTS

In 32 of 41 aspirin-sensitive asthmatic subjects (78%), the nasal challenge test with L-ASA led to definite decrease in nasal flow (fall from postsaline baseline value greater than 40%, lasting at least 10 minutes) during a 2-hour observation period. In two thirds of the patients, the decrease was pronounced and accompanied by almost total nasal obstruction. Such considerable fall in nasal flow was frequently observed only in one nostril; a unilateral reaction was noted in 22 of 32 patients (68.8%). In the remaining 10 patients (31.2%), nasal flow became depressed bilaterally. The reductions in nasal flows occurred 10 to 110 minutes after L-ASA

nasal instillation and lasted, on average, 64 minutes. No relationship was found between the initial (baseline) nasal flow values and the intensity of the reaction to L-ASA. In 57.3% of the patients, a significant drop in nasal flow was observed in that nostril in which the flow was lower just before L-ASA administration. In the remaining subjects (42.7%), a remarkable reduction in flow was found in the nostril with initially higher flow values.

In all patients with depression of nasal flow ( $n = 32$ ), watery discharge and the sensation of nasal blockage were noted during a 2-hour observation period. Other less frequent symptoms included itching of the nose, ears, and/or palate (34.4%); sneezing (31.2%); and lacrimation (28%). The maximum intensity of clinical symptoms ranged between a score of 3 to 11 points (average, 5.96 points). Twenty-six of 32 (81.2%) subjects observed at least one of these symptoms at the maximal intensity during the course of a 2-hour observation period. Nasal symptoms appeared 10 to 70 minutes after L-ASA administration and lasted 30 to 110 minutes (average, 73.4 minutes). In 18 of 32 (56.2%) patients clinical symptoms preceded a decrease in nasal flow by 10 to 70 minutes (mean, 26.7 minutes). In nine patients (28.1%) they occurred simultaneously, and in five decreased nasal flows were followed shortly by clinical symptoms (Figs. 1 and 2).

Pulmonary function tests showed no changes, including five patients with aspirin-induced asthma whose initial FEV<sub>1</sub> ranged between 48% and 69% of the predicted value (Table I). In seven patients the NPT was performed twice within a 2-month interval, with similar results.

In three of 41 patients, clinical symptoms and significant decreases in nasal flow were observed only at the end of the second hour of the challenge (Table II). Prolongation of the observation period for up to 3 hours led to a typical nasal response manifested by a significant fall in nasal flows accompanied by clinical symptoms. In

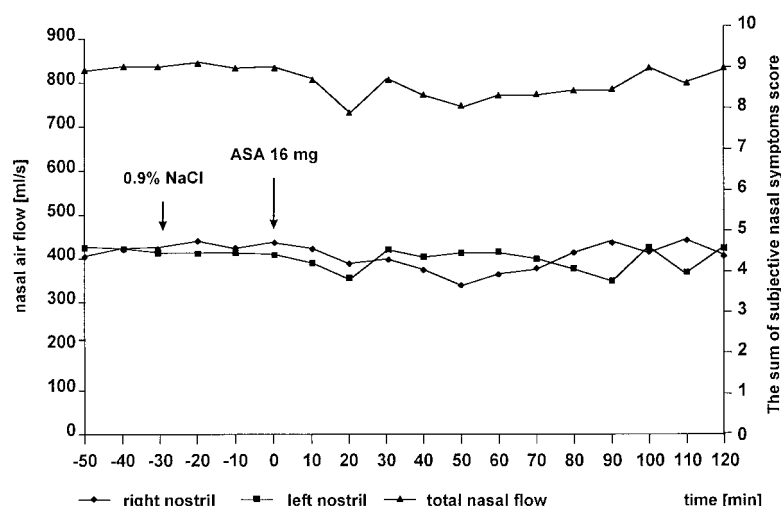


FIG. 2. Example of NPT in healthy subject (subject age, 28 years). ASA, Aspirin.

TABLE II. The reliability of the NPT with L-ASA in AIA

|                                          | Positive<br>NPT results | Negative<br>NPT results |
|------------------------------------------|-------------------------|-------------------------|
| Aspirin-sensitive asthmatic subjects (A) | 32                      | 9                       |
| Control groups (C)                       | 1                       | 22                      |
| A versus C                               | $p < 0.001$             |                         |
| Accuracy (%)                             | 84.4                    |                         |
| Sensitivity (%)                          | 78                      |                         |
| Specificity (%)                          | 95.6                    |                         |
| Positive predictive value                | 96.9                    |                         |
| Negative predictive value                | 71.0                    |                         |

The criteria for positive nasal provocation test results with L-ASA are nasal flow decrease greater than 40% in at least one nostril, duration of at least 10 minutes, and presence of clinical symptoms (minimum 3 points of predetermined score) during 2-hour observation period.

those three patients the test results thus proved to be positive.

Nasal challenge tests with L-ASA, extended to a 3-hour observation period, showed negative results in six subjects with AIA. In five of these subjects, neither clinical symptoms nor depression of nasal flow were evoked by aspirin. In one individual we noted watery discharge, obstruction of the nose, and dry cough, but without a predetermined fall in nasal flow; FEV<sub>1</sub> values also remained unchanged. In these six patients we did not decide to use higher doses of aspirin because our previous experience<sup>16</sup> taught us that 24 and 40 mg doses caused a marked, though passing, irritation of nasal mucosa and did not improve the sensitivity of the test.

Nasal challenge test results were negative in nine of 10 healthy subjects and in all aspirin-tolerant asthmatic subjects. In one healthy individual we noted meaningful bilateral fall in nasal flow (47%) accompanied by mild rhinorrhea and moderate nasal blockage. This test result

was regarded as positive. This patient underwent an oral challenge test with 500 mg aspirin. The test result was negative. In the other three subjects from control groups (two asthmatic subjects and one healthy subject), considerable decreases (42% to 57%) in nasal flow without any concomitant nasal symptoms were noted; the test results were regarded as negative.

The sensitivity and specificity of the test during 2-hour observations were 78% and 95.6%, respectively. Prolongation of the observation time up to 3 hours increased sensitivity of the test (89.1%) without change in specificity (95.7%). There is an almost 97% chance of a patient with positive nasal challenge test results to be confirmed as intolerant to aspirin by oral challenge test. Negative nasal challenge test results do not exclude possible intolerance (predictive value of a negative result = 71% and 78.6% during 2- or 3-hour observation periods after L-ASA nasal deposition) (Table II).

## DISCUSSION

There is a close relationship between diseases of the upper and lower respiratory tract.<sup>17-19</sup> Nasal challenge tests with histamine, methacholine, and allergens have been used for research purposes and in clinical studies.<sup>20-24</sup> The nasal tests with L-ASA were sporadically applied for assessment and diagnosis of aspirin-sensitive asthma, although not in a routine way. They differ in dose and methods of aspirin administration, duration of observation period, criteria for evaluation of the test results as positive, and final assessment.<sup>25-29</sup>

This article demonstrates that in patients with aspirin-induced asthma, the one-dose application of L-ASA (16 mg acetylsalicylic acid) on the nasal mucosa causes significant decrease in inspiratory nasal flows and appearance of clinical symptoms, mainly watery discharge and nasal blockage. The aspirin dose has been established empirically during our previous studies.<sup>16</sup> It is similar to that used by Picado et al.<sup>30</sup> (12 mg) but

different from that used by the Swiss otolaryngologists (1.25 mg).<sup>28</sup>

It has been reported that unilateral allergic stimulation of the nose induced bilateral responses during the early reactions.<sup>23, 24</sup> The contralateral response could be due to nasal cycling or could result from central reflex.<sup>31, 32</sup> An alternative explanation,<sup>33</sup> not involving the central nervous system, suggests that a mediator released into circulation could travel through the blood to the contralateral nostril. This route would involve the systemic circulation because blood does not flow directly from one nasal cavity to another. In our preliminary experiments<sup>16</sup> we noticed that unilateral nasal aspirin challenge led to clinical responses on the side of the challenge site, the unchallenged site, or both. The baseline nasal flows proved to be of no predictive value concerning the side of response. We therefore decided to apply aspirin to both nostrils and follow the reaction bilaterally.

To reduce the irritating effect of numerous aspirin applications, a single-dose application was performed in this study. The inferior nasal concha was chosen for aspirin application because of its marked contribution to total nasal resistance and easy access for deposition of L-ASA.

In our study no serious systemic reactions were noticed. FEV<sub>1</sub> and mean maximal expiratory flow taken before and after the nasal challenge test did not show any significant differences. Dry cough without changes in FEV<sub>1</sub> occurred in only one patient during the test. It should be stressed that in five patients in whom FEV<sub>1</sub> before the test was below 70% of the predicted value, no significant fall in FEV<sub>1</sub> was observed after nasal L-ASA application. Our results are in contrast with those of Pawlowicz et al.<sup>27</sup> who observed, in all seven patients studied, a fall in FEV<sub>1</sub> of at least 15%. The reason for this difference could be an alternative method of aspirin administration (L-ASA was sprayed into the nostril from an atomizer driven by compressed air) and a higher provocation dose (total dose of L-ASA was 36 mg).

In six of 41 patients with confirmed intolerance to aspirin, the results of the nasal challenge test were doubtful or negative. In three of these patients, an oral aspirin challenge test evoked no nasal symptoms. Another two patients were receiving amitriptyline or aldomet therapy, which could have altered the reaction of the nasal mucosa. One female patient was receiving a rather high level of prolonged oral corticosteroid therapy (15 mg prednisone per day) and also nasal steroid (budesonide 400 µg/day) therapy. The protective effect of corticosteroids on bronchial reactions precipitated by oral challenge with aspirin was previously described in aspirin-sensitive asthmatic subjects.<sup>33</sup>

One of the drawbacks of nasal challenge tests with L-ASA is that they cannot be performed in a proportion of patients. These are the subjects with total nasal blockage or with large fluctuations in nasal flow at baseline. In our study population the percentage of such patients, characterized by extensive edematous and hy-

pertrophic changes in the nasal mucosa, amounted to 19.6%.

The test developed is highly sensitive (86.7%) and specific (95.7%). A positive result indicates high probability (value confirming diagnosis, 97.2%) of intolerance to aspirin. However, the negative result does not exclude the possibility of aspirin intolerance (value excluding diagnosis, 78.6%).

In conclusion, the NPT with L-ASA is a simple, safe, and quick test for diagnosis of aspirin-sensitive asthma. It can be used in patients with instability of the bronchial tree in which bronchial or oral provocation tests with aspirin cannot be carried out. It is a method of choice to confirm hypersensitivity to aspirin manifested only by symptoms of the upper respiratory tract. It is advisable to use this test as the initial one in the diagnosis of hypersensitivity to aspirin. Patients suspected of aspirin intolerance with negative results on NPTs should undergo bronchial or oral challenge tests with aspirin.

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