

Inhalation and nasal challenge in the diagnosis of aspirin-induced asthma

A. PAWLOWICZ, W. R. WILLIAMS & B. H. DAVIES

Asthma and Allergy Unit, Sully Hospital, Cardiff, Wales, UK

Inhalation and nasal aspirin challenge has been investigated in asthma patients with co-existing rhinitis. Eight of 39 asthma patients were diagnosed as aspirin-sensitive on the basis of inhalation challenge. Seven aspirin-sensitive asthmatics were subjected to nasal aspirin provocation. During nasal challenge, all seven patients experienced a fall in FEV₁ of at least 15%, two showed a significant increase (> 400%) in nasal airways resistance (NAR) and one developed urticaria. No significant changes in FEV₁ or NAR were observed in nine normal subjects after aspirin inhalation and nasal challenge. There were no significant changes in FEV₁ or NAR in six aspirin-tolerant asthmatics when aspirin was given intranasally. The results of this study show that aspirin nasal provocation impairs lung function in aspirin-sensitive asthmatics. In comparison with inhalation challenge responses are generally milder and easier to control. Nasal challenge is also less time-consuming than other methods of aspirin challenge and is therefore more suitable for routine use.

Key words: aspirin sensitivity; asthma diagnosis; rhinitis diagnosis.

Accepted for publication 1 November 1990

Although aspirin has been known to cause bronchospasm in some asthma patients for almost 90 years (9), there is still no satisfactory diagnostic test for clinical use. Skin tests with aspirin derivatives and serology are not successful in detecting aspirin-induced asthma (6, 8, 14, 16, 17), and challenge testing (7) remains the only known method for diagnosing this disorder.

The traditional oral aspirin provocation test may provoke significant asthma attacks, and as they are lengthy procedures they have been restricted predominantly to research work on aspirin sensitivity. Aspirin inhalation challenge, introduced by Bianco (2) in 1981 and adopted for use by other workers (1, 5, 15), facilitates the diagnosis of aspirin-induced asthma. The authors reported that with this method bronchial responses are quicker and easier to control. The test is, however, still too time-consuming to be considered suitable for clinical

practice. Further, it is unsuitable for the diagnosis of aspirin-induced rhinitis or aspirin-induced urticaria as adverse reactions are confined only to the respiratory tree.

It is well known that aspirin may produce adverse reactions in several organs. Apart from the respiratory tree, the nose and skin are frequently involved and in particularly severe cases of intolerance, these organs may be simultaneously affected. This study was carried out to investigate the diagnostic value of nasal aspirin administration and its effect on nasal and lung function in aspirin-sensitive asthma patients with co-existing rhinitis.

MATERIAL AND METHODS

Aspirin inhalation challenge was carried out on 39 patients (18 men and 21 women) with bronchial asthma and perennial rhinitis (age range

24-69 years) attending an outpatients department. Twenty of them had undergone polypectomy, only two had definite histories of aspirin intolerance, 11 were atopic and none were smokers. Eight patients with aspirin-induced asthma, diagnosed on the basis of inhalation challenge, were subjected to nasal challenge at least 1 week later. All patients were in remission of their asthma (baseline value for forced expiratory volume in 1 second (FEV_1)) at least 70 % of predicted and above an absolute value of 1.5 l). Drug therapy in all cases consisted only of inhaled B stimulants, inhaled corticosteroids and long-acting antihistamines. The time intervals between the last use of anti-asthma drugs and challenge testing were those recommended by Cropp et al. (4). Thus, inhaled B stimulants and corticosteroids were discontinued 8 h before testing while long-acting antihistamines were stopped 1 week before challenge. No cyclooxygenase inhibitors were taken in the week preceding challenge.

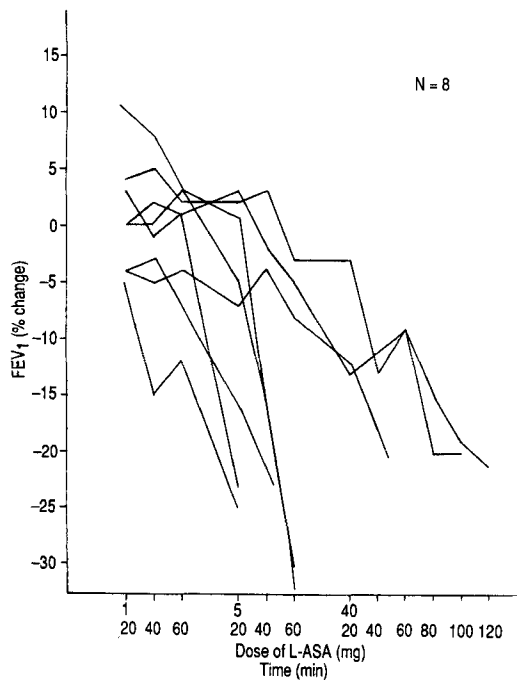


Fig. 1. FEV_1 in aspirin-sensitive asthmatics during aspirin inhalation challenge.

The control group consisting of nine (5 men and 4 women) healthy atopic, non-smoking volunteers (age range 21-61 years), had no history of aspirin sensitivity and were not taking medication.

Ethical approval for the study was obtained from the South Glamorgan Division of Medicine and informed consent was obtained from all participants.

Chemicals used were lysine-acetylsalicylic acid (Aspisol) provided by Bayer UK Ltd. and DL-lysine from Sigma.

Lung function tests were carried out with a compact Vitalograph. The best of two recorded measurements was compared with predicted values (3). FEV_1 was monitored during aspirin inhalation and aspirin nasal challenge.

Rhinomanometry (passive anterior rhinometry) was measured with a Nasal Airways Resistance Tester (P.L. Morgan mark III) using the method described by Roath et al. (13).

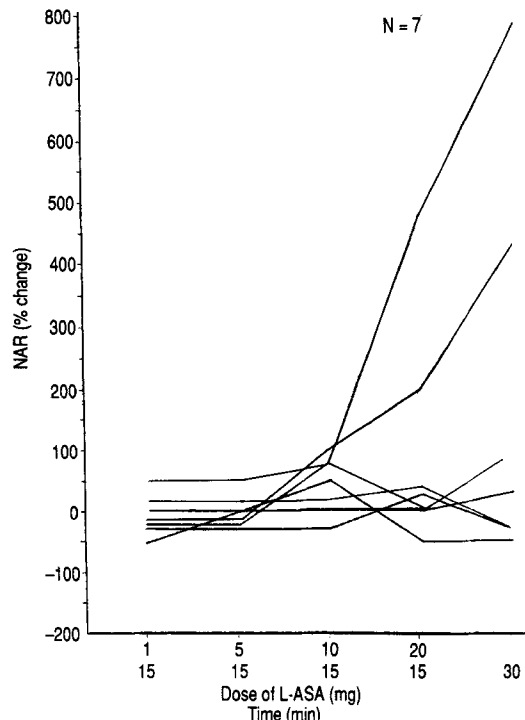


Fig. 2. NAR in aspirin-sensitive asthmatics during aspirin nasal challenge.

NAR was established by taking the mean of 5 measurements over 1 min.

Aspirin inhalation provocation was carried out following the technique described by Bianco et al. (2). A freshly prepared solution (18% w/v) of lysine acetylsalicylic acid (L-ASA) in distilled water diluted 1:3 with saline and adjusted to pH 7.4, with sodium hydroxide, was administered through a nebuliser (Monaghan type) driven by compressed air (output 0.2/min). The drug solution was inhaled through a mouthpiece, with the patient wearing a nose-clip and breathing normally with half-open mouth. The patient's FEV₁ was measured every 20 min after each exposure. A positive reaction was defined as a fall in FEV₁ of at least 20% below the patient's baseline value. The initial exposure time was 30 s (aspirin inhaled 1 mg). If no reaction occurred within an hour, the next exposure was 2 min (5 mg). In the absence of a

reaction in the following hour the final exposure was for 5 min with undiluted L-ASA (40 mg). The lack of bronchial response in the following 2 h was taken as an indication that the patient was not aspirin-sensitive. If a positive response was obtained a control test with lysine solution was carried 1-2 weeks later, to exclude non-specific bronchial hyperactivity.

Nasal provocation was carried out if the resting resistance did not exceed 0.8 KPa⁻¹/s. The nostril with the lower resting resistance was selected for challenge. A control solution of 200 µl lysine in PBS (100 mg/ml) was sprayed into the nostril from an atomiser driven by compressed air (3lb/in²). NAR was measured every 5 min over a 15-min period, to estimate baseline resistance. Four concentrations of L-ASA (5, 25, 50, 100 mg/ml) buffered at pH 6.5 were used for testing. Two hundred µl of each aspirin solution (containing 1, 5, 10 and 20 mg L-ASA) was sprayed into the nostril at 15-min intervals and NAR was measured every 5 min after each exposure. After the last exposure, NAR was monitored for a further 15 min. An increase in NAR > 200% above the baseline value was considered to be a positive reaction. Lung function tests were carried out 15 min after the administration of aspirin.

RESULTS

Aspirin inhalation challenge

The total dose of inhaled aspirin was well tolerated by the nine control subjects. The maximum observed fall in FEV₁ during the tests was

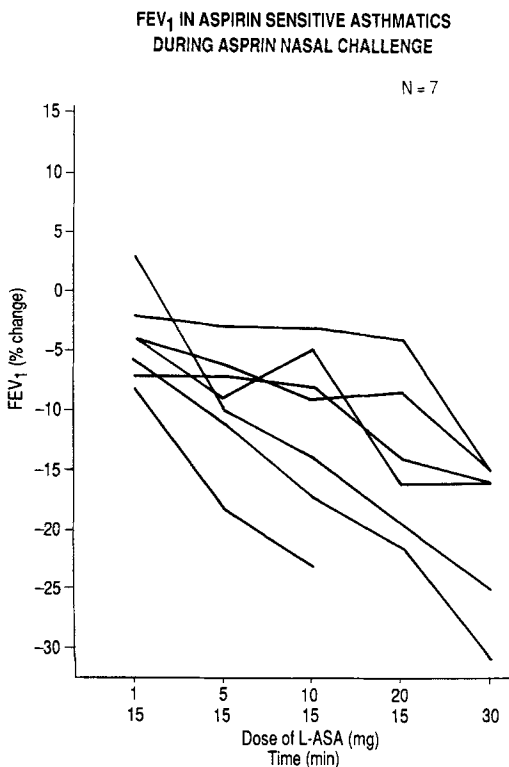


Fig. 3. FEV₁ in aspirin-sensitive asthmatics during aspirin nasal challenge.

Table 1.

Reproducibility of NAR and FEV₁ during nasal aspirin challenge

Patients	NAR % change		FEV ₁ % change	
	I	II*	I	II*
1	50	0	-25	-22
2	0	0	-16	-13
3	480	600	-15	-8
4	760	800	-15	-16
5	100	133	-16	-15

* challenge tests repeated 6 months after I.

6%. In the group of 39 asthma patients, 31 were diagnosed as aspirin tolerant and eight as aspirin sensitive (Fig. 1). Two of the eight aspirin-sensitive asthmatics were atopic (25%) and seven had polyps (88%), while in the aspirin-tolerant group 10 (32%) were atopic and 13 (32%) had polyps. Before the test the average baseline FEV₁ in aspirin-sensitive asthmatics was 91%. Significant decreases in FEV₁ were obtained in five patients after the second exposure to L-ASA and in the other three patients after the third exposure. The mean fall in FEV₁ was 25% (range -20 to -35%). In all cases, except one, bronchospasm reverted to the baseline value before challenge within 15 min after 200 µg of inhaled Ventolin. One patient, who deteriorated by 35% below baseline FEV₁, required nebulised Ventolin and this patient was excluded from nasal challenge. Placebo tests with lysine in all eight aspirin-sensitive asthmatics were negative. No changes in NAR were observed in any asthmatic with adverse bronchial responses, during aspirin inhalation challenge.

Aspirin nasal challenge

Nasal challenge of the nine control subjects produced no significant changes in NAR. The highest observed increase in NAR was 100%. There were also no significant differences in NAR or FEV₁ during nasal challenge in six aspirin-tolerant asthmatics.

In seven asthmatics with aspirin sensitivity diagnosed by inhalation challenge, the intranasal administration of 20 mg L-ASA induced extensive rhinorrhea with sneezing and significant increases in NAR (480%, 760%) in two patients (Fig. 2). No significant changes in NAR were observed in the other four patients but, interestingly, one patient developed urticaria during the test. During nasal provocation, all seven asthmatics showed a decrease in FEV₁ of 15% or more (15-31%) (Fig. 3). One patient developed significant bronchospasm (-23%) after 10 mg and the other six exhibited falls in FEV₁ ranging from 15 to 31% after 20 mg L-ASA. There was no statistically significant

difference between the FEV₁ values obtained in inhalation and nasal challenge tests (Wilcoxon matched paired signed ranks test).

In five aspirin-intolerant asthma patients, nasal aspirin challenge was repeated 6 months later. Nasal resistance parameters were comparable in these two studies (Table 1) and there were no significant differences in FEV₁ values (Student's paired t test).

DISCUSSION

Interest in the use of nasal aspirin provocation for the diagnosis of aspirin-induced asthma has been neglected. To date, only two studies on aspirin nasal challenge have been published. One showed that the nasal administration of aspirin, to patients with allergic rhinitis, did not significantly change nasal airways resistance (NAR) and NAR responses to histamine and metacholine (10). The other study, of patients with aspirin-induced asthma and rhinitis, found significantly higher levels of mediators of anaphylaxis (LTC₄ and SRS-A) in nasal wash fluids, after nasal aspirin provocation (11). However, the authors did not monitor pulmonary and nasal function. The present study is the first to measure objectively the effects of nasal aspirin administration on nasal and pulmonary responses, in aspirin-sensitive asthma patients (12).

Aspirin nasal challenge produced significant changes in NAR values in two of seven patients with aspirin-induced asthma and this was accompanied by extensive rhinorrhoea and sneezing. It is interesting that nasal challenge, in contrast to inhalation challenge, is able to produce adverse nasal responses in aspirin-sensitive subjects. However, it is difficult to estimate the sensitivity of this test, as the prevalence of this condition among the seven aspirin-sensitive asthma patients could only be estimated by oral aspirin challenge. Of more importance, was the observation that nasal provocation also impaired lung function in aspirin-intolerant asthmatics. During nasal provocation, bronchial responses were generally milder although all patients experienced a fall in FEV₁ of more than 15%. This degree of impairment in FEV₁ appears to be sufficient to diagnose adverse bronchial responses to aspirin,

during nasal provocation, as the bronchi are not challenged directly. Nasal aspirin challenge should, therefore, always be undertaken with caution and only in asthma remission.

Nasal challenge has several advantages over other methods of challenge, for the diagnosis of aspirin intolerance in asthmatic subjects. Of the different challenge tests, nasal aspirin provocation is the quickest method for detecting aspirin-induced bronchospasm, taking 90 min; in comparison, oral challenge requires 2×8 h and inhalation challenge 2×4 h (including the placebo test). As in our study none of the aspirin-intolerant asthmatics was affected by 1 and 5 mg L-ASA, it should, in future, be possible to omit the first exposure and complete the test in 75 min. Nasal provocation excludes the non-specific bronchial response that occurs in some asthmatics when the lungs are challenged directly, making a placebo test mandatory after every positive inhalation challenge. A placebo test is also necessary in oral challenge to exclude the spontaneous deterioration in pulmonary function, which results from the patient abstaining from anti-asthma drugs for a long period (at least 16 h). Our results also show that during nasal challenge, it is possible to simultaneously investigate other organs that may be affected by aspirin.

In conclusion, aspirin nasal provocation is a simple, safe and quick test for investigating aspirin sensitivity. It is well tolerated by patients and may therefore be more suitable for diagnosing aspirin-induced asthma and perhaps aspirin-induced rhinitis on an outpatient basis. The advantages of this method now need to be confirmed on larger numbers of patients.

ACKNOWLEDGEMENTS

This work was supported by grants from the Wellcome Trust and Asthma Research Council. The authors would like to thank Drs A. Fennerty, K. Sharma and J. Thomas for their help in this study and Mr D. A. Lee of Bayer, Ltd. for kindly providing Aspisol.

REFERENCES

1. Adachi M, Matsui K, Nizuma T, et al. Study on aspirin sensitivity. *Ann. Allergy* 55, 317, 1985 (abstract).

2. Bianco S, Robuschi M, Pettrigni G. Aspirin sensitivity. *Br Med J* 282, 146, 1981.
3. Cotes JE. Lung function assessment and application in medicine. Blackwell, Oxford, 1979.
4. Cropp GJ, Bernstein IL, Boushey Jr HA, et al. Guidelines for bronchial inhalation challenges with pharmacologic and antigenic agents. *ATS News*, II, 1980.
5. Dahlen B, Zetterstrom O. Inhalation of lysine-acetylsalicylic acid (L-ASA): An easy and safe method to diagnose aspirin asthma. *Allergy* 7, Suppl 76, 1988.
6. Delaney JC, Kay AB. Complement components and IgE in patients with asthma and aspirin idiosyncrasy. *Thorax* 31, 425-427, 1976.
7. Genton C, Frei PC, Pecoud A. Value of oral provocation tests to aspirin and food additives in the routine investigation of asthma and chronic urticaria. *J Allergy Clin Immunol* 76, 40-45, 1985.
8. Girard JP, Hildebrandt F, Favres H. Hypersensitivity to aspirin. Clinical and immunological studies. *Helv Med Acta* 35, 86-95, 1969.
9. Hirschberg. Mitteilung uber einen fall von nebenwirkung des aspirin. *Dtsch Med Wochenschr* 28, 416, 1902.
10. McLean JA, Bacon JR, Mathews KP, Banas MS, Capati D, Bayne NK. Effects of aspirin on nasal responses in atopic subjects. *J Allergy Clin Immunol* 72, 187-192, 1983.
11. Ortolani C, Mirone C, Fontana A; et al. Study of mediators of anaphylaxis in nasal wash fluids after aspirin and sodium metabisulphite nasal provocation in intolerant rhinitic patients. *Ann Allergy* 59, 106-112, 1987.
12. Pawlowicz A, Williams WR, Davies BH. Inhalation and nasal challenge in the diagnosis of aspirin induced asthma. *Thorax* 1989, (abstract) (in press).
13. Roth RP, Cantekin EI, Bluestone CD, Welch RM, Cho YW. Nasal decongestant activity of pseudoephedrine. *Ann Otol Rhinol Lar* 86, 235-42, 1977.
14. Schlumberger HD, Lobbecke EA, Kallos P. Acetylsalicylic acid intolerance. Lack of N-acetylsalicylic acid specific skin sensitising antibodies in the serum of intolerant individuals. *Acta Med Scand* 196, 451-458, 1974.
15. Schmitz-Schumann M, Menz G, Virchow C. Analgesic challenge as a tool in diagnosis, therapy and research of bronchial asthma. Third International Symposium on Platelets, Analgesics and Asthma, Davos Platz, Switzerland. Sept. 7-9, 1986.
16. Vatanasuk M, Hornbrook MM, Kohler PF. Serum IgE and passive transfer in aspirin intolerance (abstract). *J Allergy* 47, 109, 1971 (abstract).
17. Yurchak AM, Wicher L, Arbesman CG. Immunological studies on aspirin: Clinical studies with aspiryl protein conjugates. *J Allergy* 46, 245-253, 1970.

Address:

Dr. Anna Pawlowicz

Sully Hospital

Cardiff CF6 2YA, U.K.