

Editorial

Testing for aspirin hypersensitivity

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Aspirin (acetylsalicylic acid, ASA) and other nonsteroidal anti-inflammatory drugs (NSAIDs) are among the drugs most commonly used all over the world. NSAIDs were reported to be the cause of 21–25% of all adverse drug reactions (1). Their clinical manifestations vary. A classification of these reactions has been recently proposed (2). The only way to make a definitive diagnosis is through provocation challenge testing. Let us then discuss briefly the methods used in diagnosing these most common and dangerous, aspirin-related syndromes, i.e. aspirin-induced asthma and rhinitis.

There is a group of adult patients with asthma in whom ingestion of aspirin and other NSAIDs precipitates asthmatic attacks. This is a distinct clinical syndrome, called aspirin-induced asthma (AIA) (3). The natural history and clinical picture of AIA were recently described in a large survey comprising 500 patients from 10 European countries participating in the European Network on Aspirin-Induced Asthma (AIANE) (4). In most patients, throughout Europe, the sequence of symptoms has been of similar character. First, persistent rhinitis usually occurs during the third decade of patient's life. Over a period of several months, asthma, aspirin hypersensitivity (5), and nasal polyposis also appear. The asthma attacks following ingestion of NSAIDs are usually severe and sometimes life-threatening. In a large French study, 25% of asthmatics requiring mechanical ventilation were found to be aspirin hypersensitive (6). Occasionally, aspirin hypersensitivity is manifested only in the upper respiratory tract as an attack of rhinitis with discharge, sneezing and nasal obstruction. Rarely urticaria or gastrointest-

inal symptoms appear (7). Hypotension with loss of consciousness, which is not distinguishable from anaphylactic reaction, is uncommon, but is a possible manifestation of aspirin hypersensitivity.

The prevalence of AIA differs according to the diagnostic methods used. Based on patient history alone, it was estimated to be about 3–5% in adult asthmatics. However, when aspirin challenges were performed, the frequency increased to 8–20% (8, 9). Aspirin hypersensitivity is largely under-diagnosed among the asthmatics. In a population-based, random sample of 4300 adult women and men in Finland, the prevalence of aspirin hypersensitivity causing a shortness of breath or attacks of asthma was 1.2% (10). It was higher among patients with doctor-diagnosed asthma than those without (8.8% vs 0.8%). The reason for under-reporting of aspirin-sensitivity may be the avoidance of NSAIDs by asthmatic patients, who are aware of adverse reactions, or a lack of recognition by patients of mild NSAID-induced reactions, due to their delayed onset of action (11). In the AIANE study, 15% of asthmatic patients had been unaware of their aspirin hypersensitivity and realized it only after provocation tests were carried out on them (4). Under-diagnosis of aspirin hypersensitivity indicates the necessity for more extensive use of aspirin challenge tests in medical practice.

Clinical picture and patient history can only raise a suspicion of AIA and so it should always be confirmed by provocation test. There are four types of provocation test, depending on the route of aspirin administration: oral, bronchial (inhaled), nasal, and intra-

venous tests, seldom used (only in Japan). They consist of delivering increasing doses of acetylsalicylic acid by different routes and measuring bronchial and extra-bronchial symptoms. The protocols of provocation tests differ between the various centres. The tests are sometimes coupled with measurement of urinary excretion of leukotriene E_4 , the values of which rise several-fold in the vast majority of cases. Although LT- E_4 estimation is a valuable tool in research, its measurement is not required for establishing the clinical diagnosis, or for interpretation of the test (12).

Oral challenge tests with ASA were introduced into clinical practice in the early 1970s (13). Over the following years they were duly validated (9, 14) and came into use on a more frequent basis. They mimic the natural exposure to the drug and are commonly accompanied not only by bronchial, but also by extrabronchial and general symptoms. A four-day protocol used for many years in the authors' department (13) has been replaced by the abridged approach (four days *vs* two days) (15). The proper aspirin challenge test is preceded on the day before by the administration of placebo capsules every 2.5 h. This is necessary for estimation of bronchial stability; FEV₁ values are not allowed to vary by >15% from baseline. If greater falls in FEV₁ should occur, the patient is then temporarily excluded from further testing. On the second day, increasing doses of aspirin, in geometric progression, are administered to the patient until a total cumulative dose of 500 mg is reached. During the challenge, pulmonary function tests (FEV₁) are carried out every 30 min. The patient is also observed for bronchial reactions (broncho-spasm, tightness of chest, wheezing), upper airway reactions (rhinorrhea, nasal congestion) and general reactions (ocular injection, periorbital swelling, erythema of the skin, etc.). The test is interrupted if a fall of 20% in FEV₁ is recorded, or strong extrabronchial symptoms appear, or if the maximum cumulative dose of ASA is reached. The proposed cumulative dose of ASA (500 mg), administered only during one day, seems to be high enough to detect existing hypersensitivity to ASA. It is similar to the dose used by other authors (7, 14) and helps to avoid possible desensitization to ASA (16).

An inhalation test for diagnosis of aspirin intolerance was introduced into a clinical practice by Bianco et al. in 1977 (17). In the following years it was used by others (14, 18–20). The inhalation test differed in the consecutive dosages of lysine-aspirin (L-ASA) administered, in the intervals separating them, and the total cumulative dose of ASA administered.

The inhalation protocol (14) has been recently modified by using geometrically progressively increasing doses of L-ASA, up to a total cumulative dose of 182 mg. The test begins with the inhalation of 0.9%

sodium chloride. If post-saline FEV₁ does not fall by more than 10% from baseline, the provocation with L-ASA is commenced.

L-ASA solutions, prepared by dissolving crystalline L-ASA in 0.9% sodium chloride, are administered by inhalation from a dosimeter-controlled jet nebulizer. The consecutive doses are inhaled every 30 min and FEV₁ values are measured at 10, 20 and 30 min after each dose. The test is interrupted when FEV₁ falls >20% from the post-saline baseline value, or if the strong extrabronchial symptoms occur, as well as when the maximum cumulative dose of L-ASA is reached. Like the oral provocation test, the bronchial test should always be preceded by challenge with placebo on the day before. The patient inhales a solution of lysine and glycine with the same pH and osmolarity as the solution of L-ASA, and in the same manner. Introduction of the placebo-day into the protocol of both types of test makes them somewhat longer, but allows exclusion of bronchial instability. In oral as well as bronchial provocation tests carried out in such a manner, both oral and bronchial (inhaled) PD₂₀ ASA values can be calculated.

Both tests, when performed in the manner referred to above, have a similar specificity, but the oral test has somewhat higher sensitivity (15). The inclusion of extrabronchial symptoms into the assessment criteria increases the diagnostic value of both procedures.

It should be remembered that patients undergoing provocation tests must be clinically stable and must have baseline FEV₁ at least 70% of the predicted value. Theophylline, inhaled long- and short-acting bronchodilators, cromones, and antileukotriene agents should be stopped for an adequate length of time before the test (21). Rarely, the result of the challenge may be false negative. This might occur in patients who are on high doses of oral corticosteroids.

There are patients suspected of aspirin hypersensitivity whose asthma is not in clinical remission, and their FEV₁ is lower than 70% of the predicted value. In some other patients aspirin elicits only nasal symptoms (22). In both situations the nasal provocation test with L-ASA is a viable option.

This test was employed in the late 1980s (23–26), but the protocols differed in doses used, in method of aspirin administration, in duration of observation period, and in criteria for evaluation of the results. In our department the nasal L-ASA challenge test was developed using a total dose of L-ASA of 16 mg, instilled bilaterally into the inferior nasal conchae (27). The response is assessed clinically and by anterior rhinomanometry. The results are regarded as positive if: 1) the nasal flow decreases more than 40% in at least one nostril, as compared with the post-saline baseline value; 2) these decreases are sustained for at least two consecutive rhinomanometric measurements; and 3) are accompanied by clinical symptoms.

One of the drawbacks of nasal challenge tests with L-ASA is that they cannot be performed on patients with total nasal blockage, or who have large fluctuations in nasal flow at baseline. Positive results of the test indicate a high probability of hypersensitivity to aspirin. However, the negative results do not rule out the possibility of aspirin hypersensitivity. Thus, nasal provocation challenge – a simple, safe and quick test – should be recommended in patients with instability of the bronchial tree, in whom bronchial or oral provocation tests with ASA cannot be carried out. It can also be used as a screening procedure in outpatient clinics. It is the method of choice to confirm hypersensitivity to aspirin manifested only by symptoms of the upper respiratory tract. It may be used as the initial test in diagnosis of hypersensitivity to aspirin. The diagnostic value of the nasal test has been confirmed in a study of Alonso-Llamazares et al. in this issue of *Allergy* (28) Patients suspected of aspirin hypersensitivity, who have negative results during nasal provocation tests, should undergo bronchial or oral challenge tests with ASA.

In conclusion, the provocation tests with aspirin should become a routine diagnostic procedure in patients suspected of hypersensitivity to aspirin and other NSAIDs. Oral and bronchial aspirin challenges should be performed in specialized centres and the patient must be under the supervision of a doctor and a nurse. If trained staff carry out these tests, on properly selected patients, the safety of the tests is assured and they provide a valuable diagnostic instrument.

Establishing the right diagnosis is of utmost importance. It provides the patient with a long list of common drugs that must not be taken in view of the high risk of a dangerous reaction (29). It indicates which NSAIDs can be taken with impunity (30–33). It diagnoses a particular type of asthma with a special sequence of symptoms and allows choice of a specific therapy, i.e. aspirin desensitization. For those interested in understanding the pathogenesis of the disease, it provides a fascinating model to study the mechanisms of asthma.

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