

Allergy and Intolerance to Nonsteroidal Anti-Inflammatory Agents

Alain Arnaud

*Pneumology-Allergology Department,
Centre Hospitalier et Universitaire Nord, 13009 Marseille, France*

Introduction

Intolerance to aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) usually includes severe bronchial asthma, nasal polyposis, and diverse systemic manifestations. These manifestations may be reproduced by challenge tests. Patients with aspirin and NSAID intolerance can be desensitized. Intolerance to aspirin and NSAIDs has been related to an alteration of arachidonic acid metabolism. Aspirin and NSAIDs inhibit the cyclo-oxygenase (CO) enzyme which leads to the synthesis of prostaglandins and thromboxane. In intolerant patients, there is an up-regulation of the lip-oxygenase (LO) pathway, which leads to an overproduction of leukotrienes (LTs). LTs are potent spasmogens for nonvascular smooth muscles and exhibit chemotactic activity for neutrophils and proinflammatory properties. Moreover, it has been shown that intolerant asthmatics had a bronchial hypereactivity to LTE₄.

Based on these observations, it has recently been shown that administration of LT receptor antagonists and LO inhibitors might decrease or abolish adverse reactions to aspirin and NSAIDs in intolerant asthmatics.

Like all analgesic drugs, NSAIDs can lead to various side effects, including IgE-dependent allergy and pharmacological intolerance owing to changes in metabolism of arachidonic acid (AA). Although the incidence of these adverse reactions is not precisely known, pharmacological intolerance appears to be far more common than allergy. The incidence of NSAID intolerance varies depending on the method of evaluation used. It is approx 4% when based on patient interviews, but there are numerous false positives and false negatives. When provocation tests are used, the reported incidence ranges from 10–20% (1).

NSAID intolerance usually occurs in nonatopic subjects over the age of 40 yr. It is more common in females than males (1,2). Symptoms include severe bronchial asthma requiring administration of corticosteroids by the inhaled or oral route and rhinosinusitis with nasal polyposis. There appears to be a higher incidence of HLA-DQ-W2 in NSAID-sensitive subjects than in nonsensitive controls (3).

Intolerance of NSAIDs is characterized by a number of symptoms, namely: severe bronchospasm, rhino-conjunctivitis, urticaria, cervicofacial erythema, angio-edema, digestive disturbances, and hypotension (1,2,4). These symptoms may occur in isolation or in any combination (4). The onset of these manifestations usually occurs from a few minutes to 2–3 h after ingestion of the agent. In sensitive subjects, even small doses of aspirin can lead to severe attacks (1). The manifestations of NSAID intolerance are repeatable during challenge tests with administration by the oral or nasal route or by bronchial inhalation. Subjects with NSAID sensitivity can be desensitized using several techniques that are described in this article.

Until now, the mechanisms of sensitivity to NSAIDs were unclear, but recently some progress has been made. This general review of allergy and intolerance of NSAIDs will deal successively with offending agents, underlying mechanisms, diagnosis, and treatment. Since most studies that have been carried out about the side effects of NSAIDs concern intolerance to acetylsalicylic acid or aspirin, this study is devoted mainly to aspirin intolerance.

Offending Agents

Many nonsteroidal drugs can cause reactions (1,2). The common feature of all these agents is the capacity to inhibit CO. The incidence of side effects for each drug varies depending on the therapeutic class, the dose administered, and the potency of inhibition of CO (5). The great diversity of chemical structures of these agents suggests that the underlying mechanism is nonallergic.

Here are a few examples to illustrate the kinds of agents that can cause intolerance as well as some alternative agents that can be used in intolerant subjects:

1. Salicyclates, diflunisal, carbasalates;
2. Polycyclic acids: indomethacine; sulindac;
3. Derivatives of phenylpropionic acid: naproxene, ibuprofene;
4. Fenamates: mefenamic acid;
5. Glafenine and related products; and
6. Hydrocortisone hemisuccinate: should be avoided in patients intolerant of NSAIDs (6).

Derivatives of salicylates are generally well-tolerated by subjects with asthma (1,2).

Acetaminophen is well-tolerated by most asthmatics intolerant of NSAIDs. However, intolerance occurs in 6% of cases (2). Since intolerance of acetaminophen is dose-dependent (7), it is advisable not to use a dose higher than 1 g in subjects with NSAID intolerance (2).

The mechanism of intolerance of acetaminophen is unknown. Allergic-like reactions have been reported (8). Some additives used in food and drug products (e.g., sodium benzoate, metabisulfites, and sodium glutamate) can cause asthma attacks in patients with NSAID intolerance. These additives are weak inhibitors of CO (9).

Pyrazolated derivatives deserve special mention since they can cause reactions by allergic or nonallergic mechanisms. The main pyrazolated derivatives are noramidopyrine, phenylbutazone, and sulfinpyrazone (2). Allergic reactions can be suspected in patients presenting anaphylactic manifestations. These patients generally do not have asthma or nasal polyposis. Skin tests using solutions containing the drug at increasing concentrations are often positive. Nonallergic reactions present the same manifestations as those caused by NSAID agents (5).

Mechanisms of NSAID Intolerance

Cell membrane phospholipids serve as the substrate for phospholipase A₂, an enzyme involved in the synthesis of AA. AA is metabolized by two pathways, i.e., the CO pathway (which leads to synthesis of prostaglandins [PGs] and thromboxane) and the LO pathway (which leads to synthesis of LTs). LTA₄ is synthesized first and then broken down by various enzymes into LTB₄ or LTC₄. LTC₄ is further cleaved into LTD₄ and LTE₄. LTs are potent spasmogens for nonvascular smooth muscles. LTs also exhibit chemotactic activity for neutrophils and proinflammatory properties. To gain insight into NSAID intolerance, several groups have developed methods to measure precursor mediators (5,10,11).

It was initially thought that inhibition of CO was the main factor in NSAID intolerance (5). This hypothesis was based on the following evidence (2):

1. All analgesics and NSAIDs inhibiting CO lead to asthma in intolerant patients.
2. Analgesics that do not affect CO do not lead to respiratory effects in subjects with NSAID intolerance.
3. The intensity of adverse reactions in NSAID intolerant asthmatics is correlated with the *in vitro* potency of the analgesic in inhibiting CO.
4. Desensitization for one NSAID leads to cross-desensitization for all NSAIDs.

Another explanation that has been proposed for NSAID intolerance is the diversion of AA from the CO pathway to the LO pathway (12). This theory is based on the *in vitro* observation that pretreatment of sensitized human airway with indomethacin enhances generation of LTC₄ after allergic challenge (13). However, the results of this study on sensitized human airway are difficult to extrapolate to NSAID intolerance and do not explain why only a limited number of asthmatics are intolerant to NSAIDs.

More recently, further evidence suggesting that LT plays a key role in determining NSAID intolerance has been obtained. It was shown that ingestion of small doses of aspirin by sensitive subjects led only to moderate nasal and ocular reactions. The fact that the quantity of histamine and LTC₄ in nasal wash fluid increases significantly in these subjects while the quantity of PGE₂ produced remains the same, suggests activation of the LO pathway with no change in the CO pathway (11). Moreover, it has been observed that after desensitization to aspirin, ingestion of high doses leads to a decrease in PGE₂ levels in nasal wash fluids that is not associated with an increase in LTC₄ and histamine. These results confirm another study showing that intranasal instillation of lysin acetyl salicylate leads to enhanced generation of histamine and LTC₄ in sensitive subjects but not in nonintolerant asthmatics (14).

LTE₄, a stable metabolite of LTC₄, is excreted in the urine. Thus, measurement of urinary concentrations provides a marker of systemic generation of LTC₄ (12,15). It has been shown that the mean baseline urinary level of LTE₄ was six times higher in sensitive than nonsensitive asthmatic patients (12,16). Administration of aspirin at a dose inducing a decrease in FEV₁ 15% leads to a four-fold increase in urinary LTE₄ (16). This increase in urinary LTE₄ was not observed after administration of a placebo to aspirin-sensitive patients. These findings, which were confirmed by inhalation tests using lysine acetyl salicylate (17), prove that generation of LT is higher in NSAID-sensitive patients.

NSAID-intolerant patients may also present hypersensitivity of the target organs. It has been shown that bronchial reactivity to LTE₄ was significantly higher in asthmatic patients intolerant of aspirin (on average 20-fold higher than nonsensitive patients). This hypersensitivity decreased significantly after aspirin desensitization. Bronchial reactivity to histamine was comparable in these two subsets of patients (*i.e.*, aspirin-sensitive and nonaspirin-sensitive) and did not change after aspirin desensitization (18).

Based on these observations, it has been proposed that administration of LT receptor antagonists or LO inhibitors might decrease or abolish adverse reactions to NSAIDs. This hypothesis was confirmed by aerosol administration of SK&F 104453, a potent inhibitor of LT receptors, to aspirin-sensitive subjects (19). Similarly, another LT

receptor inhibitor, MK 0679, blocked provocation of bronchospasm with lysine acetyl salicylate (10).

Several authors have supplied further insight into the role of LT in the mechanism of asthma induced by NSAIDs. In a particularly pertinent controlled study, it was shown that Zileuton, an LO inhibitor with no direct effect on bronchial diameter, blocked adverse reactions in a carefully selected group of patients who previously presented nasal, ocular, cutaneous, digestive, and asthmatic manifestations after ingestion of aspirin. The protective effect of Zileuton was not associated with an increase in urinary concentrations of LTE₄. Conversely, in patients that received a placebo, urinary LTE₄ levels increased (20).

More recently, challenge tests with aspirin demonstrated that another LO inhibitor, ZD2138 (21), also provided a prophylaxis in a group of aspirin-intolerant patients. FEV₁ was measured for 6 h following ingestion of aspirin. Inhibition of LO was assessed by measurement of urinary levels of LTE₄ and by in vitro assay of the quantity of LTB₄ produced by leukocytes after stimulation with calcium ionophore agent. ZD 2138 blocked the occurrence of asthma as well as the increase in LTB₄ and LTE₄, whereas the placebo had no prophylactic effect.

The cells responsible for abnormally high productions of LT in NSAID-intolerant asthmatic patients are unknown. Some authors have implicated platelets since platelets from subjects displaying aspirin intolerance have been shown to release cytotoxic mediators and free radicals of oxygen in response to various NSAIDs. This response is not observed in NSAID-tolerant subjects and is blocked by aspirin desensitization (22).

However, conflicting evidence has been reported concerning the participation of platelets in the pathogenesis of aspirin intolerance (12). In patients presenting systemic manifestations after ingestion of aspirin, a drastic increase in plasma histamine levels has been observed. This finding suggests activation of mast cells and basophils (23).

Diagnosis

Accurate diagnosis of NSAID intolerance can only be achieved using provocation tests. The most frequent challenge agent is aspirin. Since these tests can cause severe manifestations, several precautions must be taken. FEV₁ should be monitored and testing should be stopped if the FEV₁ value decreases more than 15% of baseline. Tests should be performed in patients with an initial FEV₁ > 70%.

Oral challenge can be obtained by administering aspirin in increasing doses of 10, 20, 50, 100, 300, and 500 mg at 24-h intervals (1). A more rapid sequence of 10, 20, 30, 60, 120, 300, and 600 mg every 2 h has also been used (24). Provocation can be achieved by inhalation of lysine

acetyl salicylate starting with an initial dose of 1 mL of a solution containing 1.25 mg aspirin/mL. FEV₁ is measured at 15 and 30 min later. Unless there is no significant decrease in FEV₁, the concentration of the solution is doubled up to a maximum concentration of 25 mg/mL (25). Nasal provocation is another alternative (14).

Tolerance to aspirin and other NSAIDs can be induced using several protocols (1,26). These protocols consist in administering increasing daily doses of aspirin from a starting dose of 10–20 mg to 500–600 mg. Tolerance lasts during ingestion of aspirin and disappears 48 h after the end of treatment. Induction of tolerance has a greater effect on nasosinus manifestations than on asthma (26). Recent data indicates that NSAID intolerance could be prevented by administration of drugs that modulate LT metabolism.

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