

NSAIDs intolerance: clinical and diagnostic aspects

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The prevalence of intolerance or idiosyncrasy to aspirin (ASA) and/or non-steroidal anti-inflammatory drugs (NSAIDs) is approximately 10–30% in adult's asthma. NSAIDs intolerance (NI) prevalence in asthma and nasal polyposis or rhinosinusitis is 30–40%. Although diagnosis is usually based on clinical history, asthma induced by ASA has been established using oral challenge tests (OCTs) in 8.8% of chronic asthma without a history of NI. The use of repeated OCTs have also confirmed that NI can disappear after 2 or more years [1].

NI prevalence in chronic urticaria is 20–30%. Aspirin usually impairs the pre-existing urticaria, but does not provoke it during asymptomatic periods. However, a small group of patients without chronic urticaria and who develop urticaria and angioedema after the intake of ASA and/or other NSAIDs also exist [2]. NI appears between the third and fourth decade of life, is more frequent in females, in patients with a respiratory response, and it is infrequent in childhood.

The mechanisms involved in NI are unknown, although it is widely accepted that cyclo-oxygenase inhibition is the central event, based on a great number of negative immunological findings and that different structural NSAIDs share the capacity to induce reactions. The cyclo-oxygenase inhibition would activate the lipo-oxygenase way, increasing leukotrienes (LT) generation which has been proven to be an increment in bronchoconstriction LTs: LTC₄, LTD₄ and LTE₄ [3,4], an increment of the airway response to inhaled LTE₄, an attenuation by LT-antagonists, in asthma induced by ASA, and an abnormality of the altered target organ can contribute to ASA sensibility. The increment of LTC₄ synthesis could be the result of interaction between platelets and leucocytes. All of this suggests that LTs play an important role in NI pathogenesis.

Other mechanisms have been suggested: neurohormonal acetylation, altered response of kinin receptors, tissue enzyme activation, activation of alternative way of the complement, participation of the mast cells in the initial phase, viral infection that facilitates the appearance of cytotoxic T cell clusters [5] and autoimmune disease [6].

Mularkey demonstrated that the prevalence of HLA-DQw2 locus is significantly greater in leucocytes of asthmatic patients sensitized to ASA than in non-sensitized patients [7]. Other authors have not confirmed these results

but have detected a significant decrease in incidence of DPB1 alleles in NI asthmatics and in non-NI asthmatics [8].

NI presents with respiratory symptoms (rhinitis and asthma) that can be severe or with cutaneous symptoms (urticaria and angioedema). Settupane was the first author who described these two clinical patterns. Occasionally both reactions can coincide in the same patient. Respiratory reactions used to be associated with rhino-sinusitis or nasal polyposis and asthma (ASA-triad). Asthma use to be intrinsic and corticoid-dependent and with rare exceptions the aetiology of asthma is allergic. Symptoms can appear between 30 min and 4 h after ingestion, but they usually start after 2 h and could be deadly.

It is thought that these reactions are dose-dependent and with higher bronchial hyperreactivity, there would be a greater probability of reaction. Our group have demonstrated unspecific bronchial hyperreactivity in a cutaneous NI group that has been significantly different from the general population [9,10].

There is no universally accepted protocol for the diagnosis. Neither cutaneous nor *in vitro* tests exist. Ameisen demonstrated that washed platelet supernatant from NI asthmatics showed a different response than that found in non-NI asthmatics and healthy people [11].

Definitive diagnosis is established when a reaction appears after NSAIDs ingestion. The only way to demonstrate or to detect it is usually a control oral challenge test until reaching a therapeutic dose, established by simple blind vs placebo method. Due to risks and severity of reactions, challenges should be performed under controlled conditions and by qualified technicians. Occasionally it is necessary to use double-blind versus placebo methods. Using this method, results are only valid for the population under study at that precise moment [12].

In respiratory clinics, pulmonary function tests have been of value. Usually FEV₁ and/or PEFR were measured. Positive test was considered when FEV₁ decreased a 20% and PEFR a 25% from basal values. Classical response is asthma and rhinoconjunctivitis (80%), although it is possible the appearance of only asthma or only rhinoconjunctivitis [13].

ASA tolerance can appear during the refractive period (2–5 days) that occurs after an ASA adverse reaction or after ASA desensitization.

The degree of crossreactivity between different NSAIDs is equivalent to the drug dose necessary for *in vitro* inhibition of

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the cyclo-oxygenase. The capacity to react would be related to the inhibition potential. However, clinical practice does not always confirm this hypothesis and the tolerance to every NSAID is conditioned by individual sensibility. It appears that there is no cross reactivity at the normal doses of dextropropoxiphen, paracetamol, sodium and coline salicylates, salsalate, salicylic acid, salicylamide, coline magnesium trisalicylate and codeine. With higher doses symptoms can be induced. All dextropropoxiphen studies have been negative. Two patients had asthma with doses of 2 g of salsalate [14] and reactions have been observed with doses above 1 g of paracetamol [15,16]. Good tolerance to pyroxicam has been described but only in patients with cutaneous symptoms [17].

In an alternative diagnosis test, bronchial challenge test (BCT) lysine acetylsalicylate (LAS), is being more frequently used because of its shorter technique, its lesser risk and the better bronchospasm control than in OCT. Bronchial responses are less and better controlled. Some authors have observed immediate, long and dual bronchial responses [18–20].

Nasal challenge test (NCT) controlled by rhinomanometry is also used with good results. ASL concentrations are 20 times lower than in bronchial challenges and 1000 times lower than in oral challenges. Responses were not associated with systemic or bronchial reactions [21].

We believe that LAS-BCT method is of great utility to diagnose asthma caused by NSAIDs and could substitute OCT to become the 'gold standard' method. More studies will be necessary to further evaluate its sensibility, specificity and profitability.

Cutaneous responses after NSAIDs ingestion used to exacerbate chronic urticaria or just to appear like an urticaria without any other disease associated. ASA OCTs are normally used in simple blind versus placebo control and occasionally in a double-blind method. For chronic urticaria it was performed using the nine rules.

ASA can provoke urticaria through an immunological mechanism. ASA anhydrase, a commercial ASA contaminant has been associated to IgE responses. Aspirin polylysin cutaneous tests have been negative in most of the cases, although in some of them specific IgE to ASA has been detected [22].

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