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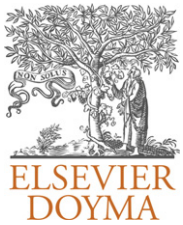

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ORIGINAL ARTICLE

The values of nasal provocation test and basophil activation test in the different patterns of ASA/NSAID hypersensitivity

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KEYWORDS
Nasal provocation test;
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Summary
Background: The oral provocation test (OPT) is the current gold standard to diagnose aspirin hypersensitivity syndrome although it is time-consuming and contains some systemic risks. Other reliable methods with lower side effects and shorter test duration are being investigated.
Objective: The purpose of this study was to evaluate the efficacy of the nasal provocation test (NPT) and the basophil activation test (BAT) in the diagnosis of different subtypes of aspirin sensitivity.
Methods: Thirty aspirin sensitivity patients with cutaneous and respiratory manifestations underwent NPT and BAT with lysine-ASA. NPT result was interpreted as recommended in EAACI/GA2LEN guidelines and receiver operating characteristic analysis of BAT was performed by using 15 NSAIDs tolerant volunteers as a control group.
Results: NPT was positive in 60% (18/30) of patients and BAT was positive in 76.7% (23/30) of patients. The incubation of basophils with 0.31 mg/ml of lysine-aspirin and using 4.6% activated basophils gives the best predictive values to diagnose aspirin sensitivity. The combination of both tests yielded positive results in 80% and 93.3% of aspirin-induced cutaneous and respiratory patterns. The agreement between NPT and BAT results was 63.3%.
Conclusions: NPT and BAT are beneficial to detect patients with aspirin sensitivity. The combination of both tests have additional diagnostic values; less time-consuming than OPT and their complications are negligible. A reliable alternative method with minimum side effects is needed to diagnose aspirin sensitivity in suspected patients who have contraindications for OPT.

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Introduction

The immediate reaction to aspirin (ASA) and other non-steroidal anti-inflammatory drugs (NSAIDs) is one of the common problems in allergy practice.[1,2] Clinical manifestations vary from cutaneous symptoms such as urticaria or angio-oedema to respiratory symptoms such as naso-ocular oedema or asthmatic attacks, or in rare cases a mixed type or systemic reaction.[3] Although clinical onset reactions generally occur within minutes to a few hours after drug exposure mimicking type I hypersensitivity, specific IgE to the responsible drug is rarely discovered, suggesting that the mechanism is most likely non Ig-E mediated. Current data indicates that the imbalance of arachidonic acid metabolism may play a role in this syndrome leading to erratic mast cell degranulation in patients exposed to the drug.[4] Several NSAIDs with non-selective cyclooxygenase inhibitor properties exacerbate the derangement of leukotriene pathways and aggravate clinical symptoms in susceptible patients.[5]

The diagnosis of this syndrome largely depends on a patient's clinical history since skin testing and specific IgE measurements are not helpful. Unfortunately, using a patient's clinical history has several limitations and is often unreliable. Currently, the oral provocation test (OPT) with aspirin is the diagnostic gold standard test.[6] This procedure is very time-consuming as it requires at least two days and places patients at risk of systemic reactions from oral aspirin challenge. As a consequence, OPT is not routinely performed in clinical practice. An alternative method to confirm the diagnosis of ASA/NSAIDs hypersensitivity is required to avoid this time-consuming process and to minimise patient risk while still preserving the accuracy of the test.

The bronchial provocation test (BPT) and the nasal provocation test (NPT) have been introduced in the last decade as alternative procedures to diagnose ASA/NSAID hypersensitivity syndrome.[7,8] However, the studies of bronchial and nasal challenge tests with lysine-aspirin (L-ASA) were mainly performed on patients with aspirin-induced respiratory reaction, not in patients with aspirin-induced cutaneous reaction.[9] In contrast to North American studies, reports of aspirin hypersensitivity in southern Europeans and Asians suggest that clinical manifestations of aspirin-induced cutaneous reaction and blended type are not uncommon.[10–13] The role of bronchial and nasal provocation tests with L-ASA to diagnose aspirin-induced cutaneous reaction is still unclear. To date, only a few papers report the applicability of nasal provocation test in the diagnosis of aspirin-induced urticaria.[14]

Basophil activation test (BAT) has been introduced in the evaluation of immediate hypersensitivity reaction to drugs.[15] CD63 and CD203c are markers of activated basophils representing basophil activation and degranulation.[16] Both basophils and mast cells share common characteristics in mediator release by IgE and non-IgE dependent pathways upon allergen exposure. Therefore, BAT is potentially helpful to diagnose this syndrome since drug-specific IgE is not necessary for the test.[17] Basophil activation tests have been studied in patients with ASA/NSAID hypersensitivity; however, the value of BAT in this syndrome has yet to be concluded as the reported sensitivities varied from 16% to 70%.[18–21] Some researchers reported that basophil responses to in vitro aspirin challenge had low predictive values to identify aspirin sensitivity.[22]

NPT is recommended in aspirin-induced respiratory reactions but only few studies mentioned its role in aspirin-induced cutaneous reactions. The magnitude of basophil activation response and the applicability of BAT to diagnose aspirin sensitivity are currently under hot debate again. The value of each test in different manifestations of aspirin sensitivity has not much been emphasized. The purpose of this study was to evaluate the diagnostic value of NPT and BAT in different manifestations of aspirin sensitivity, the relationship between NPT and BAT results, and the possibility of combining both tests in the diagnosis of ASA/NSAID hypersensitivity in clinical settings where the standard OPT is not available or in patients with suspected aspirin sensitivity who have contraindications for OPT.

Materials and methods

Thirty patients (aged 15–70 years) with a clear cut history of immediate hypersensitivity reactions to ASA/NSAIDs (probability drug allergy category A, $P > 0.9$, according to Nyfeler, B. and Pichler, WJ.) were recruited into this study and underwent nasal provocation testing (NPT) with lysine-aspirin (L-ASA).[23] All patients experienced at least two episodes of immediate hypersensitivity reactions from aspirin or NSAIDs, or had several reactions from different NSAID types, and/or had a positive oral provocation response with aspirin. Fifteen patients developed acute urticaria and/or angio-oedema and 15 patients developed naso-ocular symptoms and/or acute asthmatic attack after ASA or NSAID consumption. Prior to the performance of the nasal provocation test, subjects were asked to stop nasal and oral sympathomimetic drugs for 24 h, short-acting antihistamines for three days, leukotriene modifiers, nasal and systemic corticosteroids for one week. Subjects who had factors interfering with the nasal provocation test such as a massive nasal polyp, nasal septal perforation, or total nasal obstruction of at least one nostril were not included in the study. Patients who were pregnant, had an exacerbation of allergic rhinitis/asthma, had an upper respiratory tract infection within two weeks prior to the test, had nose surgery within eight weeks prior to the test, or had severe systemic disease(s) were also excluded from the study. Fifteen healthy individuals with no history of ASA/NSAID hypersensitivity were enrolled as normal controls.

The single-blind placebo controlled nasal provocation test (NPT) with L-ASA was performed and interpreted according to EAACI/GA2LEN guidelines.[24] After non-specific nasal hyper-reactivity had been excluded by nasal instillation of 0.9% NaCl, 30 min later L-ASA (Aspegic, Sanofi-Aventis, France) 80 μl was instilled into each nostril using an Eppendorf pipette (the total dose equivalent to 16 mg of aspirin). Nasal symptoms were recorded based on thirteen-point symptom score method and the total nasal volume