DRUG ALLERGY TRACK – Practical Approaches to Aspirin and NSAID Hypersensitivity, 6th Dec 2012, 09:00AM – 10:30AM, HICC, G.03

DIAGNOSTIC TESTING

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The first step in the evaluation of a patient with possible aspirin/NSAID hypersensitivity is to classify the reaction based on the onset (acute or delayed), spectrum of symptoms, reaction to single or multiple NSAIDs and presence or absence of underlying chronic disease. Appropriate diagnostic testing, if deemed necessary, is then carried out.

A thorough history should include the following: the timing of reaction in relation to drug intake, the symptoms, the number of episodes and timing of the last episode, whether there is history of reaction to more than one NSAID or tolerance to other NSAIDs (not forgetting paracetamol, a weak COX-1 inhibitor), presence of underlying asthma, rhinosinusitis, nasal polyps, chronic urticaria, and atopy. Remember to rule out association of the adverse reaction with food intake.

A diagnosis of NSAID-induced rhinitis/asthma (Aspirin-Exacerbated Respiratory Disease or AERD) is often based on the history of exacerbation of symptoms in a typical adult patient with asthma and/or chronic eosinophilic rhinosinusitis complicated by recurrent nasal polyps. However, studies have shown that AERD could be both under- or over- diagnosed when relying exclusively on such a history. In patients without a clear history, provocation tests are necessary to confirm or exclude hypersensitivity. Both European and American guidelines on aspirin provocation tests have been published and these protocols could be obtained from the relevant literature. (Allergy 2011;66:818-29, Allergy 2007;62:1111-8, Ann Allergy Asthma Immunol 2007;98:172-4). Aspirin provocation tests may be via oral, inhalational or nasal route. Oral aspirin challenge is considered to be the ‘gold standard’ for confirmation of hypersensitivity. Contraindications for oral challenge and general considerations when carrying out the procedure are found in these guidelines. In general, all challenges should be carried out under the direct supervision of a physician and technicians skilled in performing provocation tests with aspirin. Emergency resuscitation equipment should be readily available and the patient should have an intravenous line attached. Three in vitro testing methods have been proposed: sulfidoleukotrienes release assay, basophil activation test and 15-HETE generation assay (ASPITest - Aspirin Sensitive Patient Identification Test). As their sensitivity and specificity are not tested on large enough number of patients and results are inconsistent, none can currently be recommended for routine diagnosis of AERD.

In aspirin/NSAIDs exacerbated urticaria/angioedema, oral provocation test is also the ‘gold standard’ for diagnosis. The oral aspirin challenge procedure is similar

to that for the diagnosis of AERD. Challenge protocols for NSAIDs other than aspirin can be found in Messaad D et al. (Ann Intern Med 2004) and other recent literature. As in the case of AERD, skin testing is of no relevance in view of the pathogenic mechanism and at present, no in vitro test has been approved for routine diagnosis.

The diagnosis of multiple NSAIDs-induced urticaria/angioedema is based on a history of reactions to more than one NSAID in an otherwise healthy person. There is no necessity for further diagnostic testing if history is convincing. The indications for provocation tests and its diagnostic value in these patients have not been established. Skin testing is unnecessary if a history of cross-reactivity is convincing. The diagnostic value of in vitro test is presently not known.

Patients with acute single NSAID-induced reactions experience generalized urticaria and/or angioedema within minutes after administration of the culprit drug. The reaction may progress to anaphylactic shock and death. A higher prevalence of atopic background has been reported. Oral provocation with the culprit drug is controversial and risk-benefits must be carefully considered. It should only be considered if skin testing (both prick and intradermal) is negative. On the other hand, oral challenge with aspirin and a structurally different NSAID should be performed to exclude cross-reactive type of hypersensitivity and to confirm the safety of alternative drugs. As these are IgE mediated reactions, skin testing should theoretically be useful. In practice however, standards for skin testing have not been universally accepted. There is significant variability in specificity and sensitivity reported for different NSAIDs. Commercially available immunoassays for specific IgE seem to be less useful than skin testing. The assessment of noraminophenazone-induced CD63 expression on basophils (BAT) has been shown to be sensitive to detect hypersensitivity to pyrazolones.

There is a variety of delayed reactions to NSAIDs. Diagnostic approach is dependent on the type of reaction. Patch testing and delayed reading intradermal test (ID reading at 24hr and 48hrs) with the culprit drug is simple and generally safe but not well standardized and sensitivity and specificity for a particular reaction remain unknown. When photoallergy is suspected, photopatch testing can be carried out. Just as for delayed reactions to other drugs, skin biopsy and histopathologic assessment may be useful in coming to a diagnosis of drug allergy in some cases. Lymphocyte transformation test(LTT) may be used but validation for most NSAIDs is lacking. NSAID re-challenge is contraindicated in patients with severe generalized reactions e.g. toxic epidermal necrolysis.

In summary, the diagnostic approach to aspirin/NSAID hypersensitivity is dependent on the suspected mechanism of the reaction in the individual. Diagnosis should be confirmed by a challenge with a culprit drug if appropriate and similarly the safety of the alternative drug should be confirmed by oral challenge. Skin tests (prick and intradermal) and in vitro testing should be restricted to suspected IgE-mediated reactions. Patch test, delayed reading ID

and LTT may have a role in the various delayed adverse reactions. Further studies on the value of these diagnostic tests have to be carried out before they become routine procedures.

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Suggested reading list:

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16. Szczeklik A, Nizankowska E, Duplaga M, AIANE Investigators. Natural history of aspirin-induced asthma. Eur Respir J 2000; 16: 432–6
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18. Gomez E, Blanca-Lopez N, Torres MJ, Requena G, et al. Immunoglobulin E-mediated immediate allergic reactions to dipyrone: value of basophil activation test in the identification of patients. Clin Exp Allergy 2009; 39: 1217-24
19. Barbaud A. Skin testing in delayed reactions to drugs. Immunol Allergy Clin N Am 2009; 29: 517-35