

Diagnostic approach in patients with hypersensitivity reactions to drugs

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Adverse reactions to drugs constitute a common cause for consultation in general practice as well as in allergology clinics. They are present in 10 to 15% of hospitalized patients and account for 3 to 6% of all hospital admissions. One third of such reactions are mediated by immunological mechanisms. In hospitalized individuals the incidence of allergic reactions has been estimated in 2.2 per 100 patients and 3 per 1000 courses of drug therapy, while severe reactions are less frequently observed (for example, Stevens Johnson syndrome [SJS] occurs in 0.4 to 1.2 per million people per year, and toxic epidermal necrolysis [TEN] in 1.2 to 6 per million people per year).

Since the clinical picture is highly polymorphic and patient's interrogation may be difficult, the diagnosis of drug allergy is a challenge to the clinician, and generally is based in a detailed clinical history, including information on symptoms, temporal relationship with drug exposure, previous risk factors, ruling out of other potential etiologies of the clinical picture, and laboratory investigations (hematology, liver function tests, urinalysis, serum chemistry, etcetera).

The probable pathomechanism, either allergic or non allergic, should be taken into consideration when further diagnostic tests are chosen¹. For example, if an IgE-mediated reaction is suspected, immediate-type skin prick or intradermal tests or *in vitro* drug-specific serum IgE measurements are useful. For drug-induced hemolytic anemia Coomb's test is applicable, whereas for T cell-mediated hypersensitivity lymphocyte transformation test and patch tests are suitable^{2,3}. Serum levels of tryptase and urinary methyl-histamine can be measured for confirmation of anaphylaxis.

Flow cytometric basophil activation test, based on the evaluation of CD63 activation marker on basophils by flow cytometry, and cellular allergen stimulation test (CAST-ELISA), that measures cysteinyl-leukotriene release from drug-stimulated blood leukocytes, are also being used in Europe for the evaluation of immediate reactions to certain drugs such as non steroidal anti-inflammatory drugs (NSAIDs) and beta lactam antibiotics^{4,5}.

Since many of the above mentioned tests are not widely available, have low sensitivity or specificity, or are not completely standardized, drug provocation tests are commonly employed by allergology specialists, although in patients with severe, potentially lethal reactions such as anaphylaxis, drug hypersensitivity syndrome, SJS, and TEN they are contraindicated. They are to be performed under strict medical supervision, in the hospital, by experienced allergists, and with emergency equipment and medications to treat reactions if they occur during the test.

In this issue of *Revista Brasileira de Alergia e Imunopatologia* Aun et al. report their experience with single-blind placebo-controlled drug provocation tests performed in patients with a history of adverse drug reactions. They observed a higher prevalence of reactions in female patients, with a mean age 39.9 years, and overall 4.1% of challenges were positive to various drugs including antibiotics, selective NSAIDs, paracetamol and local anesthetics. Since only two patients developed anaphylaxis as the only severe reaction observed during 243 challenges, they concluded that drug provocation tests are safe. It has to be mentioned that in this study most patients were challenged with alternative drugs more likely to be tolerated, and not with the primary offending medication⁶.

Drug provocation tests are indicated for various reasons:

1. Exclusion of hypersensitivity when patient and/or physician erroneously label the clinical picture as drug-related.
2. Exclusion of cross-reactions with other drugs.
3. Confirmation of the diagnosis in cases where other tests are not contributory or not available.
4. Identification of alternative treatments⁷⁻¹⁰.

Up to now adverse reactions to drugs, in spite of being commonly observed, have been largely neglected in the Latin American medical literature. One reason for this is that there is little interest from the pharmaceutical industry to sponsor studies on drug hypersensitivity, and other sources of funding are lacking.

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However, I would like to mention two recent initiatives that may help to encourage research in this area in Latin America. The first one was the publication of a Drug Allergy Handbook ("Manual de Alergia a Medicamentos"), written in Spanish, and presented during the World Allergy Congress in Buenos Aires in December 2009. This handbook, sponsored by the Latin American Society of Allergy, Asthma and Immunology and the Argentinian Association of Allergy and Clinical Immunology, was the result of the work of a number of Latin American allergists under the coordination of Professor Edgardo Jares⁹. Presently, this book is being disseminated all over Latin America, and in our view it constitutes a comprehensive recompilation of the information available on drug reactions, useful in the hospital or medical office for the management of these frequent conditions.

The second one is the establishment of allergy services specifically interested in adverse reactions to drugs such as the one functioning at the Hospital das Clínicas, Medical Faculty of São Paulo University. This group of young allergists and investigators recently held in Sao Paulo the First Allergy School on Drug Hypersensitivity, a successful educational activity supported by the Brazilian Association of Allergy and Immunopathology. This course, directed to young allergists from all over Brazil, covered all the clinical, diagnostic, and therapeutic areas of reactions to major drug groups with a theoretical and practical approach. These efforts open a clear opportunity for the development of centers devoted to the research and management of drug allergy in this country, and I can envision that, thanks to this initiative, during the next few years health care of people suffering drug reactions will be significantly improved and research productivity on this subject will be greatly enhanced. We hope that this can be replicated in other Latin American countries for the sake of a better allergologic practice in this subcontinent. Then, by recognizing these developments, I want to congratulate our Brazilian colleagues by this important contribution to the progress of our specialty.

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