



Advances in drug hypersensitivity reactions

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The study of drug hypersensitivity reactions continues to evolve, in this issue we wish to concentrate on the evaluation and subsequent assessment of patients suffering a potential drug reaction. Drug reactions can be divided into two major groups: those where a specific immunological mechanism is involved (allergic reactions); and those where vasoactive and other inflammatory mediators are released without the participation of a specific immunological mechanism (nonallergic hypersensitivity) [1]. Often it is not possible, based on clinical observations, to differentiate them. Drug hypersensitivity reactions are becoming increasingly complex with more drug classes becoming commonly implicated, such as NSAIDs and quinolones. Traditionally, most antibiotic allergy was directed against β -lactam antibiotics; however, with more widespread use of second-line antibiotics, increasing reactions are seen to them [2].

A major problem in drug allergy is that the classical approach to assess a potentially allergic patient with skin testing and in-vitro studies is not sensitive or specific [3,4]. The aim of the diagnostic tests is to prove that the reaction is either IgE-mediated (immediate) or T-cell mediated (nonimmediate). Attitudes have shifted in expert opinion regarding how to optimally assess patients with a greater emphasis on drug provocation testing (DPT) in low-risk patients rather than skin testing or in-vitro studies. As with most in medicine, the situation is never clearly black or white and careful assessment and risk stratification is needed if proceeding straight to a provocation test.

DPT has become a widely used procedure in those centers involved in the diagnosis and management of drug hypersensitivity reactions. In the work of Savic and Garvey [5], guidelines are provided for the stratification of individuals in DPT. The use of DPT has contributed significantly to delabeling patients with antibiotic allergy with an important reduction in the costs and risks induced by alternative antibiotics [6,7]. The procedure is often the only option for establishing a firm diagnosis; however, it is very important for it to be performed in the safest possible way. Beginning with clinical history, it is essential to confirm that the symptoms and signs were consistent with a drug reaction. If DPT is being scheduled, risk stratification is required in each case

based on the timing of the reactions, the clinical symptoms induced, the drug involved and any other cofactors. In addition, other factors, such as ischemic heart disease and asthma, may contribute to the risk involved. For example, in asthma and NSAID exacerbated respiratory disease, the cysteinyl leukotriene receptor type 2 is involved in the amplification of the response to eosinophils and the development of tissue inflammation in the airways [8,9]. This can be extended to the rest of receptors involved in the response to NSAIDs [10]. The second important application for DPT is for assessing cross-reactivity, such as with β -lactam antibiotics. The assessment of cross reactivity in allergic individuals cannot accurately be made by in-vitro test. For example, in the case of immediate hypersensitivity reactions to penicillin, there may be some cross reactivity between the specific IgE to penicillin and to aztreonam *in-vitro*. However, it has been proven that aztreonam can administered safely to individuals with IgE reactions to penicillin [11]. Studies with monoclonal antibodies have shown that the side chain of beta-lactam antibiotics contributes in an important way to the formation of the antigenic determinant, these findings need to be considered in in-vivo or in-vitro testing [12,13].

Hypersensitivity reactions to NSAIDs are an important cause of drug hypersensitivity reactions as stated in the review of Lee *et al.* [14]. The immunological mechanisms include both allergic and nonallergic hypersensitivity [15]. Several phenotypes have been now identified that include responses to several NSAIDs with good tolerance to acetyl salicylic acid [16]. Although the best studied model in NSAIDs hypersensitivity is the respiratory tract [17], the skin is the most frequent organ involved [15]. A good number of cases have skin and airways involvement and we proposed to use the term anaphylaxis for these [18]. DPT is essential in

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the diagnosis of NSAID hypersensitivity and, particularly in cases with skin involvement, it is a safe procedure [19,20]. It seems that more phenotypes will emerge in the future.

Gomez [21] provides an update regarding T cell-mediated drug allergy. The role of T cells in non-immediate reactions is varied and while most are mild nonimmediate reactions, a range of severe reactions is also seen. Four major subtypes have been recognized [22], with a further added recently consisting of accelerated reactions to amoxicillin where it has been shown that T cells are involved [23]. What causes activated T cells in different individuals to display such heterogeneous reactions is not fully understood. Certainly in the severe drug reactions, such as Stevens–Johnson syndrome/toxic epidermal necrolysis, there are higher risk culprit drugs as well as strong associations with certain human leukocyte antigen (HLA) alleles [24]. In addition to the parent drug, the metabolites can also lead to sensitization and the induction of a reaction [21]. It is essential to understand the chemical structures fully to gain insight into mechanisms and also cross reactivity with other drugs [21,25].

An important aspect is the monitoring of the immunological response during the acute phase of the reaction by the analysis of gene expression [26]. It is known that individuals with allergic reactions have signs in the peripheral blood and tissue that can provide diagnostic information. This has been done in individuals with atopic dermatitis [27], as well as in drug reactions [28,29]. In one study, 92 genes with distinct expression patterns of both severe and benign disease were present during the acute phase [30]. In patients with severe bullous diseases, a characteristic gene expression pattern with lower expression of genes encoding T cell-specific proteins and high expression of cell cycle-related genes and genes coding for inflammatory-related mediators, including damage-associated molecular patterns and alarmins, are seen. In these patients with severe cutaneous adverse reactions (SCARs), it is essential to establish an accurate diagnosis, so appropriate management can be started. Arderon-Jones and Mockenhaupt [31] describe how to recognize SCAR as well as reviewing the latest evidence regarding management and investigations. The timeline from drug initiation to the development of the SCAR can be up to 8 weeks and initially there can be signs that are confused with milder T cell-mediated reactions [32]. Although the priority remains to stop the culprit drug [33], the further management regarding the type of immunosuppressive treatment remains controversial [31]. In SCAR, once the culprit drug is identified, it should be avoided for life, often this

is based on the clinical history and patch testing as DPT is contraindicated [34]. Other noninvasive and safe tests to improve diagnostic accuracy include evaluating HLA risk alleles and performing in-vitro assays, such as the lymphocyte transformation test and drug-induced cytokine assays [31,35].

In patients with HIV, the picture is complicated further because of added complexities of comorbidities and polypharmacy. Peter *et al.* [36] review the latest evidence and best practice in patients with HIV. The most frequent culprit drugs for drug reactions include antiretroviral therapy and anti-infective agents. The risk of a hypersensitivity reaction is up to 100 times higher in patients with HIV [37]. The reasons for this are multifactorial and include immune dysregulation, increased danger signals from HIV-infected cells and depletion of immunoregulatory cells [36,38]. Challenges in these patients include systemic reactions to patch testing as well as the need to attempt a slow reintroduction or desensitization to the culprit drug in some patients because of clinical necessity [39].

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