

Adverse drug reactions with an immunological basis: from clinical practice to basic research

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Allergic drug reactions with an immunological basis (ADRI) are an important problem affecting many people. However, despite all the clinical and basic research carried out, ADRI have not been sufficiently evaluated (1). The magnitude of the problem, in terms of the number of people affected, is not known, because there is a lack of adequate pharmacoepidemiological studies (2–4). A large number of people have been labelled as allergic to different drugs on the basis of the mere description of a temporal association between drug intake and different symptoms compatible with an allergic or pseudoallergic/idiopathic reaction (1, 5). These reactions are often induced by diverse drugs, such as nonsteroidal anti-inflammatory drugs (NSAID), opioids, contrast media and muscle relaxants (1, 6). This implies that very often patients diagnosed with drug allergy, pseudoallergy or falsely labelled drug allergy are not given adequate treatment, and serious consequences may arise. Furthermore, expensive or even restricted drugs are often used.

ADRI can be classified as immediate, accelerated or delayed, according to the time interval between intake of the drug and occurrence of the reaction (7, 8). Although this classification was set up by Levine on the basis of his experience with penicillin allergy (7), different studies reported in the medical literature, as well as clinical practice, show that this classification can be applied to the whole world of drug allergy (8, 9).

From the clinical standpoint, immediate (IR) and nonimmediate reactions (NIR) differ in the time interval between drug intake and appearance of clinical manifestations. In IR they appear within 1 h, and often within just a few minutes, after drug intake and the main clinical manifestations are urticaria/angioedema and/or anaphylaxis (1, 8). NIR appear hours, days, or even weeks after drug intake, and elicit a spectrum of manifestations ranging from mild urticaria or exanthema to severe toxic epidermal necrolysis (8, 10). A number of organ-specific diseases can also be considered as ADRI, and often appear within the context of a systemic reaction (10–12).

The diagnostic approaches for evaluating IR and NIR are different. In IR, mostly reactions to penicillin, IgE antibodies can be revealed by skin testing and also by the *in vitro* assay of specific IgE antibodies (13, 14). In NIR, only intradermal or patch tests are widely accepted (15–17); the value of other methods will be discussed below. However, apart from IgE mediated reactions to betalactams (18), for both IR and NIR, the *in vivo* and *in vitro* diagnostic methods are of limited value and very often the clinical evaluation is the most important, or sometimes the only, approach for establishing whether the patient is allergic to the drug or not (1, 6). This implies that we need to rely upon a detailed clinical history, often in association with a controlled administration of the drug, to assess

tolerance. Sometimes nontherapeutic concentrations are given to elicit minimum symptoms in order to establish a causal relationship between the suspect drug and the manifestation.

In this review we will discuss the role of the clinical evaluation of the patient in conjunction with skin tests and classical *in vitro* assays, such as IgE antibody determination. We will show that this is not only valid for completing the diagnosis, but also for generating inferences which provide valuable information in basic research in drug allergy and immunology (9).

Although already reported, it is relevant to state that most of the initial evidence for proving the existence of side chain specific IgE antibodies to betalactams comes from clinical observations (19, 20). Our first observation of this was the case of a woman who, after having developed an anaphylactic reaction to amoxicillin, subsequently had good tolerance of benzylpenicillin (19). A detailed investigation of this case and, later on, of a group of patients with similar characteristics, showed that these subjects had IgE antibodies that mainly recognized the side chain of amoxicillin (18–20). As a result of these findings, we investigated further, and preliminary studies led us to discover selective reactions to other betalactams, including cephalosporins (9, 21). These findings have now been supported by different groups for both IR (18, 22–25) and NIR to betalactams (16, 17, 26, 27). In NIR to penicillin, where T cells have been shown to be involved (28, 29), our experience in both urticaria and exanthematic reactions to aminopenicillins indicates that selective responses to these compounds exist, and that their frequency is higher than that reported for IgE-mediated reactions (16). Although lymphocyte proliferation studies used for evaluating NIR are useful for predicting sensitivity and specificity (28, 29), we have not been able to fully confirm such findings (30).

The clinical classification of allergy to penicillins and other drugs based on the time interval between intake and occurrence of the reaction and on the pattern of clinical symptoms has enabled allergists and other specialists involved in this field to establish the diagnosis and to indicate the immunopathological mechanisms that may be involved (31). A number of reports, as well as studies in progress, indicate that the profile of cytokine production is in agreement with the clinical classification (31–33). In brief, we can say that subjects with IR show a Th2 cytokine profile and subjects with NIR show a Th1 pattern in peripheral blood during the course of the allergic reaction that normalizes once the clinical episode has resolved (31). In this sense, the clinical classification seems to be adequate for validation of the tests and for further analysis (9). Follow-up with skin tests shows that the natural evolution of their sensitivity depends on the specificity of the IgE antibody that induced the reaction

(34). Furthermore, loss of tolerance and resensitization also depend on the specificity of the IgE antibody (34–36).

Controlled administration for assessing tolerance, plus skin testing for cephalosporins, has enabled us to establish four groups of patients allergic to these compounds, depending on the skin test reactivity to different penicillin and cephalosporin derivatives (21, 37). These data can help immunochemists identify the cephalosporin determinants that can be recognized by specific IgE antibodies.

A number of studies have shown that the pattern of clinical reactivity (20, 24, 38, 39), as well as the immediate allergic response to betalactams, varies from country to country, reflecting the different consumption of betalactams (4, 21, 38). This indicates that pharmacoepidemiological and detailed clinical studies are required in each country in order to provide an adequate evaluation of allergy to betalactams (18).

After a clinical diagnosis of immediate allergy to betalactams, comparison of skin tests, radio-allergosorbent tests (RAST), and lymphocyte transformation tests (LTT) suggests that skin testing is the most adequate approach and the one that provides the most diagnostic information. In recent studies by our group, skin test sensitivity in IR was 77%, while RAST was 70% and LTT 61% (30, 40). For NIR, controlled administration of the drug seems to be the most sensitive approach, since skin test sensitivity is below 50% (16). Although the LTT had a higher sensitivity, the great variability in its reproducibility and its lack of specificity in cases of selective responses to penicillins show that this test cannot be used for diagnostic purposes (30). Thus, *in vitro* tests need to be improved to at least match the sensitivity of skin tests in evaluating subjects with betalactam allergy.

In patients allergic to penicillins, the evaluation of cross-reactivity with related compounds is complex (41), and depends on whether the reaction is an IR or a NIR. To study cross-reactivity in IR, there are two main approaches: to quantify specific IgE antibodies to different compounds by RAST inhibition and to carry out a histamine release assay (42–45). When we compare these assays with controlled administration of the drug, the results indicate that controlled administration is the only valid approach for establishing tolerance or cross-reactivity (46). In fact, controlled administration is often the final step for a definitive diagnosis in subjects with adverse reactions to penicillins, because of the nonoptimal sensitivity of *in vitro* and *in vivo* tests, in both IR and NIR (16, 20, 47).

In addition to ADRIB, there are a number of other adverse reactions where the release of inflammatory mediators occurs (48, 49). Often allergists have to evaluate patients with urticaria, angioedema, anaphylaxis or bronchospasms related to different compounds (18, 50). Although most studies have been carried out on asthma (50–52), NSAIDs induce a wide range of

manifestations, including urticaria, angioedema, Stevens–Johnson syndrome, Lyell syndrome, fixed drug eruption and organ specific reactions. In our experience, urticaria and anaphylactic reactions to these compounds are the most common manifestations (48). In these reactions, two main groups have been identified: those with cross-reactivity between two or more compounds, and those with a selective response to a specific analgesic or anti-inflammatory drug. It is estimated that from 40% to 60% of subjects with urticaria or anaphylactic reactions develop selective

reactions to a single drug, with good tolerance of the others (48). Although IgE involvement has been proposed in these reactions (53), further research is required to establish the underlying mechanisms.

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