



Anaphylactic reactions—value of skin and provocation tests

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Abstract

Drug hypersensitivity reactions are a daily worry for the clinicians, in particular anaphylactic reactions. The tools allowing a definite diagnosis are few and poorly validated. They include a thorough clinical history, standardized skin tests, reliable biological tests, and sometimes drug provocation tests. These tools are currently being evaluated by the European Network of Drug Allergy, under the aegis of the EAACI drug hypersensitivity group of interest.

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1. Introduction

Drug hypersensitivity reactions may affect up to 5% of hospitalised patients and can be life threatening (Demoly and Bousquet, 2001). A variety of reaction types have been described (Demoly and Bousquet, 2001; Johansson et al., 2001; Gruchalla, 2000). These include: (i) non-immunological reactions, (ii) IgE-mediated allergic reactions in the form of immediate anaphylactic shock, generalised urticaria, angioedema and/or bronchospasm, (iii) non-immediate allergic reactions (which may occur several days after the last drug has been administered) such as urticaria, maculopapular eruptions, fixed drug eruptions, vasculitis, toxic epidermal necrolysis, Stevens-Johnson syndrome or drug reaction with eosinophilia and

systemic symptoms. Reactions occurring within a few hours following the last administration of the drug may be due to IgE-dependent or non-immunological mechanisms. The former could be lethal. The latter occur in only a small percentage of patients and in general cannot be predicted. The etiologies of these reactions include non-specific histamine release (e.g. opiates, radiocontrast media and vancomycin), bradykinin accumulation (angiotensin-converting enzyme inhibitors), complement activation (radiocontrast media and protamine), induction of leukotriene synthesis (non-steroidal anti-inflammatory drugs) and bronchospasm (e.g. S₀₂ released by drug preparations containing sulphites). Moreover, some reactions such as urticaria could even be not related to the drug itself, but to the underlying (e.g. infectious) disease.

Therefore, a complete drug allergy work up is required, which includes a detailed clinical history and

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physical examination, followed by one or more of the following procedures: skin tests, laboratory tests and ultimately, drug provocation tests (Gruchalla, 2000; Demoly et al., 1999; Demoly and Bousquet, 2002; Brockow et al., 2002; Aberer et al., 2003; Messaad et al., 2004). Under the aegis of the European Academy of Allergy and Clinical Immunology, the European Network on Drug Allergy (ENDA) has been working for the establishment of clinical tools for the daily practice (Demoly et al., 1999; Brockow et al., 2002; Aberer et al., 2003; Torres et al., 2003).

2. Clinical history

Clinical history should be extremely thorough and address the symptomatology (compatible with an allergy?), the chronology of the symptoms (previous exposure, delay between the last dose and the onset of symptoms, effect of stopping treatment), other medication taken (both at the time of the reaction and other drugs of the same class taken since), and the medical background of the patient (any suggestion of previous allergies whether associated with medications or not). Data should be taken in a uniform format and to harmonize our drug hypersensitivity diagnostic procedures in Europe, members of ENDA have first developed a questionnaire (Demoly et al., 1999), available into many different languages. It also includes some procedures as skin tests, provocation tests and biological tests.

The history is in fact often not reliable since different drugs are often taken simultaneously and can account for the symptoms, and it is often unprecise. Finally, the clinical picture of drug allergy is very heterogeneous, mirroring many distinct pathophysiological events. Thus, many doctors rely on history and some reference manuals for drug allergy diagnosis, without attempting to prove the relationship between drug intake and symptoms or to clarify the underlying pathomechanism of the reaction. Such an attitude leads to a misunderstanding of the epidemiology and the pathophysiology of this highly relevant field. In cases where a hypersensitivity reaction is suspected, if the drug is essential and/or frequently prescribed (e.g. β -lactams, paracetamol and non-steroidal anti-inflammatory drugs) a certified diagnosis should be performed and tests carried out in a specialist centre. Only a formal diagnosis of drug hypersensitivity reactions allows one to bring into play

the measures required for prevention and treatment. For these drugs, the prudent principle of eviction may be insufficient. It would mean elimination of drugs which do not necessarily give rise to reactions and which are widely used. However, it is a valid option until a specialist consultation can be scheduled.

3. Skin tests

The diagnostic value of skin tests has not been fully evaluated and the experience in different centres has rarely been exchanged during the last decades. Thus, reliable skin test procedures for the diagnosis of drug hypersensitivity are generally missing and test concentrations are unknown or poorly validated for most drugs. Skin tests have to be applied according to the suspected pathomechanism of the hypersensitive drug reactions. For immediate β -lactam hypersensitivity reactions for example, an IgE-mediated mechanism can be demonstrated by a positive skin prick and/or intradermal test after 20 min (Brockow et al., 2002; Torres et al., 2003; Blanca et al., 1990).

Therefore, skin prick tests and intradermal tests are particularly important for reactive haptens in order to demonstrate an IgE-dependent mechanism (Gruchalla, 2000). They should be performed 4–6 weeks after the reaction, in a specialist environment, since the tests themselves can induce, although in rare cases only, an anaphylactic reaction (Brockow et al., 2002). Their sensitivity and predictive value vary depending on the drug from excellent (penicillins, myorelaxants, heterologous sera, enzymes) through satisfactory (vaccines, hormones, protamine, opiates, thiopental) and poor or unknown (local anesthetics, paracetamol, sulfonamides, iodine radiocontrast media, quinolones, non-steroidal anti-inflammatory drugs, cephalosporins and other anti-infectious agents).

4. Provocation tests

A drug provocation test is carried out for diagnostic/therapeutic purposes and consists of the controlled administering of the drug to a patient with a history suggesting a drug allergy. This drug is either an alternative, a structurally/pharmacologically related drug or the suspected drug itself. Although there are some

criticism, the European Network for Drug Allergy from the European Academy of Allergology and Clinical Immunology (Aberer et al., 2003) recommends their use to confirm drug hypersensitivity reactions when skin tests and biological tests are not available or not validated. However, with the exception of some drugs such as aspirin (Stevenson, 1993), cyclooxygenase-2 inhibitors (Dahlen et al., 2000) and β -lactams (Torres et al., 2002), there exist only data on small cohorts reporting the results of drug provocation tests. To demonstrate the outcome of drug provocation tests in the evaluation of patients with a history suggesting drug anaphylaxis, we have carried out 1372 drug provocations using a variety of drugs, including β -lactams, aspirin and other non-steroidal anti-inflammatory drugs, paracetamol, macrolides and quinolones (Messaad et al., 2004). The major result of this study is that a true drug hypersensitivity was represented in less than one quarter of the patients (17.6%). This was of crucial importance for the therapeutic future of these patients. It was found that non-hypersensitive patients did not need to avoid these drugs in the future. The continuous search for alternatives leads to fear and often only less potent alternatives are found. Drug provocation tests reproduced the same symptoms, albeit milder and of a shorter duration. Prednisolone, H1-antihistamines and epinephrine in cases of hypotension were administered, allowing a rapid and complete clearing of the reaction. Drug provocation tests should nevertheless be regarded as a serious and potentially dangerous procedure (Aberer et al., 2003). It is important to document the patient's personal details, medical history and concomitant drug therapy and to have full resuscitation facilities available during the tests.

5. Conclusion

The diagnosis of immediate drug hypersensitivity reactions is often difficult. It remains largely clinical.

Skin tests are validated for some drugs. Provocation tests have the best sensitivity, are cumbersome and may be harmful. Better care for these patients, available to all clinicians, requires new and validated biological tools for diagnosis.

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