

DRUG HYPERSENSITIVITIES: THE NEED FOR STANDARDIZATION

Werner Aberer (1)

SUMMARY: Owing to differences of opinion, the evaluation of adverse drug reactions in clinical practice is still somewhat arbitrary. In order to obtain reliable results, we need standardized testing procedures, well defined test preparations, and the application of specific algorithms for the different groups of drugs and their reactions. A few milestones have been achieved in this regard; the full accomplishment of these goals still entails a lot of work.

Key-words: Drug allergy - Skin test - *in vitro* test - provocation test - standardization.

INTRODUCTION

Hypersensitivity reactions to drugs are some of the most common, diverse, and significant immunopathological processes in modern clinical medicine. Given the vast and numerous differences of opinion, the evaluation of such reactions in clinical practice is still somewhat arbitrary. The immense variety of drugs in daily use, the enormous diversity of potential adverse reactions to these drugs, and the complexity of diagnostic procedures to evaluate these reactions, underline the necessity of standardized test procedures for any drug and any type of reaction. Such standardized tests must be based on standardized test preparations. This goal is yet to be achieved, as demonstrated by the fact that the results of drug skin tests are false negative in 30-50% of patients, even when performed according to reviewed guidelines (reviewed in 1). Besides reliable test procedures based on standardized drug preparations, algorithms that include an estimation of the link between the untoward clinical event and the suspected drug are needed in order to determine the underlying causes of the identified drug reactions (2, 3).

This report will describe current problems regarding standardization and some of the progress that has been made in the last few years. Tables and figures from recent publications will be used to highlight this progress (Tables 1 and 2, Figure 1).

(1) Department of Environmental Dermatology - Medical University of Graz - Auenbruggerplatz 88036 Graz (Austria)

EVALUATION OF DRUG HYPERSENSITIVITY REACTIONS

A detailed history is of paramount importance for the question of whether a certain disease reflects drug hypersensitivity as well as the question of which drug is causing it. To facilitate this recording of an appropriate history a well-structured protocol has been developed that provides a guide for the further steps regarding appropriate test procedures (4).

Testing includes skin testing, *in vitro* testing (detection of IgE antibodies, biologic tests) and/or drug provocation. These procedures should follow defined algorithms: Each type of reaction necessitates a different procedure, e.g. an urticarial reaction after oral intake of penicillin is evaluated by IgE detection and skin prick and/or intradermal testing, whereas contact allergy or fixed drug eruption requires a patch test. The procedures mainly depend on the type of clinical reaction under investigation. Therefore, different test preparations are used. With regard to skin tests, a specific preparation (commercial product, a pure chemical, or the specific haptenic group), a defined concentration, and the suitable vehicle have to be evaluated. In *in vitro* tests, preparation and concentration depend on the test method. Thus, IgE testing requires coupling to a carrier, whereas biologic tests may need soluble preparations in serial dilutions. When evaluating a specific reaction to a drug, defining the correct test substance and the proper concentration requires a large number of intricate multicenter studies using well defined and strict protocols. We still are at the beginning of this process.

DRUGS AS ANTIGENS

In principle, drugs may either act as complete antigens or as incomplete antigens (5).

Drugs acting as complete antigens include substances with a high molecular weight such as hormones, enzymes, heterologous sera, dextran and proteins. Quaternary ammonium muscle relaxants, despite their low molecular weight, act as complete antigens because there is a sufficient distance between terminal determinants to permit them to act as bivalent antigens without the need for conjugation to a carrier (6). This is also true for aminoglycoside antibiotics. Skin tests for these drugs may be performed by directly using the commercially available form. Nevertheless, such tests are not easy to perform. For example, skin tests for insulin allergy are sensitive but

Hapten	Dose	Units
BPO	5×10^{-5}	mmol/L
MDM	2×10^{-2}	mmol/L
Amoxicillin	20-25	mg/ml
Ampicillin	20-25	mg/ml
Cephalosporin	1-2	mg/ml

Table 1: Concentrations recommended for prick and intradermal testing with betalactams (from Torres *et al.*) (10).

may be nonspecific – i.e. the skin test may be positive in chronically treated patients without any obvious adverse reaction (7).

Most drugs have a low molecular weight and are haptens, not antigens. In order to sensitize, they need to be conjugated with a carrier protein. Suitable skin

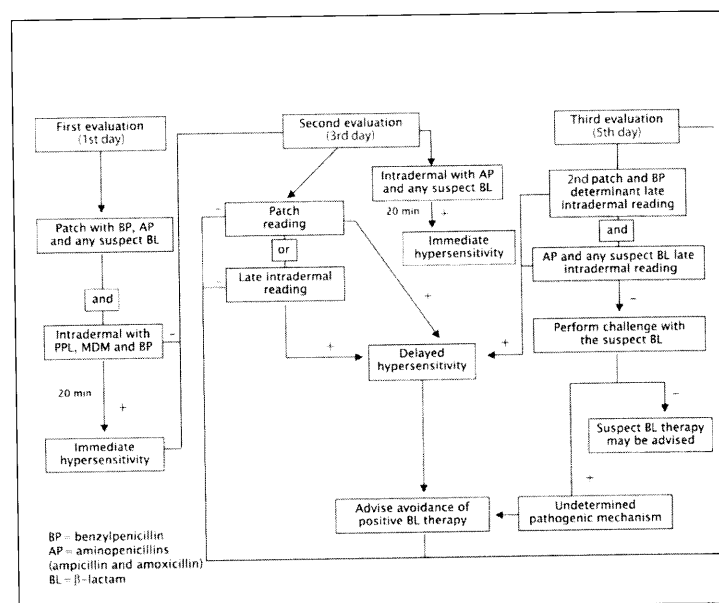


Figure 1: Algorithm for *in vivo* allergologic work-up of non-immediate reactions to β -lactams (from Romano *et al.*) (11).

Antibiotic	DKG ¹	De Groot (23)	Barbaud (24)	Others (25,26)
Penicillin G	5% pet	Pure 1% pet 10000 IU pet	Pure in powder with sodium citrate*	Romano: 5000 IU/g pet Bruynzeel: 20% w/w
Other penicillins	5% pet	Pure 1% pet	Pure in powder*	Romano: 5% pet (20 controls) Bruynzeel: 20% w/w
Cephalosporins	5% pet	20% pet or pure 0.5% water	Pure in powder	Bruynzeel: 20% w/w
Cotrimoxazole	Trimethoprim 5% pet Sulfamethoxazol 5% pet	Sulfonamide (not specified): 5% pet	80 mg/ml in water	
Tetracycline-HCl	2% pet	3% pet 5% pet	Doxycycline: 20 mg/ml in water	
Gentamycin sul fate	20% pet	20% pet	Norfloxacin: in powder from pill*	
Ciprofloxacin, ofloxacin	5% pet		Pure in powder*	
Erythromycin	1% pet	1% pet 5% pet 10% pet		
Pristinamycin			Pure in powder*	
Carbamazepine			Pure in powder*	

¹DKG: German contact allergy group (test concentrations in German practice).

*All these preparations were tested pure and diluted to 30% in water and in petrolatum.

pet=in petrolatum (vaseline); w/w=watery solution.

Table 2: Patch test concentrations used in the published literature and in practice (from Brockow *et al.*) (8).

tests can be performed only with a drug-protein conjugate, and these are readily available only for the investigation of penicillin allergy; meanwhile even these have been withdrawn from the market. Thus, currently no standardized commercial test substances for drugs acting as incomplete antigens are available in the market. Individual test substances have to be prepared and their test concentration standardized.

SKIN TESTING (PRICK AND INTRADERMAL TESTING VS. PATCH TESTING)

Skin tests are reliable only for those drugs which cause reactions through an IgE-mediated mechanism or a type-IV mechanism. But even in these cases they are valid only for a limited number of compounds (5).

The general principles for skin test procedures in the diagnosis of drug hypersensitivity have been delineated in a position paper of the EAACI (European Academy of Allergology and Immunology)(8). The latter has issued general recommendations for test preparations, test vehicles and solutions. The correct test concentrations have been described for *already well-studied substances* only (8, Table 1). The authors mention that *for other substances and through collaborative studies, it will be possible to provide sensitivity and specificity data for each drug and drug concentration*. Clinical studies are under way; yet the task is far from complete (9).

Regarding skin tests with drugs for the investigation of cutaneous adverse drug reactions, the ESCD guidelines prescribe general rules and provide a summary of the current literature (1). The authors mention that *a crucial point is the interpretation of results of drug skin tests, whether negative or positive*. Multicenter studies were recommended to determine the sensitivity and specificity of drug skin tests in investigating cutaneous adverse drug reactions.

In both papers (1,8) the importance of negative control testing was emphasized. The ethical problems relating to this issue were also highlighted. Skin testing is potentially dangerous, and the use of non-standardized and arbitrarily defined test concentrations is a handicap. Too high a concentration may cause systemic general reactions as well as local irritation while too low concentrations may lead to false negative results.

Currently, unanimous agreement about skin test concentrations exists only for a small number of drugs. These include prick tests for betalactams (10,11), cephalosporins, some proteins such as insu-

lin, ACTH, trypsin, antisera and vaccine (5). For several groups of drugs, local organizations have defined the critical concentrations (e.g. muscle relaxants) (12). With regard to patch tests, the number of drugs with recommended test concentrations is even smaller: a few antibiotics, pristinamycin and carbamazepine (Table 2) (1).

IN VITRO TESTING

Immunoassays may detect serum IgE antibodies to certain drugs (penicillin, a few cephalosporins, succinyl choline, insulin, ACTH, protamine, tetanus toxoid, chymopapain, and gelatine). Sensitivity and specificity vary from substance to substance; false positive and false negative test results are quite common. The same reservations as those for skin tests apply here. Therefore, positive as well as negative results must be critically evaluated. Patients with extremely high total IgE values are at special risk for false positive results to penicillins. Test kits for IgE detection are offered in the market for more than 150 different drugs, although an IgE-mediated reaction in a significant number of patients has not been proven for more than 100 of these substances (the list extends from acetyl salicylic acid [13] to zinc chloride). This, however, is not a question of standardization but one of credibility.

Biologic tests such as the lymphocyte transformation test (14), the CAST-ELISA (15,16) and 15-HETE-determination (17), flow cytometric basophil activation tests (18), or leukocyte cytotoxicity assays (19) are now widely propagated for the evaluation of drug allergies. However, standardization is still in its infancy. This may explain why the current published reports are highly controversial: While some authors deny any diagnostic utility of the tests (16), others are convinced of their usefulness (15). Better standardization is urgently required. Negative predictive values need to be systematically investigated for any test system and any individual drug. A general position paper on these biologic tests is currently being completed by the EAACI interest group on diagnostic tests (20).

PROVOCATION TESTING

The principles of testing, the indications, contraindications, test methods, interpretation and limitations of drug provocation testing have been summarized in a position paper of the EAACI interest group on drug hypersensitivity (21). The definition of the general principles for drug provocation tests in this position paper should help to establish specific protocols for

the different groups of drugs on one hand, and the different clinical signs of hypersensitivity on the other. It was again emphasized here that well controlled protocols do exist only for allergic contact dermatitis, fixed drug eruptions, maculopapular eruptions after aminopenicillins and cephalosporins, immediate and non-immediate reactions to betalactam antibiotics, urticaria and angioedema after NSAID, local anesthetics, and muscle relaxants (summarized in 21).

STANDARDIZED ALGORITHMS

The need for a decision table algorithm approach toward the development of an operational system for the identification of adverse drug reactions was expressed many decades ago (2). However, general algorithms for disease management of drug hypersensitivity were defined only recently (3). Currently, specific algorithms exist only for two groups of drugs, i.e. for the diagnosis of immediate allergic reactions to betalactam antibiotics (10) and non-immediate reactions (Figure 1) (11). Further studies on iodinated contrast media and other groups of drugs are under way (22).

CONCLUSION

The evaluation of adverse drug reactions in clinical practice will remain somewhat arbitrary until well standardized algorithms, based on well-defined procedures using extensively evaluated test substances and concentrations, have been established for the different groups of drugs. Much progress has been made in this field in the last few years, yet the goal is far from accomplished. Apart from drugs with proven immunopathogenesis, the mechanisms responsible for many drug reactions are still unknown. The same holds true for testing procedures.

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