

Provocation Tests in Diagnosing Drug Hypersensitivity

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Abstract: A position paper by the European Network for Drug Allergy (ENDA), the European Academy of Allergology and Clinical Immunology (EAACI) interest group on drug hypersensitivity, defines drug provocation tests (DPTs) as “the controlled administration of a drug in order to diagnose drug hypersensitivity reactions”. The DPT is widely considered to be the “gold standard” to establish or exclude the diagnosis of hypersensitivity to a certain substance, as it not only reproduces hypersensitivity symptoms, but also any other adverse clinical manifestation, irrespective of the mechanism. The DPT can be harmful and thus should only be considered after balancing the risk-benefit ratio in the individual patient.

The ENDA position paper specifies two main indications for DPTs with the suspected compounds:

1. to exclude hypersensitivity in non-suggestive histories of drug hypersensitivity and in patients with non-specific symptoms, such as vagal symptoms under local anesthesia;
2. to establish a firm diagnosis in suggestive histories of drug hypersensitivity with negative, non-conclusive, or non-available allergologic tests.

A positive DPT result optimizes allergen avoidance, while a negative one allows a false label of drug hypersensitivity to be removed. For these reasons, DPTs are often carried out to exclude a diagnosis of hypersensitivity to β -lactams when other allergologic tests are negative. DPTs are also performed when the sensitivity of allergologic tests for evaluating allergic reactions to certain drugs, such as non- β -lactam antibiotics, heparins, and glucocorticoids, is limited. On the other hand, DPTs are also performed to diagnose hypersensitivity reactions to nonsteroidal anti-inflammatory drugs in subjects with the cross-reactive pattern, because both skin tests and *in vitro* diagnostic methods are ineffective in such patients.

Key Words: Challenges, diagnosis, drug allergy, hypersensitivity, provocation tests.

1. INTRODUCTION

Assessing a drug allergy or hypersensitivity is not a simple task. Many tests, including *in vitro* ones, have been developed in addition to skin and patch tests. The sensitivity of allergologic tests is not 100%; in selected cases, therefore, drug provocation tests (DPTs) are necessary. The DPT is widely considered to be the “gold standard” to establish or exclude the diagnosis of hypersensitivity to a certain drug, as it not only reproduces hypersensitivity symptoms, but also any other adverse clinical manifestation, irrespective of the mechanism.

A position paper by the European Network for Drug Allergy (ENDA), the European Academy of Allergology and Clinical Immunology (EAACI) interest group on drug hypersensitivity [1], defines the DPT as “the controlled administration of a drug in order to diagnose drug hypersensitivity reactions”.

This position paper specifies the following four main indications for DPTs:

1. to exclude hypersensitivity in non-suggestive histories of drug hypersensitivity and in patients with non-specific symptoms, such as vagal symptoms under local anesthesia;
2. to establish a firm diagnosis in suggestive histories of drug hypersensitivity with negative, non-conclusive or non-available allergologic tests, for example a maculopapular eruption during aminopenicillin treatment with negative allergologic tests;
3. to provide safe pharmacologically and/or structurally non-related drugs in proven hypersensitivity, such as other antibiotics in patients allergic to β -lactams. This may also be helpful for anxious people who would refuse to take the recommended drug without proof of tolerance;
4. to exclude cross-reactivity of related drugs in proven hypersensitivity, for example a cephalosporin in a penicillin-allergic subject or an alternative nonsteroidal anti-inflammatory drug (NSAID) in an aspirin-sensitive asthmatic.

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In the first two cases, DPTs are performed with the suspected drug itself in order to make a definitive diagnosis; in the other two, they are carried out with alternative compounds.

The present review addresses the literature regarding the use of DPTs with suspected compounds in diagnosing drug hypersensitivity reactions.

DPTs should be distinguished from desensitization protocols. In the latter, the aim, the condition, and the sequence of increasing doses are different. Desensitization is performed when a drug must be taken by the patient and no alternatives are available. The number of doses is usually higher for a desensitization protocol and, of course, even if a moderate reaction occurs during the desensitization, the protocol still has to be followed, which is not the case in a DPT protocol.

2. ELIGIBLE SUBJECTS

2.1. Selection of Compatible Reactions

All drugs can induce adverse reactions, but only few of the latter are allergic. Moreover, the prevalence of self-reported drug allergy is important, and can differ from the “true” prevalence. For instance, in a recent Portuguese study [2] involving 2,309 subjects a rate of self-reported drug hypersensitivity of 7.8% was observed. Other studies regarding Turkish [3] and German [4] children found rates of such hypersensitivity of 2.8% and 4.2%, respectively. It is therefore not possible to test the whole population for a supposed “allergic reaction”.

A 3-step strategy might be helpful to identify drug hypersensitivity reactions (Fig. 1). The first step is the selection of patients with a compatible history. In order to help the physician, standardized questionnaires, such as the one published in several languages by the ENDA [5], can be used. The clinical assessment includes the full description of the reaction, the delay between the drug intake and the clinical reaction, and the association of other risk factors. It is important to distinguish between immediate and non-immediate reactions. The former occur within the first hour after the last drug administration and are manifested clinically by urticaria, angioedema, rhinitis, bronchospasm, and anaphylactic shock. Non-immediate reactions occur more than one hour after the last drug administration. The main non-immediate reactions are maculopapular eruptions and delayed-appearing urticaria/angioedema. In addition, drugs can elicit fixed eruptions, exfoliative dermatitis, acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) [6].

The second step focuses on allergologic tests. In selecting such tests, it is important to consider whether the reaction is immediate or non-immediate [7]. Clinical and immunological studies suggest that type-I (IgE-mediated) and type-IV (cell-mediated) pathogenic mechanisms are involved in many immediate and non-immediate reactions, respectively. Prick tests and immediate-reading intradermal tests are the most readily available tools for diagnosing immediate reactions [8]; determination of specific IgE levels is still the most common *in vitro* method for evaluating such reactions. De-

layed-reading intradermal tests and patch tests, as well as lymphocyte transformation tests (LTTs), are the most common *in vivo* and *in vitro* methods for the diagnosis of non-immediate reactions. New diagnostic tools, such as the basophil activation test (BAT) and the lymphocyte activation test (LAT), have been developed for evaluating immediate and non-immediate reactions, respectively, and are under validation. The routine use of the BAT and the LAT could increase the sensitivity of diagnostic work-ups, thus reducing the need for DPTs.

For instance, the ENDA devised two different diagnostic algorithms for the evaluation of either immediate or non-immediate reactions to β -lactams (penicillins and cephalosporins) [9, 10].

If allergologic tests are positive, patients can be tested for an alternative drug; otherwise, in selected cases, they can undergo a DPT (third step).

2.2. Drug to be Tested

The DPT should be performed only if other, less potentially harmful tests do not allow the physician to establish or exclude the diagnosis of hypersensitivity to a certain drug and if its outcome might contribute to make a firm diagnosis. A positive DPT result optimizes allergen avoidance, while a negative one allows a false label of drug hypersensitivity to be removed.

For example, DPTs are often carried out to diagnose hypersensitivity reactions to NSAIDs. In fact, most such reactions are not due to an allergic hypersensitivity and both skin tests and *in vitro* diagnostic methods are ineffective [11, 12]. DPTs are also performed when the sensitivity of allergologic tests for evaluating allergic reactions to certain drugs, such as heparins [13] and glucocorticoids [14], is limited. On the other hand, DPTs are often carried out to exclude a diagnosis of hypersensitivity when other allergologic tests, specifically skin or patch tests, are negative and the negative predictive value of such tests is high. This is the case of β -lactams; in fact, both the ENDA diagnostic algorithms for evaluating either immediate or non-immediate hypersensitivity reactions to these antibiotics include DPTs [9, 10].

However, the risk-benefit ratio must be acceptable: the culprit drug must be either important (i.e., substantially more effective than other alternatives) or irreplaceable.

2.3. Contraindications

According to the ENDA position paper [1], DPTs with a suspected drug should not be performed in pregnant women or in patients at increased risk because of co-morbidities, such as acute infections, uncontrolled asthma, or any underlying diseases, in whom exposure might provoke a situation that is beyond medical control. However, exceptions can be made if the drug under suspicion is essential for the patient (e.g., neurosyphilis and penicillin therapy).

DPTs should never be performed in patients who have experienced severe, life-threatening immune-cytotoxic reactions, vasculitic syndromes, exfoliative dermatitis, bullous exanthems, DRESS, AGEP, SJS, or TEN. Finally, drug-induced autoimmune diseases, such as systemic lupus erythematosus, *pemphigus vulgaris*, and bullous pemphigoid,

or specific organ manifestations, like blood cytopenia, hepatitis, nephritis, and pneumonitis, constitute contraindications to DPTs. In selected cases, however, subjects who suffered anaphylactic reactions can undergo DPTs. In fact, these reactions can be managed effectively and promptly.

2.4. Human Immunodeficiency Virus (HIV)

Subjects infected by the HIV need drugs (HIV treatment, as well prevention and treatment for any opportunist disease), to which they often react. This induces an increase of morbidity and mortality. However, the pathogenesis of these adverse reactions to drugs is not well defined. For these reasons, instead of a DPT, a desensitization protocol might be considered. Moreover, even if the DPT is negative, there will always be the possibility of a false-negative result [15].

3. THE DPT

3.1. General Considerations

Certain co-medications are contraindicated if they may either interfere with any emergency treatment (e.g., β -blocking agents) or mask symptoms of any positive response to tests (e.g., H-1 antihistamines and glucocorticoids) [16-19] (Table 1). According to the ENDA position paper [1], avoidance of angiotensin-converting enzyme (ACE)-inhibitors is also advisable (Table 1). Additionally, in case of bronchial hyper-reactivity, some drugs have to be stopped (β -2-agonists, ipratropium bromide, long-acting theophylline etc.) (Table 1).

DPTs can induce life-threatening reactions; therefore, these tests should be performed under medical supervision.

Before each test, an individual protocol must be prepared and an expert must manage the procedures. Resuscitation facilities should be available for emergencies. Monitoring must be designed in such a way that early signs of the relevant disorder arising from the DPT can be detected. Moreover, the recommendations made by the American Academy of Asthma, Allergy and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) on anaphylaxis [20, 21], and by the EAACI-ENDA [1] should be followed.

The drug should be administered, if possible, in the same way as it was given when the reaction occurred. The different routes of administration include: oral, parenteral (intravenous, intramuscular, subcutaneous), topical (nasal, bronchial, conjunctival, cutaneous), and others. The oral route is preferred, because the absorption is slower and any adverse reactions can be treated earlier as compared to the parenteral route. However, if the drug is not available by the oral route, an alternative can be the intravenous one.

As a general rule, DPTs should be performed no earlier than 4 weeks after the drug hypersensitivity reaction.

Dosage and timing are dependent on numerous variables, including the type of drug, the severity of the hypersensitivity reaction under investigation, the route of administration, the expected time latency between application and reaction, the state of health of the patient, and any co-medication.

As the intensity of the reaction after a DPT is not absolutely predictable, a careful assessment of the dosage is essential, the objective being to introduce a medication cautiously in order to reduce the risk for a severe reaction [1,

Table 1. Drugs to be Avoided Before Performing a DPT (Adapted from Messaad *et al.* [23])

Drug class	Immediate Reaction	Non-Immediate Reaction	Free Interval	Consequences
H1 anti-histamines	+	-	3 to 7 days	Mask the reaction
Antidepressants (imipramines, phenothiazine)	+	-	5 days	
β -2-Agonists				
- Short-acting	+	-	6 to 8 hours	Mask the reaction
- Long-acting	+	-	1 to 2 days	
β -Blocking agents				
- Per os	+	+	1 to 2 days	Aggravate the reaction
- Eyes drops	+/-	-	1 to 2 days	
Corticosteroids				
- Short-term, low dose (<50 mg)	+/-	-	3 to 5 days	Mask the reaction
- Short-term, high dose (>50 mg)	+/-	+	1 week	
- Long-term	+/-	+	3 weeks	
Ipratropium bromide	+	-	6 to 8 hours	Mask the reaction
Leukotriene modifiers	+	-	> 1 week	Mask the reaction
Long-acting theophylline	+	-	1 to 2 days	Mask the reaction
ACE inhibitors	+	+	1 day	Aggravate the reaction

22]. According to the ENDA position paper [1], one should start with a low dose, carefully increasing this, and stopping as soon as the first objective symptoms occur. If no symptoms appear, the maximum single dose of the specific drug must be achieved, and the administration of the defined daily dose is desirable.

In case of a previous immediate reaction, the starting dose should be between 1:10,000 and 1:10 of the therapeutic one, depending on the severity of the reaction; the time interval between doses should be at least 30 minutes, but many drugs and specific situations might require longer intervals.

In case of previous non-immediate reactions, the starting dose should not exceed 1:100 of the therapeutic one and the

time-interval between each dose should vary from 3 days to one week, depending on the time-interval between drug intake and adverse reactions reported in clinical histories.

Specific protocols for every single drug or at least groups of drugs would be helpful, where indications, contraindications, substances, dosing, grading of the reaction, and scoring criteria are defined. However, the development of individual DPT protocols is difficult because of the countless drugs that may cause hypersensitivity reactions and the number of factors that might influence the outcome. Nevertheless, a study by Messaad *et al.* [23] provided useful information on the sequences of increasing doses of numerous drugs (Tables 2-5).

Table 2. Sequence of Increasing β -Lactam Doses During Drug Provocation Tests (Adapted from Messaad *et al.* [23])

Drug	Drug Class	Doses†	Route	Usual Daily Dose for Adults‡
Amoxicillin	Penicillin	1, 5, 25, 100, 500, 1000	Oral	1000–2000 mg
Ampicillin	Penicillin	1, 5, 25, 100, 500, 1000	Oral	2000 mg
Cloxacillin	Penicillin	1, 5, 25, 100, 500, 1000	Oral	2000 mg
Cefaclor	Cephalosporin	1, 5, 25, 125, 500	Oral	750 mg
Cefadroxil	Cephalosporin	1, 5, 25, 100, 500, 1000	Oral	2000 mg
Cefatrizine	Cephalosporin	1, 5, 25, 50, 250, 700	Oral	1000 mg
Cefazolin	Cephalosporin	1, 5, 25, 100, 500, 2000	Intravenous	1500–3000 mg
Cefuroxime	Cephalosporin	1, 5, 20, 80, 400	Oral	500 mg
Ceftazidime	Cephalosporin	1, 5, 25, 100, 500, 2000	Intravenous	3000 mg
Cefixime	Cephalosporin	1, 5, 25, 100, 225	Oral	400 mg
Ceftriaxone	Cephalosporin	1, 5, 25, 100, 500, 1000	Intravenous	1000–2000 mg

† Ten times less than the first dose for anaphylactic shocks; same units as fifth column.

‡ According to the recommendations of the French Agency on Drug Safety (www.AFSSAPS.sante.fr).

Table 3. Sequence of Increasing Non- β -Lactam Antibiotic Doses During Drug Provocation Tests (Adapted from Aberer *et al.* [1])

Drug	Drug Class	Doses†	Route	Usual Daily Dose for Adults‡
Azithromycin	Macrolide	1, 5, 25, 75, 125, 250	Oral	500 mg
Clarithromycin	Macrolide	1, 5, 25, 100, 500, 1000	Oral	1500–2000 mg
Erythromycin	Macrolide	1, 5, 25, 100, 500, 1500	Oral	2000–3000 mg
Josamycin	Macrolide	1, 5, 25, 100, 500, 1000	Oral	1000–2000 mg
Roxithromycin	Macrolide	1, 5, 25, 100, 150	Oral	300 mg
Spiramycin	Macrolide	15 000, 75 000, 325 000, 750 000, 1 500 000, 4 500 000	Oral	6–9 mIU
Ciprofloxacin	Quinolone	1, 5, 25, 100, 500	Oral	500–1500 mg
Ofloxacin	Quinolone	2, 10, 50, 100, 200	Oral	400 mg
Pefloxacin	Quinolone	4, 20, 100, 200, 400	Oral	800 mg

† Ten times less than the first dose for anaphylactic shocks; same units as fifth column.

‡ According to the recommendations of the French Agency on Drug Safety (www.AFSSAPS.sante.fr).

Table 4. Sequence of Increasing NSAID Doses During Drug Provocation Tests (Adapted from Messaad *et al.* [23])

Drug	Doses†	Route	Usual Daily Dose for Adults‡
Diclofenac	1, 5, 20, 80	Oral	100–150 mg
Ibuprofen	1, 5, 20, 80, 150, 300	Oral	200–1200 mg
Ketoprofen	1, 5, 20, 80	Oral	100–200 mg
Tiaprofenic acid	1, 5, 20, 80, 200	Oral	300–400 mg
Meloxicam	1, 3, 7.5	Oral	7.5–15 mg
Piroxicam	1, 3, 6, 10	Oral	20 mg
Niflumic acid	1, 5, 25, 125, 625	Oral	750–1000 mg
Aspirin	1, 5, 20, 50, 100, 200, 500	Oral	500–3000 mg
Paracetamol	1, 10, 50, 250, 500, 1000	Oral	500–4000 mg

† Ten times less than the first dose for anaphylactic shocks; same units as fifth column.

‡ According to the recommendations of the French Agency on Drug Safety (www.AFSSAPS.sante.fr).**Table 5. Sequence of Increasing Drug Doses During Drug Provocation Tests (Adapted from Messaad *et al.* [23])**

Drug	Drug Class	Doses†	Route	Usual Daily Dose for Adults‡
Betamethasone	Steroid	0.2, 1, 2, 4	Oral	3–12 mg
Methylprednisolone	Steroid	1.6, 8, 16, 32	Oral	16–64 mg
Prednisolone	Steroid	2, 10, 20, 40	Oral	20–80 mg
Omeprazole	Proton-pump inhibitor	1, 5, 10, 20	Oral	20–40 mg
Pristinamycin	Synergistin	1, 5, 25, 100, 500, 1500	Oral	2000–3000 mg
Tetrazepam	Benzodiazepin	1, 2.5, 25, 50	Oral	50–100 mg
Any vaccine	Vaccine	0.1, 0.4, (0.5)	Subcutaneous	0.5 (1.0) mL
Lidocaine / Articaine	Local anesthetic	0.1, 1, 2	Subcutaneous	1–3 mL

† Ten times less than the first dose for anaphylactic shocks; same units as fifth column.

‡ According to the recommendations of the French Agency on Drug Safety (www.AFSSAPS.sante.fr).

If several drugs are suspected, they have to be tested one by one. Otherwise, it is not possible to differentiate the culprit drug from the others.

Hypersensitivity to excipients, even if it is a rare event, should also be considered, particularly in patients who suffered hypersensitivity reactions to several compounds [24]. Therefore, provocation tests with excipients might be necessary. The latter include encapsulation agents (carboxymethyl cellulose, gelatin), emulsifying agents or solvents (dextran, egg albumin), synthetic sweeteners (saccharin, aspartame), stabilizing agents or antioxidants (sulfites, ethylenediamine), dyes (tartrazine, xanthene dyes), preservatives (benzoates, parabens), or adjuvants (aluminium hydroxide, zinc oxide) [25].

3.2. Results

A DPT can be termed positive if it reproduces the original symptoms, or at least objective ones. If patients report only subjective symptoms, a placebo-controlled challenge

must be performed. A negative result is defined by the absence of reaction during the test and after the observation period, which includes a certain delay after the end of the test (days or weeks depending on the drug and the immunologic pathway). When the clinical history is well defined and the DPT positive, the diagnosis of drug allergy/hypersensitivity can be confirmed. In the same way, if the test was performed in order to exclude a drug allergy, a negative test indicates the absence of drug allergy/hypersensitivity. This is more difficult when a negative test is observed with a history strongly compatible with a drug allergy, or when a positive test is observed with a history weakly compatible. Reasons for false-negative or false-positive results should be taken into account. If the results are doubtful, a placebo-controlled test or another DPT can be performed.

According to the ENDA group [1], reasons for false positive results in DPTs are psychological symptoms, pre-existing symptoms (e.g., urticaria), a drug-induced aggravation of pre-existing disease, or a self infliction. False-

negative results might be due to several reasons: the use of anti-allergic drugs (corticosteroids, anti-histamines), the fact that possible co-factors (light, concomitant medications, viral infections, and physical exercise) are no longer present, too short exposure and/or observation time, a too short time interval between the reaction and testing (refractory period), a too long such interval (natural desensitization), a tolerance induction or “desensitization” by testing, or an erroneous attribution of responsibility to the tested drug.

3.3. β -Lactams

DPTs are included in both the ENDA diagnostic algorithms for evaluating either immediate or non-immediate hypersensitivity reactions to β -lactams [9, 10]. Indications are extensive for the ENDA group [9, 10], and more restricted for the American Academy of Allergy Asthma and Immunology [26].

As far as immediate reactions to β -lactams are concerned, both the long and the short diagnostic algorithm devised by the ENDA [9] include DPTs. According to this position paper [9], however, patients who display negative results in DPTs should be re-tested 2 to 4 weeks later. In fact, immediate hypersensitivity to β -lactams may be a transient condition. Skin-test negativization has been observed in both children and adults with IgE-mediated hypersensitivity to penicillins retested after at least one year [27, 28]; some subjects tolerated penicillin again [27]. However, in some studies a conversion to skin-test positivity has been described in patients re-tested about one month after negative challenges followed by full therapeutic courses [29-34], with a frequency ranging from 0.9% in the study by Mendelson *et al.* [29] to 27.9% in the study by Goldberg and Confino-Cohen [34]. Therefore, in patients with immediate reactions to β -lactams negative challenges should be followed by full therapeutic courses and re-evaluations 2 to 4 weeks later. In our experience, this is crucial when evaluating patients with immediate reactions to cephalosporins. Recently, we studied 76 patients with immediate reactions to cephalosporins using skin tests and specific IgE assays [35]. Thirteen subjects displayed negative results in the first allergologic evaluation; 8 of them agreed to undergo DPTs: 2 reacted, while 6 tolerated challenges and subsequent therapeutic courses. In re-evaluations, the 2 patients who had reacted to DPTs and 5 of the 6 who had tolerated them presented skin-test positivity.

In any case, DPTs may contribute to the diagnosis of immediate reactions to β -lactams, particularly penicillins [23, 36, 37]. Messaad *et al.* [23] performed DPTs in 416 subjects with histories of immediate hypersensitivity reactions to β -lactams and negative results in skin testing: 35 (8.4%) reacted to challenges with the relevant drugs. In a study by Torres *et al.* [36], 89 (26.9%) of 330 subjects with such reactions displayed negative results in both skin tests and serum specific IgE assays; 49 (55%) of the 89 reacted to challenges.

With regard to non-immediate reactions to β -lactams, the ENDA diagnostic algorithm [10] does not advise repeating allergologic tests after negative challenges. In effect, unlike IgE-mediated hypersensitivity, delayed hypersensitivity to β -lactams seems to be a persistent condition. In evaluating non-immediate reactions to β -lactams, results of allergologic

exams do not appear to be influenced by the time interval between adverse reactions and allergologic evaluations [38, 39]. Moreover, some studies re-evaluated patients with this kind of hypersensitivity from one year to more than 10 years after the first allergologic exam: only 2 (1.8%) out of 108 patients had become negative [40-43]. Therefore, negative results in the allergologic work up should be a fairly reliable indicator that the manifestation which occurred during β -lactam therapy was not an allergic phenomenon.

In effect, a large percentage of patients who suffered non-immediate reactions and display negative results in delayed-reading intradermal tests and/or patch tests tolerate challenges with the suspected β -lactam. In a study concerning 259 subjects with non-immediate manifestations, mostly maculopapular rashes and delayed-appearing urticarial eruptions, associated with penicillin therapy [44], among the 117 patients, who presented negative results in the aforementioned allergologic tests and accepted challenges, only 3 (2.5%) reacted to them. More recently, Lammintausta and Kortekangas-Savolainen [45] reported positive DPT results in 3 (3.8%) of the 78 subjects with histories of cutaneous eruptions, mostly maculopapular rashes, during either penicillin or amoxicillin therapy and negative results in patch tests.

However, several cases who displayed allergologic test negativity and challenge positivity have been reported [44-49].

In particular, a recent study by Padial *et al.* [49] evaluated prospectively 22 subjects who had developed maculopapular or urticarial exanthems associated with β -lactam treatments. Results indicated that after the confirmation of the history by positive DPTs, only 2 (9%) of these 22 subjects presented both positive patch tests and delayed-reading intradermal tests to the responsible β -lactams. Therefore, further studies should be performed in large samples of subjects with non-immediate reactions to β -lactams in order to fully establish the negative predictive value of skin and patch tests.

With regard to DPTs with β -lactams other than penicillins, in a recent study [45], only 1 of the 75 patients with cutaneous eruptions associated with cephalosporins and negative results in allergologic tests reacted to challenges with the suspected cephalosporins (cefadroxil or cephalexin). In another study concerning hypersensitivity reactions to cephalosporins in children [50], 105 subjects with non-immediate reactions were evaluated. Only one child presented positive immediate responses to skin tests with penicillin reagents. Among the 104 children with negative results in allergologic tests, 96 underwent challenges: 95 tolerated them and one reacted to cefaclor paediatric suspension and tolerated the challenge with a cefaclor capsule.

Several other studies performed challenges with the suspected β -lactams in order to diagnose hypersensitivity reactions to them in samples of subjects (adults and/or children) not selected on the basis of the type of reaction, immediate or non-immediate [27, 29, 32, 33, 51-56]. In such studies, the rate of positive responses to DPTs ranged from 0% [51, 52, 55] to 4.6% [56]. Thus, the drug hypersensitivity label was removed in more than 95% of subjects with positive histories and negative allergologic tests who had undergone chal-

lenges. This is of crucial importance for the therapeutic future of the subjects, particularly children.

It is interesting to note that, in our experience, the proportion of subjects with histories of hypersensitivity reactions to β -lactams displaying skin test negativity and challenge positivity has been increasing in the last few years [57]. Specifically, we evaluated a total of 1,218 subjects with such histories: 257 (21.1%) had a true hypersensitivity confirmed by skin tests (178, 69.3%) or by DPTs (79, 30.7%). The unavailability of the classic penicillin reagents (PPL and MDM) could partially explain such phenomenon.

With regard to the sequence of increasing drug doses, in case of immediate reactions, the ENDA group recommends for amoxicillin and penicillin V a 5-step oral challenge, with the following doses: 1-5 mg, 50-65 mg, 100-150 mg, 250-300 mg, and 400-800 mg (cumulative dose no higher than 1,000 mg). The delay between each step is 30-60 minutes. The first two doses should be lower (0.1-5 mg) in case of patients with histories of severe reactions. For benzylpenicillin, the intramuscular challenge starts with 10^4 IU/ml, then 10^5 IU/ml and finally 5×10^5 IU/ml, with a cumulative dose of 10^6 IU/ml [9].

As far as non-immediate reactions are concerned, the ENDA suggests to start with 1:100 of the therapeutic dose, and in case of negative responses, to administer 1:10, and a full dose; the time-interval between each dose may vary from 3 days to one week, depending on the delay between the drug intake and the adverse reaction in the clinical history [10].

3.4. NSAIDs

The DPT is considered the "gold standard" for establishing or excluding the diagnosis of hypersensitivity to acetylsalicylic acid (ASA, aspirin) and other NSAIDs [11, 12]. If positive, this test reproduces both allergic and non-allergic hypersensitivity symptoms, whereas, in case of a negative response, it allows the diagnosis of hypersensitivity to the NSAID concerned to be ruled out.

A recent review article published jointly by the GA²LEN (Global Allergy and Asthma European Network) and the EAACI [16] presented detailed protocols of oral, bronchial, and nasal ASA provocation tests, which are summarized in Table 6. This article also reviewed indications and contraindications for DPTs, as well as the rules of drug withdrawal and equipment. The present review, however, addresses only the literature regarding oral challenges with the suspected NSAIDs.

Challenge protocols for NSAIDs other than ASA, such as paracetamol, dipyrrone, diclofenac, piroxicam, indomethacin, ibuprofen, ketoprofen, mefenamic acid, and salsalate, are available in the literature [23, 58-60]. In most of these protocols [23, 58, 59], the time intervals between doses are pre-defined and, thus, do not change according to the type of reaction experienced by patients, immediate or non-immediate. On the other hand, in the study by Viola *et al.* [60], the time interval between doses is either 1 hour, in case of a previous immediate reaction, or 3-7 days (depending on the time interval between drug intake and adverse reaction), in case of previous non-immediate reactions.

In several studies [23, 58, 59, 61-65], DPTs were performed with the suspected compounds on large samples of subjects with histories of hypersensitivity reactions to NSAIDs, in order to establish a firm diagnosis. In such studies, the rate of positive responses to DPTs ranged from 4% [63] to 33.3% [58]. Specifically, in the study by Boussetta *et al.* [63], a paracetamol hypersensitivity was diagnosed in only one child, who had suffered two accelerated reactions (facial angioedema, conjunctivitis, and dyspnea with wheezing), a few months apart, 8-10 hours after paracetamol intake. In this child, an ASA challenge elicited accelerated urticaria and angioedema. Oral challenges with paracetamol were tolerated in the 24 other children, including 3 also reporting reactions to other NSAIDs. With regard to paracetamol, Kvedariene *et al.* [62] evaluated 84 patients with histories of hypersensitivity reactions to this NSAID. Overall, DPTs demonstrated paracetamol hypersensitivity in only 2 (2.45%) of the 82 subjected challenged. The remaining 2 patients were not tested because of a history of life-threatening reactions. Quirarte *et al.* [58] performed a total of 990 challenges in 240 subjects with histories of hypersensitivity reactions to NSAIDs. The order of the different drugs administered to each patient was as follows: paracetamol, isonixin, salsalate, diflunisal, mefenamic acid, clonixin, piroxicam, diclofenac, dipyrrone, ketoprofen, and ASA. Each patient underwent challenges with the first drug not involved in a previous reaction. In case of negative results, challenges with the next drug were carried out. Overall, 80 patients (33.3%) displayed positive responses to challenges with responsible NSAIDs: 52 experienced isolated periorbital angioedema, 13 cutaneous eruptions, 8 bronchial asthma (7 with associated periorbital angioedema), 3 naso-ocular reactions, and 4 anaphylactic ones. The NSAIDs most frequently positive in challenges were dipyrrone (16 of 27, 59.2%), ASA (15 of 36, 41.6%), diclofenac (19 of 54, 35.1%), ketoprofen (10 of 29, 34.4%), and piroxicam (17 of 64, 26.5%). Cross-reactivity to NSAIDs other than those involved in previous

Table 6. Aspirin Challenges (Adapted from Nizankowska-Mogilnicka *et al.* [16])

Type	Drug	Number of Doses	First Dose	Last Dose	Cumulative Dose of Aspirin	Delay between 2 Doses
Oral	Aspirin	4	27 mg	312 mg	500 mg	1.5 -2 h
Bronchial	Crystalline lysine-aspirin	8	0.18 mg	115.2 mg	181.98 mg	30 min
Nasal	l-ASA	1			16 mg	

adverse reactions (multiple intolerance) was found in most subjects. A significant ($p < 0.001$) increase in the prevalence of atopy was found among patients with isolated periorbital angioedema (100%) in comparison with other patients with NSAID hypersensitivity (45.6%). Recently, the same group [65] evaluated 223 patients with 317 documented reactions to NSAIDs performing a total of 697 challenges with an approach similar to that of the previous study. In effect, they replaced some of the previous NSAIDs with new ones. The order of the different drugs administered to each patients was as follows: celecoxib, meloxicam, paracetamol, piroxicam, diclofenac, dipyrrone, ibuprofen, and ASA. Overall, 510 (73.2%) challenges were negative and 187 (26.8%) positive; in order of frequency, ASA (in 58, 31%), diclofenac (in 51, 27.2%), piroxicam (in 35, 18.7%), dipyrrone (in 23, 12.3%), paracetamol (in 12, 6.4%), ibuprofen (in 7, 3.7%), and meloxicam (in one) were involved in positive DPTs. The authors identified 2 patterns of NSAID-induced reactions: the cross-reactive and the selective. Among the 150 subjects with the cross-reactive pattern, 40 suffered from rhinitis and/or asthma and developed naso-ocular and/or asthmatic reactions during DPTs (type 1), 59 with or without a chronic urticaria experienced urticarial/angioedematous reactions (type 2), and 51 atopic subjects developed isolated periorbital angioedema (type 3). Of the 61 patients with the selective pattern (type 4), 50 reacted to challenges with anaphylactic symptoms, while 11 with urticarial eruptions. Finally, a mixed group of reactions not matching any of above types were identified in 12 subjects.

With regard to the other studies, Messaad *et al.* [23] performed a total of 478 DPTs with suspected NSAIDs and obtained a total of 168 (33%) positive responses; the proportion of positive test results was higher for ASA (94 of 199 patients, 47.2%) and other NSAIDs (44 of 161, 27.3%) than for paracetamol (20 of 118, 17%). Lammintausta and Kortekangas-Savolainen carried out a total of 1,001 DPTs in 748 patients with suspected cutaneous drug reactions [64]. NSAIDs were used in challenges in 108 (10.7%) of the 1,001 cases, and 17 (15.7%) of the 108 were positive. ASA produced positive results in 7 (10.2%) of 68 patients; among the 36 challenges with phenazone salicylate, paracetamol, ibuprofen, and ketoprofen, 6 positive results were observed. In the study by Schubert *et al.* [59], 606 oral challenges were performed in 260 patients with histories of NSAID hypersensitivity; 55% (143 of 260) of them tolerated the suspected NSAID, while 27.7% (72 subjects) refused challenges. Overall, among the 606 DPTs only 43 (7.1%) positive reactions were observed (37 cutaneous and 6 respiratory). ASA provoked reactions in 14 (12.7%) of 110 challenges, diclofenac in 12 (12.2%) of 98, ibuprofen in 12 (12%) of 100, piroxicam in 1 (2.1%) of 47, and mefenamic acid in 1 (10%) of 10.

It is interesting to note that the clinical history is not a reliable tool in diagnosing NSAID hypersensitivity; in effect, negative results in challenges with the suspected NSAIDs have been reported, even in subjects with histories of hypersensitivity reactions to more than one NSAID [59, 63].

The present review does not include studies that performed DPTs with suspected NSAIDs in order to identify patients with true hypersensitivity reactions who underwent

further challenges with alternative NSAIDs, such as relative or selective inhibitors of cyclooxygenase-2.

3.5. Other Drugs

DPTs are essential for diagnosing hypersensitivity reactions to non- β -lactam antibiotics, such as sulfonamides, quinolones, and macrolides [66]. In fact, there are no reliable diagnostic tools for routinely evaluating hypersensitivity reactions to these drugs. Benahmed *et al.* [67] assessed 139 patients with adverse reactions to these antibiotics. Challenges allowed the authors to diagnose macrolide hypersensitivity in 8 (7.5%) out of the 107 patients who agreed to undergo such tests: 7 patients reacted to spiramycin and 1 to roxithromycin. On the other hand, intradermal tests with spiramycin at 10 mg/ml were positive in only 4 (50%) of these 8 patients.

Systemically administered glucocorticoids are sometimes responsible for non-immediate hypersensitivity reactions, mainly maculopapular exanthems and delayed-appearing urticaria/angioedema; more rarely, fixed drug eruption, exfoliative dermatitis, generalized erythroderma, and AGEP can be elicited by these drugs [14, 68].

DPTs are often necessary to evaluate non-immediate reactions to glucocorticoids. In effect, the sensitivity of patch testing and delayed-reading intradermal testing with these compounds appears to be limited. In a study by Padial *et al.* [14], only 2 of the 38 patients with non-immediate reactions to glucocorticoids displayed positive delayed-reading intradermal tests and patch tests to the responsible drugs, while 21 of the 32 patients who agreed to undergo challenges reacted to them.

Delayed-type hypersensitivity reactions to heparins are relatively common. Such reactions have been reported with un-fractionated heparins (UFHs, 10-20 kd: heparin calcium, heparin sodium), low molecular weight heparins (LMWHs, 4-6 kd: enoxaparin, dalteparin, centoparin, repivarin, nadroparin, tinzaparin), ultra low molecular weight heparins (ULMWHs, 1.7 kd: fondaparinux), and heparinoids (danaparoid sodium, glycosaminoglycane polysulfate, and pentosanpolysulfate). These reactions usually consist of erythematous, infiltrated, or vesicular (eczema-like) itchy plaques usually confined to the injection sites, but sometimes accompanied by a maculopapular rash [13, 69, 70].

A cell-mediated pathogenic mechanism has been demonstrated in patients who have delayed-type hypersensitivity reactions. In evaluating such reactions, delayed-reading intradermal tests are more sensitive than patch tests. However, subcutaneous provocation tests are considered to be the most reliable diagnostic method, because intradermal testing may produce false-negative results. Subcutaneous provocation tests are performed with 0.1 ml of an undiluted compound, and must be read until the fifth day [13].

Delayed-type hypersensitivity reactions to UFHs, LMWHs, ULMWHs, and heparinoids following subcutaneous tests show a high degree of cross-reactivity [70, 71]. However, a prospective study by Gaigl *et al.* [71] proved that an intravenous heparin challenge was tolerated by all the 28 subjects with a well-demonstrated delayed-type hypersensitivity to subcutaneous heparin who displayed a high degree

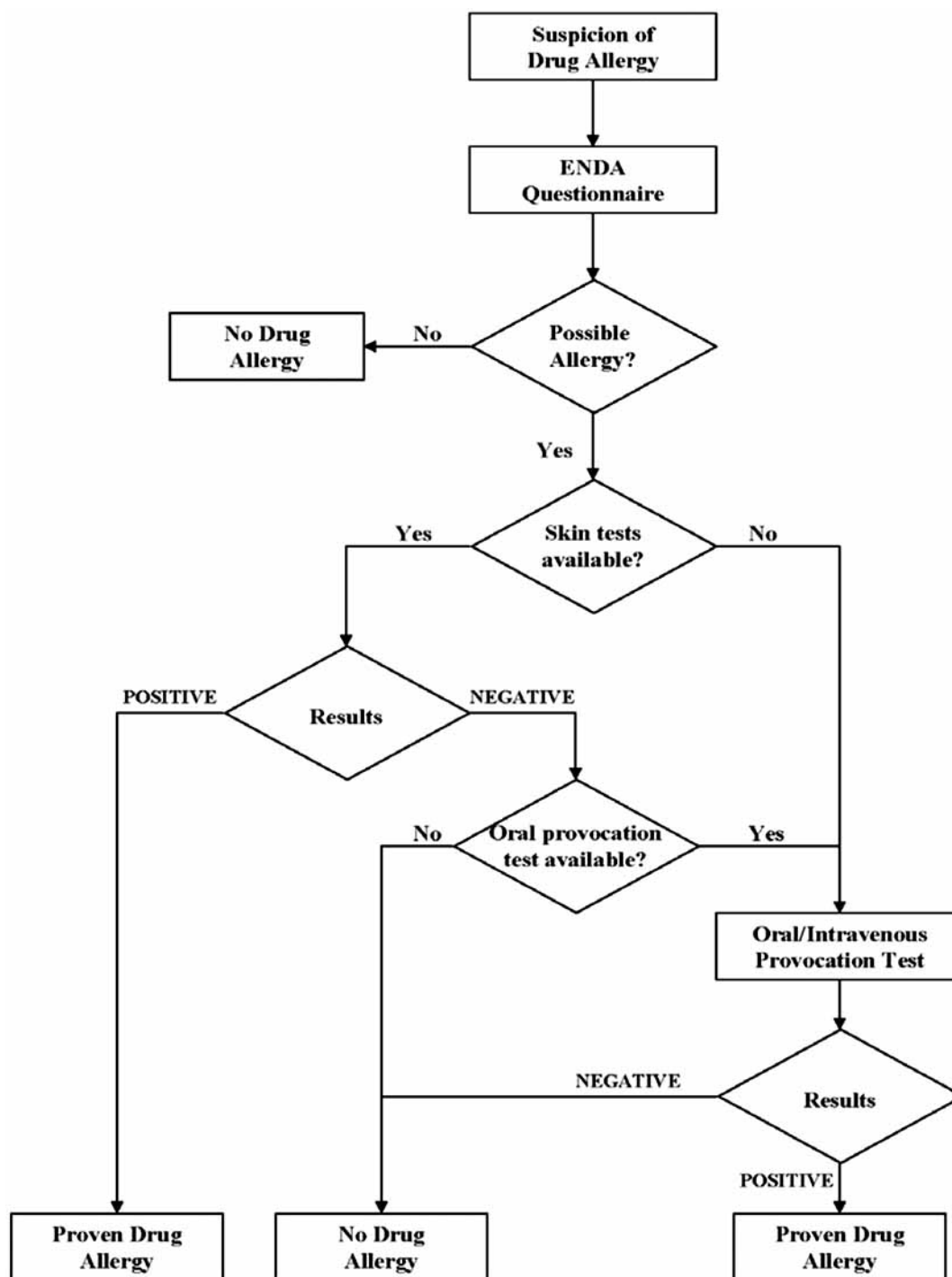


Fig. (1). Assessing drug allergy/hypersensitivity.

of cross-reactivity. Therefore, the authors concluded that, in urgent cases, heparin can be given intravenously without prior testing. The UFH, heparin sodium, was administered intravenously in a dose of 2,500 IU as a bolus on day 1 and 5,000 IU as a bolus followed by 7,500 IU for 6 hours on day 2.

DPTs have been also used in the diagnosis of hypersensitivity reactions to iodinated contrast media (ICM). In a study on 204 patients with histories of anaphylactic reactions to ICM [72], all subjects underwent an intravenous infusion

(pre-test), in which serial dilutions of the specific ICM to be used in the proposed radiographic study were given by intravenous push at 15-minute intervals; 36 (17.6%) reacted to the pre-test. Overall, 183 patients underwent ICM procedures, and 28 (15.3%) reacted to them. The highest incidence of reactions (66.7%, 12 of 18 ICM procedures) was observed among the patients with positive pre-tests.

Vernassiere *et al.* [73] assessed 15 patients with delayed reactions to ICM, such as iodixanol, ioxaglate, iobitridol, iohexol, and iomeprol, by performing patch and intradermal

tests with several compounds, including responsible ones. Patch tests were positive in 2 of the 15 patients, while intradermal tests were positive in 8; 5 of 12 subjects reacted to the administration of a compound found to be negative in intradermal and patch testing.

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