

Drug provocation tests in hypersensitivity drug reactions

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Purpose of review

Drug provocation test (DPT) is necessary to diagnose most drug hypersensitivity reactions (HSRs) due to decreased sensitivity of skin testing even when combined with in-vitro tests in immunologic drug HSR and limited availability of these tests in nonimmunologic reaction. We review the principles and controversial issues of DPT, and recent studies using DPT as a diagnostic tool.

Recent findings

DPT is recommended in the diagnosis of HSR to β -lactams, as well as other drug classes [such as acetylsalicylic acid-NSAIDs (ASA-NSAIDs), non- β -lactams antibiotics, heparin, glucocorticoids, and local anesthetic agents]. In view of the decreased sensitivity of skin testing, limited accessibility to new benzylpenicillin polylysine (PPL)/mixture of minor determinant (MDM) test reagents and limited availability of validated sensitive in-vitro tests, individuals who require DPT to β -lactams are increasing. The negative predictive value of allergologic work-up is very high, ranging from 94 to 98% for β -lactams and those reactions after negative tests are mostly nonimmediate and mild. Finally, DPT is recommended to ascertain tolerability of alternative compound when evaluating cross-reactivity among different classes of β -lactams, NSAIDs and glucocorticoids, and possibly iodinated contrast media.

Summary

DPT is often needed when evaluating patients with suspected drug HSR. More studies regarding standardization of the various protocols are needed in order to increase its acceptance and adoption as a standard practice in the diagnostic algorithm for drug HSR.

Keywords

β -lactams, cross-reactivity, drug hypersensitivity, drug provocation test, negative predictive value

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Introduction

Evaluation of a drug hypersensitivity reaction (HSR) is necessary, as cutaneous eruption during pharmacotherapy may or may not be due to the drug. This procedure should be able to prove or exclude the drug as the cause of the HSR, as well as to offer well tolerated alternatives, and possibly give insight to the underlying pathomechanism. The diagnostic work-up for drug HSR involves a step-wise procedure, beginning with clinical history, then proceeding with any of skin testing, in-vitro test, or drug provocation test (DPT) depending on the type of drug and type of HSR [1]. In this review, we summarize the general principles of DPT and some controversial issues, as well as review recent publications performing DPT as a diagnostic tool in different drug classes.

General principle of drug provocation test

A DPT is the controlled administration of a drug in order to establish or exclude diagnosis of drug HSR.

It permits testing of a patient with his or her individual metabolism and immunogenetic background, and reproduces both allergic and nonallergic symptoms, but usually with milder severity than the initial reaction because of the slow incremental dose escalations of the drug under close medical supervision [2–4]. Establishment of drug HSR is usually made when DPT reproduces the identical clinical symptoms and signs to the previous index reaction [5]; thus it is considered as the ‘gold standard’ in the diagnosis of drug HSR. However, many limitations exist, in particular the possibility of a severe and uncontrollable relapse of the reaction. Therefore it should be reserved when an important drug group is suspected to have provoked a HSR, when alternative test methods have failed to yield conclusive results, and in the absence of contraindications. Moreover, all procedures must be performed under strict medical surveillance in the presence of trained personnel [2]. For more detailed reviews on how to perform DPT, readers are referred to previously published guidelines and reviews [2,3,6].

When validated skin tests are available, a positive result helps to confirm the drug as the causative agent for drug HSR, and DPT to alternative drugs can be offered [7]. Unfortunately, the sensitivity of most skin tests is not 100% (e.g. β -lactams, heparin, glucocorticoids and macrolides) [8], and negative skin tests to these medications requires DPT to confirm the absence of drug HSR [9]. For other drug classes in which skin and in-vitro diagnostic methods are ineffective [i.e. acetylsalicylic acid-NSAID (ASA-NSAIDs) HSR] or unreliable because of false positive or local irritation (e.g. local anesthetics and quinolones), DPTs are often carried out to diagnose HSR to these drugs. Altogether, DPT is the 'gold standard' test method to establish a definitive diagnosis of drug HSR in most instances [9].

Differentiation between drug provocation test, graded challenge and drug desensitization

A DPT is a diagnostic procedure performed when the patient is in a good state of health with no sign of active disease in order to find a well tolerated drug potentially useful for the patient in the future [2,6]. Graded challenge and drug desensitization, however, are therapeutic procedures, and are likely to be performed at the time that the patient requires immediate treatment with the medication in question. As indicated in the recent US-updated practice parameter on drug HSR, graded challenge should be carried out in patients who are unlikely to be allergic to the drug with no intention to induce tolerance. Thus patients who tolerate a graded challenge are considered not to be allergic to the drug [10]. However, when a patient has a relatively higher likelihood of being allergic to a drug, drug desensitization (or an induction of drug tolerance) should be considered [10]. This procedure allows temporary modification of a patient's immune response to safely tolerate the drug as long as the patient continues to take the specific drug. However, this latter procedure does not provide the confirmation or refute the diagnosis of drug HSR, and the procedure has to be repeated every time the patient requires treatment with the drug or its potentially cross-reacting medication.

Patients suitable for graded challenge or desensitization are those with HIV infection, cystic fibrosis, or tuberculosis [11], in whom an immediate re-introduction of antibiotherapy/prophylaxis is required, and in cancer or rheumatology patients who have experienced immediate HSR to their first-line chemotherapy or monoclonal antibody, when no effective alternative drugs are available [12,13].

Drug provocation test to specific drug groups

Because DPT contributes in diagnosis of each drug differently, we summarized recent publications performing diagnostic DPT according to drug class.

Key points

- Drug provocation test (DPT) is a diagnostic procedure to confirm or exclude the drug as a cause of hypersensitivity reaction, as well as to assess the tolerability of alternative compounds.
- For β -lactams, because of decreased overall sensitivity of skin tests and limited accessibility to new commercial PPL/MDM, DPT is needed in diagnosis and evaluate cross-reactivity among different class of β -lactams.
- Acetylsalicylic acid-NSAIDs challenge remains a gold standard test in diagnosis of ASA-NSAIDs sensitivity, and safety is of particular concern in patients presenting with respiratory symptoms.
- Concerning rare prevalence of true immediate allergy to glucocorticoid and local anesthetic drugs, DPT should be included in diagnosis of immediate reaction to these compounds.
- Despite controversies of DPT, this procedure produced a very high negative predictive value as well as acceptance by patients submitted to DPT. Generalization of DPT should be encouraged, together with the effort to standardize the protocols.

β -Lactams

Since the 1970s, amoxicillin and cephalosporin have been increasingly prescribed to replace benzylpenicillin. This has led to an increasing role of their side-chain structures as specific determinants [14], whereas the accountability of major and minor determinant of benzylpenicillin is markedly decreased, apparently from over 70 to 30% [15]. The current recommended skin test battery for β -lactams comprises a combination of major, minor determinant of benzylpenicillin (including penicillin G), and side-chain structures (i.e. amoxicillin, ampicillin, and culprit drug such as cephalosporin) [14], with overall test sensitivity of about 70% [16]. The number of patients requiring DPT to confirm β -lactam allergy tends to increase as 15% of patients with positive penicillin skin tests respond exclusively to PPL and/or MDM [17] and would need DPT because of the limited accessibility to the new PPL/MDM material (Diater, Madrid, Spain) or PPL (Prepen, AllergQuest LLC/ALK-Abello). However, serum-specific IgE tests may be able to diagnose up to 13% of skin test negative patients and therefore reduce the need of DPT [15,18]. According to the European Network on Drug Allergy (ENDA) recommendation, DPT should be included in the diagnostic algorithm of both immediate and nonimmediate reaction to β -lactams [19,20], and an improvement on in-vitro tests is needed in order to reduce the need of DPT [14]. This statement can be applied to cephalosporins as well. Even though several studies conducted in a limited number of patients have

revealed that the sensitivity of skin testing seemed to be higher than that of penicillin, ranging from 76 to 85%, a DPT is still needed [21–23].

With regard to delayed urticaria and maculopapular exanthema from aminopenicillin, the value of skin testing in these cases is very low [24–26], as 4–9% of cases confirmed by DPT have a delayed intradermal skin test (IDT) or patch test positivity [24,25]. Moreover, in most instances, exanthema appearing in the course of drug treatment is due to other causes [27,28]. Among children, a recent study [22] regarding nonimmediate reaction to cephalosporin has demonstrated similar results, with low reproducibility of the reaction (two out of 105; 2%), one detected by positive response to skin tests, and another by positive DPT. In particular situations with non-cooperative young children (only 47 out of 161; 29% of children accepted skin testing in one study), DPT without previous skin testing was considered a relatively well tolerated procedure in children with a history of mild cutaneous eruption to β -lactams [29]. However, further studies in large numbers of patients and in different age groups are required before the safety of this approach can be established.

Negative predictive value of drug provocation test

Rate of resensitization (i.e. conversion to skin test positivity) from β -lactam skin testing was considered to be less than 1% [30]. However, Goldberg and Confino-Cohen [31] have demonstrated a high rate of conversion to skin test positivity in 27.9% of patients retested 2–6 years after the initial allergologic work-up. Interestingly, most patients with positive skin tests in this study tolerated DPT, and positive predictive value (PPV) of skin tests was only 2–10%, which limited the clinical significance of this study. Moreover, in patients with negative initial work-up, 52 (95%) out of 55 patients actually tolerated courses of penicillin therapy without reaction before the repeated testing was performed. High negative predictive value (NPV) of β -lactam DPT of 98 and 94% has been confirmed in other large studies involving 256 children (by Ponvert *et al.* [32]), and 457 patients (by Demoly *et al.* [33]), respectively, and most of the reactions reported by patients were nonimmediate and not severe. This information should reassure the patients and their doctors in prescribing drugs with negative work-ups.

Booster or anamnestic response

The condition usually confused with resensitization is a booster or anamnestic response, which is a conversion to skin test positivity in patients who were actually allergic to the drug but presented initially with negative allergologic work-up. This condition appears to occur mainly in patients who have experienced immediate reaction to β -lactams, as skin test or specific IgE negativization has been observed in patients retested after at least 1 year

[34]. Despite ENDA recommendation to re-evaluate patients with a positive history and negative tests, 2–4 weeks after initial work-ups, studies concerning its prevalence were lacking [14]. Prevalence of positive β -lactam skin tests of 1.8% (10 out of 548) in patients retested 2–4 weeks after negative initial tests has been observed by Matheu *et al.* [35]. Recently, Gallego Segovia and García Dumpiérrez [36] reported a patient with a history of anaphylaxis to penicillin, initially presenting with negative allergologic work-up, including DPT, who subsequently developed an anaphylactic reaction during repeated skin testing 2 weeks later. This patient was the only case from 145 confirmed penicillin allergy cases during a 15-year period (prevalence of 0.7%) at this center [36]. However, in our opinion, this recommendation should be considered only in those cases with previous severe reaction, when no other agents can be found responsible for the reaction [36], and particularly when evaluating patients with immediate reactions to cephalosporins [21]. In contrast, repeat testing after negative challenges in nonimmediate reaction to β -lactam is not advised [20].

Assessment of cross-reactivity

A search for well tolerated alternative β -lactams is recommended when β -lactam allergy has been diagnosed [14]. Although the skin tests and in-vitro tests seemed to detect most of the patients who might cross-react with the alternative β -lactam [37,38], these are not sufficient, and a DPT is still needed to confirm their tolerability [39]. Consistent with this statement, Caimmi *et al.* [7] have recently indicated that in 143 confirmed penicillin/cephalosporin allergy cases, cross-reactivity to cefuroxime was detected by positive skin tests in three patients, and by DPT in six patients. Romano *et al.* [40**] also investigated cross-reactivity to penicillins, carbapenems, and/or aztreonam in 98 patients with confirmed IgE-mediated HSR to cephalosporin, and a positive DPT to imipenem was demonstrated in one of 97 patients after negative skin tests.

Acetylsalicylic acid-NSAIDs

The DPT is considered the ‘gold standard’ in the diagnosis of HSR to ASA-NSAIDs, considering the absence of effective skin tests or in-vitro tests, except for IgE-mediated reaction to dipyrone [41,42]. Because of a variety of clinical presentation of ASA-NSAIDs HSR (respiratory, cutaneous or anaphylaxis, and single or multiple reactors), reliability of clinical history is difficult to assess, and certain number of patients require DPT to confirm or refuse diagnosis [43**]. However, for those with typical presentation (such as asthmatic reaction, multiple reactions to multiple NSAIDs, or anaphylaxis to single NSAID) [44,45**], DPT is needed to confirm tolerability of alternative compounds, particularly to

strong cyclo-oxygenase (COX) inhibitor in single responder [45**].

Regarding aspirin-exacerbated respiratory disease (AERD), performing ASA-NSAIDs DPT requires special concern with respect to safety. Clinical analysis of 420 patients with AERD by Hope *et al.* [46] has demonstrated the risk factors associated with significant bronchial hyper-responsiveness [i.e. a decrease in force expiratory volume in 1 second (FEV1) $\geq$ 21%] during ASA challenge were the following: leukotriene-modifying drug (LTMD) nonuse at the time of challenge, baseline FEV1 of less than 80% of predicted value and a history of emergency department visit for asthma. Considering that 74% of the reactions occurred after the administration of 45 or 60 mg of ASA, the starting dose of 40 or 60 mg of ASA was proposed in patients with suspected AERD with no major risk factors, provided that they all receive an LTMD.

Iodinated contrast media

Skin tests are a useful tool in the allergy work-up of HSR to iodinated contrast media (ICM), but data concerning their NPV are scarce. Caimmi *et al.* [47] recently addressed this issue involving 120 patients tested for a compatible clinical history of ICM-induced HSR; 29 patients with initial negative skin tests needing a new ICM injection were re-challenged without premedication. One patient out of 24 with a history of immediate and one out of four with history of nonimmediate reaction presented with mild reactions upon re-challenge. Two positive ICM skin test patients tolerated an alternative ICM without any reaction. Overall, the NPV of skin testing for ICM was 96% and none of the reactions was severe. However, further studies in larger number of patients are required. Due to the weak level of evidence, certain authors recommend a controlled re-administration of the ICM found to be negative in skin test, under hospital surveillance in order to reassure its tolerability. Seitz *et al.* [48] followed this approach in six out of 32 patients who had proven delayed immunologic mechanism by IDT or patch test to ICM. Two of them demonstrated skin test positivity to all agents tested, whereas in the remaining four, negative skin test results were confirmed by controlled challenges.

Glucocorticoids

Systemically administered glucocorticoids are rarely responsible for immediate reactions, despite their widespread use. It seems logical that the allergy work-up in such cases follows the general guidelines. However, the sensitivity of skin testing is limited, and DPTs are needed in order to diagnose and to assess tolerability of alternative glucocorticoids. Several investigators have performed SPT/IDT and DPT to confirm immediate HSR to methylprednisolone, and to demonstrate good

tolerability of alternative glucocorticoids, such as hydrocortisone and dexamethasone [49–51].

Local anesthetics

Prevalence of true immediate allergic reaction to amide-type local anesthetics is considered rare, and requires confirmation with subcutaneous challenge. Fuzier *et al.* [52] gathered cases from two large databases, namely the French Pharmacovigilance and GERAP (study group of perianesthetic anaphylactoid reactions). Of 16 cases documented as allergic to amide-type local anesthetics, only three underwent DPT to establish the diagnosis; two with immediate reaction to lidocaine, and one with delayed urticaria to mepivacaine who displayed cross-reactivity with other amides (lidocaine and bupivacaine). Another study by Harboe *et al.* [53] investigated 135 patients suspected of allergic reactions to local anesthetics. Skin testing was negative in all patients and 118 patients (87%) underwent subcutaneous challenge tests, with one (0.8%) displaying positivity for articaine. The frequency of the HSR to local anesthetics, including their additives, could have been underestimated, because 61% of the challenge did not include the culprit local anesthetic compound. In such cases, DPTs can merely demonstrate tolerance to an alternative drug, whereas uncertainty persists with regard to suspected local anesthetics.

Controversial issues of drug provocation test

Despite the importance of DPT in the evaluation of drug HSR, the acceptance among allergists and availability of DPT are still limited, whereas DPT is increasingly performed in selected specialized centers and is recommended by the European society [2], but rarely mentioned in US guidelines [10]. Concerning patients' perception of diagnostic DPT, recent data collected from three centers in Europe ($N=217$) have revealed that most patients accepted DPTs for diagnostic purpose irrespective of the test results, and 95% of them believed that DPTs were useful and they would recommend DPT to others [54]. Waton *et al.* [55•] surveyed patients' opinions regarding allergologic work-up; 223 of 283 (79%) patients agreed to undergo these tests again if required, and 88% of them thought that the tests were useful.

Conclusion

Drug provocation test is still needed in diagnosis of most drug HSRs as well as to assess tolerability of alternative compounds. Despite increasing studies demonstrating the role of DPTs as a diagnostic method, very few emphasize standardization of the protocol. This is associated with a variety of protocols from different centers and sometimes with different tests results. In order to increase the acceptance of DPT and its adoption as part

of a standard diagnostic algorithm in evaluation of drug HSRs, standardized protocols are needed.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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This study evaluated NPV of diagnostic methods, and demonstrated patients' opinions using questionnaire regarding the usefulness of the tests and the willingness to retest if required.