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Drug Allergy (MJ Torres Jaén, Section Editor)

How Can We Influence the Performance of Drug Challenge in Future Treatment

Aslı Gelincik, MD[1]
Gülfem E. Celik, MD[2,*]

Address
[1]Department of Internal Medicine, Division of Immunology and Allergy, Istanbul University School of Medicine, Istanbul, Turkey
[*,2]Department of Chest Diseases, Division of Immunology and Allergy, Ankara University School of Medicine, Ankara, Turkey
Email: gulfemcelik@gmail.com

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Abstract

Drug provocation tests are assumed to be the gold standard of drug allergy workup by ensuring the most objective results in clinical observation irrespective of the underlying mechanism of the reaction. Despite its some disadvantages, it is still one of the cornerstones of the drug allergy diagnosis. In this review, new methods for improving diagnostic accuracy of drug provocation tests will be discussed. In this sense, extended challenges are recently shown to have better outcome especially in diagnosing non-immediate reactions due to antibiotics. In children with non-immediate mild cutaneous reactions, provocation tests are becoming to take place of skin tests with promising results. Furthermore, drug provocation tests have been shown to prevent unnecessary desensitization protocols in newly developed drugs such as biological agents. These new data on diagnostic performance of drug provocation test seem to influence the future treatments in patients with drug hypersensitivity reactions.

Introduction

Drug hypersensitivity reactions (DHRs) are undesired conditions following the use of a drug and account for 5–10% of all adverse drug reactions [1–3]. DHRs are classified as immediate or non-immediate depending on their onset during a treatment. Immediate reactions are mainly induced by an IgE or IgG and complement-mediated mechanisms and typically occur within 1 h to as much as 6 h after first dose of the last drug administration. Non-immediate reactions are associated with T cell-dependent mechanisms and occur 1 h after the initial drug administration, but more typically multiple hours to days in sensitized patients [1–3].

The diagnostic workup for drug allergy includes a detailed and accurate history, physical examination and in vivo tests such as skin prick tests (SPT), intradermal tests (IDT), and drug provocation tests (DPTs) [4, 5•, 6•, 7•]. The diagnostic value of in vitro tests is limited; however, some encouraging results have been obtained by certain drugs [8]. Limitations have also existed with skin prick tests and only a few drugs yield acceptable sensitivity and specificity [5•]. Therefore, when the value of these diagnostic tools is limited especially obscured underlying pathogenetic mechanism is considered, DPTs seem to be the "gold standard" in diagnosing drug allergy.

A DPT is a controlled graded administration of either a culprit drug to confirm the diagnosis of drug allergy or an alternative drug to show the tolerability of that drug. DPTs usually decrease the cost of drug allergy algorithms by reducing the need for expensive and advanced laboratory tests and by avoiding unnecessary drug desensitizations [1–3, 6•]. The Pediatric Task Force of the EAACI Drug Allergy Interest Group suggested clinicians to apply DPTs without prior skin testing in non-immediate mild cutaneous reactions, and in this way, the usage of painful skin tests in younger age is reduced which may also cease the cost of drug allergy algorithm [9••]. Furthermore, in case of antibiotic hypersensitivity, the disadvantage of using broad-spectrum antibiotics is prevented by this procedure. DPTs are valuable to present the cross-reactivity in hypersensitivity reactions with antibiotics as well as with non-steroidal anti-inflammatory drugs (NSAIDs) thus further help to classify patients with NSAID hypersensitivity [10, 11].

DPTs are used as a diagnostic cornerstone for several drugs such as beta-lactam antibiotics, some other antibiotics, NSAIDs, local anesthetics, and proton-pump inhibitors especially when the weakness of history and skin tests are considered [7•, 12••]. Regardless of the underlying mechanism, it is the most objective method to reproduce the reaction during a clinical observation.

Although DPTs serve as a conformative tool for the clinician, it has some disadvantages too [7•]. Safety is one of the most important issues since the reproduced reaction can be life-threatening especially when applied with culprit drugs. Therefore, this procedure is only permitted in close clinical supervision in trained centers. Resensitization is mostly a theoretical but a possible outcome of the procedure. Lack of conclusive symptoms in certain cases can also be challenging to interpret. Standard protocols for some drugs resulting to non-immediate reactions and objective biomarkers are also lacking. Some severe reactions like vasculitis syndromes, bullous exanthemas, drug-induced hypersensitivity syndromes, and severe anaphylaxis or patient-related factors such as uncontrolled asthma and pregnancy are some contraindications for the procedure. Furthermore, in the case of general anesthetics, due to the pharmacological effects of these drugs, DPTs are not recommended [7•].

In this review, some new methods of DPTs for widely used drugs such as beta-lactam antibiotics and DPT protocols for recently developed drugs such as biologicals will be discussed in the light of already known facts.

Long-term tolerability after a negative DPT with single therapeutic doses

In traditional methods, DPT involves the administration of a total single therapeutic dose in divided administrations. However, it is of interest to see the drug's tolerability in long-term use. A few number of studies addressed this question and showed that this method had highly acceptable results owing to its high negative predictive value (NPV) [13, 14]. In this sense, Celik et al. studied the outcome in future administrations of alternative COX-2 inhibitors evaluated with single therapeutic doses in DPT in 87 patients with NSAID hypersensitivity [13]. In 54 (89%) out of 61 users, the drug(s) were well-tolerated in long-term use whereas 7 (11%) reported various adverse events in long term. Three patients reporting adverse events were re-challenged with the responsible COX-2 inhibitor and their results were negative. Another study

performed in 203 children mainly allergic to beta-lactam antibiotics also supported these findings [14]. In this study, although 11 (12%) children had allergic reactions in history in long-term use, only 2 of 9 cases had a reaction in re-challenge. In another study, 457 patients with either immediate or non-immediate reactions to beta-lactams were evaluated at least 6 months after a reaction, and their drug allergy workup yielded a NPV of DPTs with beta-lactams as 94.1% [15]. In children, Capanoglu et al. found that NPV of DPTs with diverse drugs was 95.6%, and the NPV of DPT with NSAIDs was even higher (97.8%) [16].

All these studies indicate that although DPT with single therapeutic dose is generally sufficient for predicting safe drug in future need, it is not suitable for every patient. The absence of some crucial factors, such as concomitant medication use, viral infections, physical exercise, and initial psychological status, during the test procedure may influence this result.

New methods of DPTs: extended challenges

DPT with single therapeutic doses is a safe practical method for determining particularly the immediate reactions. However, concerning the non-immediate reactions conflicting results are obtainable. T cell-mediated drug reactions can occur either in the first dose or after repeated doses, and the latter condition is usually caused by cumulative doses of a drug [17]. Recently, the safety of a 1-day protocol for immediate and some mild non-immediate reactors of beta-lactams by following the patients for 48 h was studied. Half of the patients experienced symptoms during the first day, and 57% of these cases had symptoms within 1 h of the drug administration. In 95% of all cases, reaction times matched with the original reactions when reactive time points were arranged as 24, 48, and 72 h [18]. On the other hand, there is also contradictory evidence in the literature. Borch et al. performed a 10-day penicillin provocation test to patients who had reacted on day 2 or later and found that half of the patients experienced a cutaneous reaction mostly urticaria on day 6 on average [19]. In another study performed in children with non-immediate hypersensitivity reactions to amoxicillin, a 5-day DPT was found to increase the sensitivity of the allergy workup where approximately one third of the patients reacted on day 5 [20]. Similarly, in another study, a 7-day challenge protocol yielded more positive reactions (11.4%) than a single-dose protocol (2%) in penicillin allergic patients [21]. Lezmi et al. showed that among 550 children reporting reactions to a single or several beta-lactams (674 suspected beta-lactams), non-immediate hypersensitivity to beta-lactams was diagnosed in 63 children (11.5%), DPT positivity after a median time of 3 days. No severe reaction was observed after ST or during prolonged DPT [22]. Furthermore, patients allergic to penicillin who underwent a prolonged DPT (78%) were satisfied and used the drug after diagnostic workup than those underwent a single-dose DPT (61%) [23].

DPTs before skin tests

Traditionally, in drug allergy, workup guidelines recommend DPT if skin tests are negative. However, recent studies particularly performed in children suggested that DPT can be done prior skin testing in non-serious

antibiotic allergy. In this sense, Mill et al. studied 818 children with suspected allergy to amoxicillin and a graded OPT with amoxicillin without prior skin testing was administered. Ninety-four percent of the patients tolerated the amoxicillin challenge whereas only 2 and 4% had an immediate and a non-immediate reaction, respectively. The positive reactions during the challenge were mild and presented with only skin manifestations [24]. Similarly, Vezir et al. studied the outcome of DPTs without prior skin tests in patients with non-immediate mild cutaneous reactions caused by beta-lactam antibiotics. The study assessed 184 children admitted to the hospital with compatible history of beta-lactam hypersensitivity in 1 year, and 135 (73.3%) of them had a non-immediate reaction. Only four (3.4%) out of 139 patients experienced a mild urticarial rash without concurrent systemic symptoms [25]. The authors concluded that omitting skin tests before oral provocation tests may help to increase compliance to diagnostic workup in this age group by alleviating their discomfort, prevent overdiagnosis, and also decrease the economic burden of drug allergy workup. Furthermore, a recent systematic review from Marrs et al. also recommended that suspected non-serious antibiotic allergy in children should be primarily investigated using DPT-based clinical protocols [26].

DPTs for new drugs

Monoclonal antibodies with their rapidly expanding samples are newly developed promising targeted biological agents used mainly in cancer and various chronic inflammatory diseases. In contrast to small chemical drugs, these drugs with their protein structures are potentially immunogenic and cause hypersensitivity reactions especially the ones with sequences of murine origin [27].

These agents are usually used in advanced diseases where other therapeutic options have already been applied and clinical improvements are in need. Cytokine release syndrome and IgG- or IgE-related hypersensitivity reactions are the reported immediate type hypersensitivity reactions whereas serum sickness-like reactions, vasculitis, toxic epidermal necrolysis, and bullous exanthemas are non-immediate hypersensitivity reactions [27, 28].

Skin prick tests are recommended to be followed by intradermal tests. A positive skin test result to a non-irritating concentration of the drug in a patient with an immediate hypersensitivity reaction strongly suggests an IgE-mediated mechanism, and the drug can only be re-applied through desensitization. On the other hand, in patients with negative skin test results if the initial reaction is mild or moderate, a provocation test is suggested whereas desensitization is the method to be used in patients with positive test results [27].

DPTs are not standardized for biological agents. As a general rule, a graded challenge, starting with one tenth of the target infusion rate for 15 min is followed by the target infusion rate according to the manufacturer's instructions, is recommended [27]. DPT is used in grade 1 and grade 2 immediate hypersensitivity reactions related to cytokine release or IgG-mediated mechanisms whereas in grade 3 reactions and the IgE-mediated ones, desensitization is carried on.

Recently, Alvarez-Cuesta et al. suggested to use DPTs prior desensitizations in appropriate patients. In their prospective longitudinal study, 104

(56%) out of 186 hypersensitive patients to antineoplastic drugs and biological agents underwent DPTs [12••]. DPTs were undergone at the patients' next scheduled treatment visit as standard regimes in the full dose of the culprit drug according to manufacturer instructions. Additional premedications were not used if not indicated in the instructions. After a positive DPT, a hypersensitivity reaction was immediately treated, and when resolved, a "restart protocol" with incremental doses of infusion was applied. Forty percent of taxanes, 32% of platins, and 30% of biological agents showed a negative DPT, and therefore DPT seemed to prevent further unnecessary desensitizations in the study population. Four of 37 patients with a positive DPT experienced a severe reaction which needed adrenaline intramuscularly and recovered within 30 min. Seven patients with positive skin tests to chemotherapeutics showed a negative DPT. The authors concluded with the importance of DPT in hypersensitivity reactions with neoplastic drugs and biological agents prior desensitizations.

In patients with hypersensitivity reactions due to indispensable drugs such as chemotherapeutics or biological agents, the risk-benefit ratio usually implies the clinicians to apply the culprit drugs. Standard challenge protocols evaluated with multicenter studies are in need for new therapeutic drugs in such patients.

In conclusion, although there are still some limitations, DPT is still the gold standard for diagnosis of DHR. Introduction of new methods such as extended provocations with several doses instead of single therapeutic doses provides encouraging results particularly for DHR derived by T cell-mediated non-immediate reactions. Moreover, there are also data suggesting that DPTs before desensitizations with certain drugs such as biological agents or chemotherapeutics might prevent further unnecessary desensitizations. These new data on diagnostic performance of DPT seem to influence the future treatment in patients with DHR.

Conclusion

Drug hypersensitivity reactions consist of a heterogeneous group of immunologic reactions. Patient's history and physical examination are the key diagnostic steps for drug allergy workup whereas skin tests can have limited value especially in non-IgE-mediated reactions. Therefore, drug provocation tests are considered as the gold standard of diagnosis of drug allergy irrespective of the underlying mechanism of the reaction. Experts are introducing new challenge methods for some common drugs as well as the importance of these tests for newly introduced drugs is growing in the allergy workup. Extended challenges as an example better resemble real-life reactions especially in non-immediate hypersensitivity and have been used for only beta-lactam antibiotics so far. Since skin tests with some new drugs such as biological agents pose limited value, the decision of desensitization is usually taken depending only on patients' history which can probably be prevented by provocation tests in suitable patients. Additionally, patients' psychological behaviors are becoming one of the key issues in drug allergy, and provocation tests help these patients to overcome their anxiety in most circumstances. Therefore, in future drug allergy

management, the provocation tests will still be one of the cornerstones, and studies standardizing the provocation tests for different drug groups will help the clinicians to manage difficult cases.

Compliance With Ethical Standards

Conflict of Interest
Aslı Gelincik declares that she has no conflict of interest.
Gülfem E. Celik declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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