

Outcomes and safety of drug provocation tests

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ABSTRACT

Drug provocation tests (DPTs) are considered the gold standard for identifying adverse drug reactions (ADRs). The aim of this study was to analyze DPT results and discuss severe systemic reactions associated with them. This was a retrospective analysis of 500 patients with ADRs who sought treatment and were submitted to DPTs when indicated between 2006 and 2010. We performed DPTs according to the European Network for Drug Allergy recommendations. Single-blind, placebo-controlled DPTs were performed with antibiotics, local anesthetics, and nonsteroidal anti-inflammatory drugs, as well as with other drugs. Patient characteristics, DPT results, and reactions were analyzed. The sample comprised 198 patients (80.8% of whom were female patients) submitted to 243 DPTs. Ages ranged from 9 to 84 years (mean, 39.9 years). The 243 DPTs were performed with local anesthetics (n = 93), antibiotics (n = 19), acetaminophen (n = 44), benzydamine (n = 33), COX-2 inhibitors (n = 26), dipyrone (n = 7), aspirin (n = 4), or other drugs (n = 17). The results of 4 tests (1.6%) were inconclusive, whereas those of 10 (4.1%) revealed positive reactions to antibiotics (2/19), COX-2 inhibitors (2/26), acetaminophen (3/44), and local anesthetics (3/93). Two severe reactions were observed: cephalexin-induced anaphylactic shock and bupivacaine-induced anaphylaxis without shock. Four patients (2.0%) reacted to the placebo before administration of the drug. Drug provocation tests are safe for use in clinical practice but they should be placebo-controlled and should be performed under the supervision of an allergist. To confirm a presumptive diagnosis and to manage allergies appropriately, it is crucial to perform DPTs.

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Hypersensitivity reactions are unpredictable adverse drug reactions (ADRs) to drug doses that are well-tolerated by most individuals. These can be immune-mediated (allergic) or nonimmune-mediated (nonallergic) reactions.¹ The diagnosis of an ADR is based on the taking of a detailed clinical history and on physical examination, together with one or more of the following procedures: skin tests, drug provocation tests (DPTs), and laboratory tests.^{2–6}

A DPT is defined as the controlled administration of a drug with the purpose of diagnosing a hypersensitivity reaction. Other names by which DPTs are known include drug challenge tests, reexposure, and tolerance tests.⁵ They are considered the gold standard for establishing or excluding the diagnosis of hypersensitivity to a given drug.⁵ In addition to reproducing the allergic symptoms, DPTs reproduce any clinical manifestation of hypersensitivity, regardless of the mechanism involved.⁵

In comparison with other diagnostic tests, DPTs have the advantage of allowing the clinical relevance of a given reaction to be determined. However, DPTs

should only be performed if the diagnosis can not be made with any other, safer, method and if the benefits outweigh the risks of a new reaction.^{5,7}

According to the European Network for Drug Allergy (ENDA) of the European Academy of Allergology and Clinical Immunology, DPTs should be performed in the following situations: to rule out hypersensitivity reactions in cases that are not highly suggestive of such; to rule out cross-reactivity; to confirm the diagnosis when the patient history is suggestive of hypersensitivity reaction and the remaining test results are negative, inconclusive, or unavailable; and to provide a safe therapeutic alternative.⁵

The principal relative contraindications to DPTs are as follows: pregnancy; acute infections; unstable kidney, liver, or heart disease; and uncontrolled asthma. However, DPTs are absolutely contraindicated in cases of severe, potentially fatal adverse reactions such as anaphylaxis, cellular immune reactions (cytotoxicity), vasculitis, exfoliative dermatitis, Stevens-Johnson syndrome, drug rash with eosinophilia and systemic symptoms syndrome, toxic epidermal necrolysis; and drug-induced autoimmune diseases.⁵

There have been few studies investigating DPTs, considering that drug allergy is one of the most common reasons for consultation in allergy/immunology.^{8,9} Therefore, the objective of the present study was to describe DPT results in patients with a history suggestive of hypersensitivity, as well as to address issues

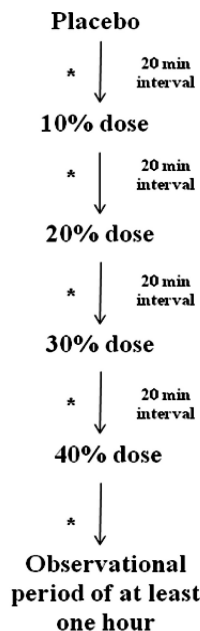
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* Evaluation of symptoms, heart and respiratory rate, blood pressure, oxygen saturation, peak expiratory flow and focused physical examination.

Figure 1. Protocol used for drug provocation tests (DPTs) for all drugs except local anesthetics. Placebo was initially administered, followed by progressive doses of the drug, until the therapeutic single dose was achieved or until an objective adverse reaction occurred. There was a 20-minute interval between each dose. At admission and before each dose, all parameters described were evaluated.

related to the safety of the tests, risks of severe reactions, and treatment of the reactions observed.

MATERIALS AND METHODS

We conducted a retrospective study to describe the experience with DPTs at an outpatient clinic specializing in ADRs. The study was approved by the Institutional Review Board of our hospital. Five hundred patients with a history of hypersensitivity reaction to drugs were evaluated. All of these patients had sought treatment between January of 2006 and April of 2010.

All patients completed a diagnostic questionnaire related to ADRs; the questionnaire was developed in accordance with the guidelines of the ENDA.⁵ The indications for DPTs and the method used were based on the same guidelines.⁵ Only patients with history of immediate hypersensitivity reactions to drugs were included,¹⁰ to make the study group more homogeneous. We included all DPTs performed in the period under study and all patients included in the present study had given written informed consent to perform the tests at the Allergy Outpatient Clinic of the University of São Paulo, São Paulo, Brazil.

We performed single-blind, placebo-controlled tests. All of the drugs tested, with the exception of local anesthetics, were performed using the protocol summarized in Fig. 1. The DPTs consisted of ingesting (or injecting) 1–2 doses of placebo, followed by increasing doses of the suspected causal drug once every 20 minutes until the therapeutic single dose was administered

or symptoms of a drug reaction occurred. In all cases, we used the same route of administration as the patient had used when the allergic reaction had occurred. Administration was performed on the ward by a physician with full resuscitation backup. Patients with a history of anaphylactic shock had i.v. catheters in place during the entire test and the interval between each dose was increased to 30 minutes. The DPT result was considered positive if any of the symptoms or signs of an immediate drug reaction described previously were documented (anaphylaxis, bronchospasm, rhinoconjunctivitis, laryngeal edema, urticaria, maculopapular eruption, or isolated generalized pruritus) up to 1 hour after the last dose was administered.

At admission and before each dose, the symptoms, vital signs, oxygen saturation, and peak expiratory flow of the patients were evaluated, and a focused physical examination was performed. After the therapeutic dose had been achieved, patients were observed for at least 1 hour. They were advised to return in case they experienced any delayed adverse reaction. We also contacted all patients by telephone to verify the presence or absence of any adverse reactions after the observation period. Patients with a history of adverse reactions to local anesthetics underwent skin-prick tests and intradermal tests before subcutaneous exposure, as previously described.¹¹

Subjects with suspected β -lactam antibiotic hypersensitivity were evaluated with both skin tests and *in vitro* tests for specific IgE before DPT. Skin tests were performed with benzylpenicillin and/or cephalosporins as previously described.¹² If either skin tests or *in*

Table 1 Single-blinded drug provocation tests performed and results obtained

Class of Drugs	Drugs	DPTs (n)	Positive Results (n)	Inconclusive Results (n)
Antibiotics	Penicillin V	2	0	0
	Amoxicillin	6	0	0
	Cephalexin	5	1	0
	Cefuroxime	1	0	0
	Azithromycin	1	0	0
	Clindamycin	1	0	0
	Ciprofloxacin	1	0	0
	Trimethoprim-sulfamethoxazole	1	0	0
	Ketoconazole	1	1	0
NSAIDs				
Nonselective	Dipyrone*	7	0	0
			1 placebo	
	Aspirin*	4	0	0
COX-2 inhibitors	Paracetamol	44	3	1
			1 placebo	
	Benzydamine	33	0	2
	Etoricoxib	24	2	0
	Lumiracoxib	1	0	0
Local anesthetics	Celecoxib	1	0	0
	Bupivacaine	43	2	1
			2 placebo	
	Lidocaine	47	1	0
Other	Mepivacaine	3	0	0
	—	17	0	0

*The drugs dipyrone and aspirin were tested in patients with a history that was not suggestive of hypersensitivity. Patients with a history suggestive of immediate hypersensitivity reaction to nonselective NSAIDs were submitted to provocation tests using drugs that are alternatives to the drug implicated in the previous reaction.

NSAIDs = nonsteroidal anti-inflammatory drugs; DPTs = drug provocation tests.

vitro tests showed evidence of specific IgE, the DPT was not performed.

All patients with hypersensitivity reactions to non-steroidal anti-inflammatory drugs (NSAIDs) were considered nonselective reactors based on clinical history. The DPT was performed using an alternative drug, generally an NSAID with a lower incidence of reactions, such as paracetamol or benzydamine. In patients with a history that was not highly suggestive of hypersensitivity, the DPT was performed using the suspected drug to rule out the diagnosis of hypersensitivity.

Patients who presented reactions to parenteral drugs were tested to rule out latex allergy with skin-prick test and serum-specific IgE. If any of these tests were positive, the patient was excluded. Although patients with latex allergy could also have hypersensitivity to an active drug, it would be difficult to confirm the diagnosis without exposing them to latex at our clinic.

Patients with underlying allergic disease (rhinitis, asthma, urticaria, or eczema) were required to have stable disease before the test. Patients were instructed

to discontinue the use of antihistamines and tricyclic antidepressants at least 7 days before the test.

RESULTS

We performed 243 DPTs in 198 patients, 80.8% of whom were female patients. The mean age was 39.9 years (range, 9–84 years).

The drugs tested and the results obtained are summarized in Table 1. Of the 243 DPTs, 10 (4.1%) yielded positive results, and the results of 4 (1.6%) were inconclusive. Another four (1.6%) tests presented a reaction to the placebo before the administration of the active drug.

Table 2 summarizes the drugs associated with positive test results and describes the signs and symptoms observed, as well as the treatment administered in each case. The skin was the organ most often affected (in 90% of the cases), and there were two episodes of anaphylaxis (Fig. 2). One of these two patients who was tested with cephalexin presented symptoms 5 minutes after the administration of 2.5%

Table 2 Drugs implicated in positive test results, clinical manifestations at the previous reaction, dose of each drug that resulted in the reaction, clinical manifestations presented during the test, and treatment administered after the reaction

Patient	Drug	Clinical Manifestations at the Previous Reaction	Dose That Resulted in Reaction during the Test	Clinical Manifestations during the Test	Treatment
1	Etoricoxib	Facial angioedema	90 mg	Facial angioedema	Antihistamine
2	Etoricoxib	Angioedema	90 mg	Facial angioedema	Antihistamine
3	Paracetamol	Facial angioedema	50 mg	Laryngeal angioedema	Antihistamine
4	Paracetamol	Urticaria	300 mg	Urticaria	Antihistamine
5	Paracetamol	Urticaria	500 mg	Urticaria	Antihistamine
6	Bupivacaine	Urticaria and angioedema	10 mg	Urticaria	Antihistamine
7	Bupivacaine	Anaphylaxis (urticaria and wheezing)	Skin prick test (2 mg/100 mL)	Anaphylaxis (pruritus, flush, and wheezing)	Epinephrine Corticosteroid Antihistamine Hospitalization
8	Lidocaine	Facial angioedema	40 mg	Laryngeal angioedema	Corticosteroid Antihistamine
9	Cephalexin	Anaphylaxis (urticaria, facial angioedema, and shock)	50 mg	Anaphylaxis (flush, dyspnea, and shock)	Epinephrine Corticosteroid Antihistamine Hospitalization
10	Ketoconazole	Urticaria and facial angioedema	60 mg	Urticaria and facial angioedema	Corticosteroid Antihistamine

Positive test results (n = 10)
Severe anaphylaxis: 2
Respiratory symptoms: 1
Urticaria/angioedema: 7

Figure 2. Organ affected in the reaction observed during the test. Two cases of severe anaphylaxis were observed: one, a respiratory, mucocutaneous reaction and the other, anaphylactic shock with cutaneous involvement. Positive test results, 10; severe anaphylaxis, 2; respiratory symptoms, 1; urticaria/angioedema, 7.

of the daily dose, although the administration of epinephrine completely reversed those symptoms within 5 minutes. The other one, who reacted to bupivacaine, presented anaphylactic symptoms during the skin-prick test with the pure drug. Patients with negative and positive test results had similar clinical manifestations at the initial adverse reaction, all of them suggestive of immediate hypersensitivity (data not shown). None of the patients reported any reaction after the observation period.

DISCUSSION

The DPT is considered the gold standard for confirming or excluding the diagnosis of hypersensitivity.^{5,13} A

definite diagnosis often requires DPT, although the frequency of positive DPT results is low when the indication is precise, because only a few patients need a challenge test to confirm the diagnosis. Previous studies have shown a low incidence of positive test results.^{13,14} A study investigating 898 patients who underwent 1372 DPTs reported that 82.4% of the results were negative.¹⁴ The authors of another study investigated 160 individuals submitted to 209 DPTs and reported that only 9.6% of the results were positive.¹³

In the present study, the test results were positive in only 4.1% and inconclusive in 1.6%. There was a positive reaction to the placebo in another 1.6%. In the DPTs, we primarily used drugs that would be alternatives to the drug that had supposedly caused the reaction. In these cases, the possibility of a positive test result is limited and it does not rule out the diagnosis of the previous reaction. It is unlikely that false negative test results occurred, because all patients were instructed not to use antiallergic drugs before the DPTs. Nevertheless, negative DPT results are significant because they allow the drug tested to be used later by the patients evaluated.

The use of the drug implicated in the previously reported reaction should be limited to cases that are not highly suggestive of ADR and cases in which allergy test results are negative or unavailable.⁵ In addition, if the drug implicated in the ADR is not an essential element of the treatment of the patient, an

alternative drug should be used. It is important to evaluate the risks and benefits of using the drug in question.⁵

The low frequency of positive DPT results in the present study can be explained by the use of alternative drugs in cases of adverse reactions to NSAIDs, which represented the class of drugs most frequently implicated in the reported ADRs that were suggestive of hypersensitivity. To adopt a safer therapeutic approach, these patients underwent DPTs with alternative drugs that have less often been implicated in ADRs than have the suspected culprit drugs, which is in accordance with the ENDA guidelines.⁵ In a study investigating a sample composed primarily of children (for whom there are few alternatives to NSAIDs), 12.2% of the patients <15 years of age tested positive, compared with only 4.8% of the older patients.¹³

As expected, we also observed a large proportion of negative results on the DPTs performed with local anesthetics.¹⁵ This can be explained by the fact that most of the patients who underwent those tests had a history that was not highly suggestive of hypersensitivity.

Of the 10 patients who tested positive, 9 presented mucocutaneous manifestations and 2 also presented symptoms of involvement of other organs, characterizing severe anaphylaxis. All mucocutaneous reactions observed subsided when the patients were treated with antihistamines, either alone or in combination with corticosteroids. A mucocutaneous reaction is the most common type of ADR.^{13,14}

The tests proved safe, and only two severe anaphylactic reactions occurred in two patients who underwent DPTs with cephalexin and bupivacaine, respectively. In those two cases, the patients were treated immediately and successfully, requiring only 24 hours of hospitalization for observation. None of those patients had a history that was highly suggestive of hypersensitivity to the drugs tested. The patient with bupivacaine-induced anaphylaxis reported multiple, atypical ADRs to different classes of drugs. They declined testing with alternative drugs after the positive DPT.

The patient who experienced cephalexin-induced anaphylactic shock had previously undergone skin tests with penicillin and screening for penicillin-specific IgE, amoxicillin-specific IgE, and ampicillin-specific IgE, all of which were negative. Studies of cross-reactivity between aminopenicillins and cephalosporins have obtained controversial results.¹⁶⁻¹⁹ In the present study, the patient in question did not undergo DPT with aminopenicillins, which would have ruled in or out hypersensitivity to both classes of β -lactam antibiotics.

Although only 2 of the 243 patients experienced a severe reaction, it is mandatory that DPTs be performed in a hospital setting or a facility equipped to

treat anaphylaxis. An experienced clinical staff involved with the challenge should be supervised by a specialist in allergy and immunology, and the test subject should be observed for a sufficient time to verify the absence of delayed reactions.

We tested only patients with a history of immediate hypersensitivity reaction, as described in the literature.¹⁴ Therefore, no late reactions were observed, which is in accordance with the findings of a previous study.¹³ The patients were observed for up to 1 hour after the end of the test and were instructed to return if signs or symptoms appeared. None of the patients reported a reaction after the observation period.

It has been suggested that DPTs should be performed in a single- or double-blind, placebo-controlled manner.^{5,14} However, in a study conducted in Portugal, DPTs were performed in an open manner, and the results obtained were similar to those described previously.^{13,14} Nevertheless, in the Portuguese study, the sample was composed mostly of children.¹³ In adults in particular, the placebo effect is common, and subjective symptoms are often observed.

According to our study, the use of a placebo is essential. We observed that some of the DPTs results were inconclusive, and four patients presented subjective symptoms after the administration of the placebo. It has been shown that the placebo effect is found in 50% of all studies that have physical outcomes, compared with only 6% of those that adopt biochemical parameters.²⁰

Another study evaluated symptoms of anxiety and depression during double-blind, placebo-controlled DPTs and showed that such symptoms were sufficiently intense to affect the validity of the tests in cases of pseudoallergic reactions.²¹ It is possible that the use of a single-blind (rather than double-blind) method in the present study contributed to the difficulty in diagnosing the cases reported as being inconclusive. However, the practical applicability of a double-blind test is limited in comparison with that of a single-blind test.

The present study showed DPT features and results in a large sample of patients. Because of the difficulty in diagnosing immediate hypersensitivity reactions to drugs, many patients are mistakenly labeled as being allergic. Therefore, although the number of positive test results is low when the indication is precise, it is of utmost importance that DPTs be performed to confirm the diagnosis of hypersensitivity and adopt a safe therapeutic approach.

CONCLUSION

We conclude that DPTs can be safely performed in clinical practice, because the indication criteria are correct. The tests should be placebo controlled and supervised by an allergist with experience in performing this

type of test. It is of utmost importance that DPTs be performed to confirm the diagnosis of hypersensitivity and to manage allergies appropriately.

REFERENCES

1. Johansson SG, Bieber T, Dahl R, et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol* 113:832–836, 2004.
2. Demoly P, Kropf R, Bircher A, and Pichler WJ. Drug hypersensitivity: Questionnaire. EAACI Interest Group on Drug Hypersensitivity. *Allergy* 54:999–1003, 1999.
3. Brockow K, Romano A, Blanca M, et al. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. *Allergy* 57:45–51, 2002.
4. Demoly P, and Bousquet J. Drug allergy diagnosis work up. *Allergy* 57(suppl)72:37–40, 2002.
5. Aberer W, Bircher A, Romano A, et al. for ENDA, and the EAACI Interest Group on Drug Hypersensitivity. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: General considerations. *Allergy* 58:854–863, 2003.
6. Nagao-Dias AT, Teixeira FM, and Coelho HL. Diagnosing immune-mediated reactions to drugs. *Allergol Immunopathol (Madr)* 37:98–104, 2009.
7. Bousquet PJ, Gaeta F, Bousquet-Rouanet L, et al. Provocation tests in diagnosing drug hypersensitivity. *Curr Pharm Des* 14: 2792–2802, 2008.
8. Dietrich JJ, Quinn JM, and England RW. Reasons for outpatient consultation in allergy/immunology. *Allergy Asthma Proc* 30: 69–74, 2009.
9. Otto HF, England RW, and Quinn JM. Inpatient allergy/immunology consultations in a tertiary care setting. *Allergy Asthma Proc* 31:244–251, 2010.
10. Romano A, and Demoly P. Recent advances in the diagnosis of drug allergy. *Curr Opin Allergy Clin Immunol* 7:299–303, 2007.
11. Nettis E, Napoli G, Ferrannini A, and Tursi A. The incremental challenge test in the diagnosis of adverse reactions to local anesthetics. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 91:402–405, 2001.
12. Torres MJ, Blanca M, Fernandez J, et al. Diagnosis of immediate allergic reactions to beta-lactam antibiotics. *Allergy* 58:961–972, 2003.
13. Palma-Carlos S, Carvalho S, Almeida T, et al. Drug hypersensitivity reactions in an outpatients' hospital: Safety of drug provocation tests. *Rev Port Imunoalergol* 15:485–497, 2007.
14. Messaad D, Sahla H, Benahmed S, et al. Drug provocation tests in patients with a history suggesting an immediate drug hypersensitivity reaction. *Ann Intern Med* 140:1001–1006, 2004.
15. McClimon B, Rank M, and Li J. The predictive value of skin testing in the diagnosis of local anesthetic allergy. *Allergy Asthma Proc* 32:95–98, 2011.
16. Pichichero ME. Use of selected cephalosporins in penicillin-allergic patients: A paradigm shift. *Diagn Microbiol Infect Dis* 57(suppl):13S–18S, 2007.
17. DePestel DD, Benninger MS, Danziger L, et al. Cephalosporin use in treatment of patients with penicillin allergies. *J Am Pharm Assoc* 48:530–540, 2008.
18. Antunez C, Blanca-López N, Torres MJ, et al. Immediate allergic reactions to cephalosporins: Evaluation of cross-reactivity with a panel of penicillins and cephalosporins. *J Allergy Clin Immunol* 117:404–410, 2006.
19. Pichichero ME, and Casey JR. Safe use of selected cephalosporins in penicillin-allergic patients: A meta-analysis. *Otolaryngol Head Neck Surg* 136:340–347, 2007.
20. Meissner K, Distel H, and Mitzdorf U. Evidence for placebo effects on physical but not on biochemical outcome parameters: A review of clinical trials. *BMC Med* 19:5–3, 2007.
21. Hermes B, Hein UR, and Henz BM. Assessment of psychological aspects during systemic provocation tests in patients with pseudoallergic drug reactions. *J Eur Acad Dermatol Venereol* 20:800–803, 2006. □

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