

Patients' Satisfaction with Diagnostic Drug Provocation Tests and Perception of Its Usefulness

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Key Words

Drug provocation test • Drug allergy/hypersensitivity • Patient satisfaction

Abstract

Background and Aim: Although still controversial, drug provocation tests (DPTs) are considered by many as the gold standard for diagnosis of drug hypersensitivity. No studies have addressed the opinion of patients submitted to DPT. We aimed to determine patient satisfaction with diagnostic DPT and their perception of its usefulness. **Methods:** Surveys were supplied to patients submitted to diagnostic DPT in 3 different drug allergy clinics which used the same diagnostic protocols for drug hypersensitivity evaluation. Seventy-three patients (33.6%) were enrolled in Porto (Portugal), 102 (47%) in Montpellier (France) and 42 (19.4%) in Vilnius (Lithuania). The patients filled in a written questionnaire within 15 days after the diagnostic procedure, and satisfaction was assessed on a 1 (very unsatisfied) to 5 (very satisfied) score. **Results:** A total of 217 surveys were collected; 144 female patients (66.4%). The most prevalent studied reactions were cutaneous (70.1%), but 17.9% of the patients had had a sys-

temic reaction. β -Lactam antibiotics were the main culprit drugs (44.3%) tested in all centres and 25.3% of the patients had a positive DPT. No patients were unsatisfied (8.8% were neither unsatisfied nor satisfied and the others were satisfied or very satisfied). The level of satisfaction did not depend on the results of the DPT; 207 (95.4%) believed DPTs were useful and almost all the patients would recommend DPTs to others. **Conclusions:** Most patients were satisfied with DPT for diagnostic purposes. Satisfaction with the procedure was independent of the results of the provocation tests and did not depend on the country.

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Introduction

Drug hypersensitivity is an imposing field within allergy partly due to the increasing awareness of clinicians and the general population of the problem of adverse drug reactions in general and of drug allergy in particular. It is a difficult area of study because of largely unknown pathophysiological mechanisms, deficiencies in the classification of reactions, lack of consensus about diagnostic

protocols and diagnostics tools, all of which lead to a poor investigation of suspected drug allergy in patients.

Diagnosis of true drug allergy implies the demonstration of an immune-mediated mechanism concerning either specific cells or antibodies involved in the reactions [1], but the necessary diagnostic tests are still far from perfect and a big effort must be put in the standardization and validation of both in vivo and in vitro procedures.

Currently, diagnosis is based on 3 major foundations, which are: (1) a detailed medical history; (2) in vitro tests, which are promising for certain drugs [2, 3] and selected populations, and (3) in vivo tests. The latter generally comprise all kinds of skin testing with the suspect drugs and the diagnostic drug provocation tests (DPTs). Despite papers written about the usefulness of these tests and their clinical indications, there are still controversies between authors defending the procedure and considering it as the gold standard for the diagnosis of drug hypersensitivity and others being against it unless used as a basis for finding therapeutical alternatives [4–6].

It cannot be disputed that DPTs represent a potential risk to the patient, are time consuming and need appropriate medical facilities and trained personnel. They are, however, sometimes the only resource available for confirmation of or exclusion of hypersensitivity when previous investigation steps are negative, nonconclusive or simply unavailable [4–6].

The degree of satisfaction of patients with healthcare services is becoming more and more important when assessing the quality of hospitals, clinics and health departments [7–9]. Asking people for their opinion about a given service provision is a well-tried and tested procedure which has proved exceedingly useful in bringing about an improvement in these services, which is now being used in health institutions, since privatization of healthcare systems is taking place in many countries and patients are now given the opportunity to choose among different facilities. To assess satisfaction with DPT, a cross-sectional study was performed in 3 different European centres.

Material and Methods

The cross-sectional study was performed in 3 centres performing DPT for diagnostic purposes under strict supervision. The centres were located in Porto (Portugal), Montpellier (France) and Vilnius (Lithuania). The Portuguese centre mainly tested children, the Lithuanian adults and the French both of them.

Table 1. Scheme of the questionnaire applied to patients submitted to DPT

Describe the inconveniences caused by the provocation
Describe the advantages of the provocation
Do you think this procedure was useful for the investigation of your disease? 1 Yes 2 No
Do you feel that it was important for you to have undergone this procedure? 1 Yes 2 No
Point out the overall degree of satisfaction with this procedure 1 very unsatisfied 2 unsatisfied 3 neither satisfied nor unsatisfied 4 satisfied 5 very satisfied
Would you recommend to other people with similar problems to do the same procedure? 1 Yes 2 No
Answers to open questions were grouped for analysis as follows: The most common inconveniences from the provocation referred to 1 time consuming, time lost from work/school 2 to be afraid of a possible reaction/stressful procedure 3 to suffer a reaction 4 others
The most common advantages of the provocation referred to 1 better knowledge about the disease/to be more certain about the diagnosis 2 to know I can take the drug or not 3 feel more reassured 4 others

During the study period, the tested patients were consecutively included and were asked to complete a self-questionnaire regarding the procedure and their satisfaction with it within 15 days of the test having taken place. None refused to participate. In the case of patients <18 years, the responsible parent filled in the questionnaire. The questionnaire focused on the perceived advantages/disadvantages of the DPT and on the general satisfaction with the test. Satisfaction was assessed, based on a Likert scale, on a 1 (very unsatisfied) to 5 (very satisfied) score. The other questions were open-ended. Open-ended questions were read by one of the interviewers. For each open question, a list of answers was precoded and implemented accordingly depending on the answers, and the results were grouped according to them (table 1).

The diagnostic protocol for drug allergy workup used is in accordance with the recommendations of the ENDA (European Network for Drug Allergy, at present the core group of the EAACI drug allergy interest group), which are described in detail else-

Table 2. General characteristics of the patients including demographic data, clinical presentation of the reactions and culprit drugs

	Portugal	France	Lithuania	Total
Cases	73	102	42	217
Sex (female)	39 (53.4)	74 (72.6)	31 (73.8)	144 (66.4)
Age, years	10 [5–18]	45 [35–58]	39 [24–49]	36 [16–50]
Clinical presentation				
Anaphylaxis	5 (6.8)	23 (22.5)	11 (26.2)	39 (17.9)
Urticaria/angioedema	21 (28.8)	56 (54.9)	13 (31.0)	90 (41.5)
Respiratory tract	10 (13.7)	4 (3.9)	2 (4.7)	16 (7.4)
Exanthema	30 (41.1)	17 (16.7)	15 (35.7)	62 (28.6)
Other	7 (9.6)	2 (2)	1 (2.4)	10 (4.6)
Culprit drug				
Amoxicillin	29 (39.7)	33 (32.4)	8 (19.1)	70 (32.3)
Other penicillin	2 (2.7)	6 (5.9)	7 (16.7)	15 (6.9)
Cephalosporin	3 (4.1)	8 (7.8)		11 (5.1)
Paracetamol	2 (2.7)	7 (6.9)	6 (14.3)	15 (6.9)
Salicylic acid	8 (11)	4 (3.9)	8 (19.1)	20 (9.2)
Ibuprofen	10 (13.7)	12 (11.8)	1 (2.3)	23 (10.6)
Ketoprofen		12 (11.8)		12 (5.5)
Other NSAIDs	2 (2.7)	8 (7.9)	10 (23.8)	20 (9.2)
Other drug	17 (23.2)	12 (11.8)	2 (4.8)	31 (14.3)

Figures are numbers of cases with percentages in parentheses or medians with 25th–75th percentiles in square brackets.

where [4, 10, 11]. Briefly, after completing the locally adapted ENDA questionnaire [10], skin tests (prick tests and intradermal tests) were performed with the culprit drug. Skin tests were done only when indicated and if a diagnostic commercial kit or an IV presentation of the drug was available and the procedure was valid for the drug, as was the case for most of the β -lactams [11]. The procedures were strictly the same in the 3 centres.

Then, only in patients with negative skin tests and in patients for whom skin tests were not available was a DPT performed. This procedure was done in day hospitals or outpatient facilities, following the ENDA recommendations [4] after appropriate explanations and the signature of a written informed consent. Challenges lasted 3–8 h. At the end of the test, the patient was given a full daily dose of the tested drug. The number of steps and the total dose were adapted to the age and to the patient's clinical history and comorbidities. DPT was stopped in case of clinical reaction, and the positive patients were asked to attend a new appointment for DPT with an alternative drug.

All procedures were used in standard evaluation for drug hypersensitivity reactions in these 3 centres and the participation of the patients in filling in the questionnaire was voluntary. According to the local ethics committees, for France and Portugal no specific authorization was needed, the study being observational and based on patient satisfaction, which is part of the daily practice. The Lithuanian centre submitted the study to the local ethics committee and it was approved.

Results are expressed in frequencies and percentages.

Results

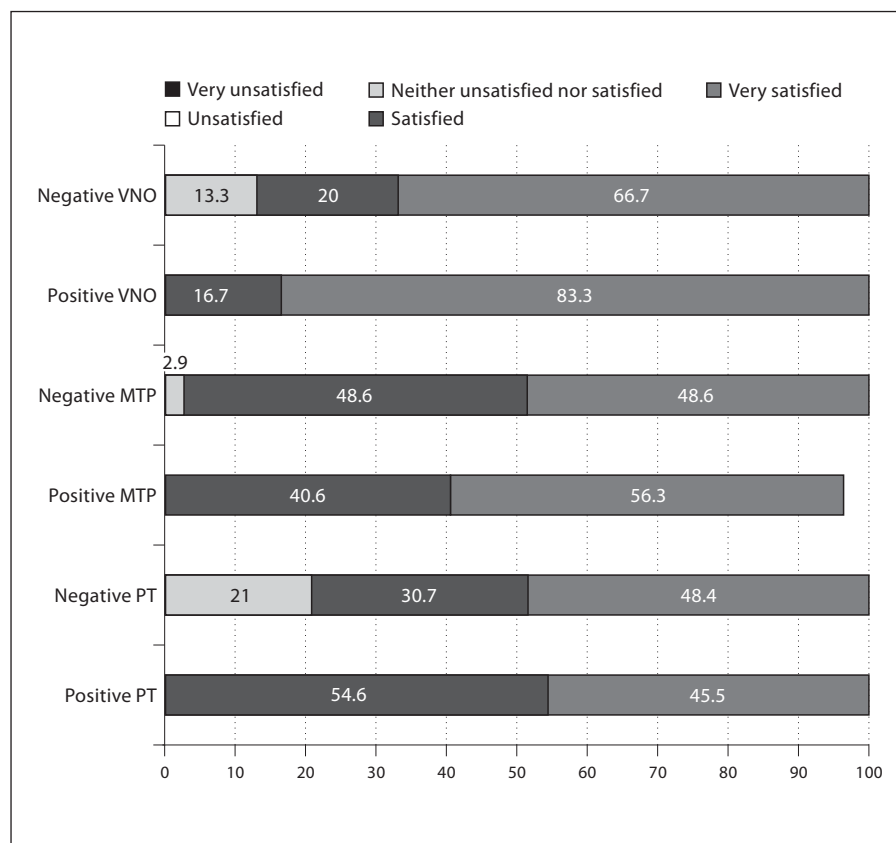
General Characteristics of the Patients

A total of 217 patients [73 (33.6%) from Porto, 102 (47.0%) from Montpellier and 42 (19.4%) from Vilnius] were recruited, including 144 (66.4%) females, median (25th–75th percentiles) age = 36 (16–50) (table 1). More than half of the patients reported a cutaneous reaction [urticaria or angioedema 90 (41.5%) and exanthema 62 (28.6%)] as the sole suspected manifestation of drug hypersensitivity, and 39 (17.9%) had a systemic reaction defined as a cutaneous or mucosal reaction associated with respiratory symptoms and/or persistent gastrointestinal symptoms and/or hypotension (anaphylaxis or anaphylactic shock) [12] (table 2).

In nearly half of the patients, the culprit and tested drug was a β -lactam: amoxicillin for 70 patients (32.3%), other penicillins for 15 (6.9%) and a cephalosporin for 11 (5.1%). Nonsteroidal anti-inflammatory drugs were the other major drug class tested (75 – 34.6%).

The DPT was positive for a fourth of the patients (25.3%). Cutaneous reactions were the most common with 25 (45.5%) urticaria and 10 (18.2%) exanthema.

Fig. 1. Overall satisfaction rates between the patients with positive and negative results of DPT. Negative = negative DPT; positive = positive DPT; PT = Porto; MTP = Montpellier; VNO = Vilnius centres.



Thirteen patients (23.6%) experienced a systemic reaction. Within each centre, the patients participating in this study did not differ from the others in terms of gender, clinical history, drugs involved and DPT positive rate.

Self-Reported Feeling about the Advantage and Disadvantage of DPT

Most of the patients reported at least 1 advantage of undergoing a DPT (177 out of 217, 81.6%). The main advantages mentioned were a better knowledge of the diagnosis: 'to be more certain about the diagnosis' – 69 (31.8%) – and 'to know I can take the drug' – 40 (21.7%). In addition, the patients wanted to feel and 'felt more reassured' after the test (61 – 28.1%).

Two thirds (135 – 62.2%) of the patients did not report any disadvantages of the DPT. The major ones mentioned were the fact that DPT is time consuming (48 – 22.1%) and the stress induced by the procedure and the possible occurrence of a new reaction (28 – 12.9%).

Satisfaction of the Patients after DPT

Most of the patients were satisfied with DPT and none unsatisfied with the procedure. This was the case whatever the result of the test (positive or negative) was, even if patients with a positive test seemed to report a higher satisfaction rate (fig. 1).

All the patients, except 2, stated they would recommend the test to someone else and thought that it was important. Nearly all the patients (207 out of 217, 95.4%) thought that it was a useful procedure. Similar results were obtained in both men and women.

Centres' Impact

Similar findings were observed across centres, in adults as well as in children. In all centres, the patients reported severe (anaphylaxis and anaphylactic shock) and less severe (urticaria or exanthema) reactions. β -Lactams and NSAIDs were the most common tested drugs in all places. There was a trend for patients in the Lithuanian centre to be more satisfied [30 (71.4%) quoted 5 on the satisfaction scale] (fig. 1).

Discussion

In this study, we found that most patients were in general very satisfied with the diagnostic DPTs. It was interesting that the patients were satisfied although mentioning quite a few inconveniences as it was a time-consuming and stressful procedure and even if they suffered a reaction in the cases of positive DPT. In addition almost all of the patients reported that they would recommend the procedure to others having the same problem. This is considered to be a very positive outcome.

There are no studies, to our knowledge, focusing on this aspect of drug hypersensitivity management.

Similar studies have been carried out with patients submitted to patch testing for diagnosis of allergic contact dermatitis. This is also a time-consuming process, uncomfortable and can also cause reactions. Those studies showed that in spite of inconveniences most patients appeared to be satisfied with the procedure, especially when allergens were identified with the patch testing [13, 14], that testing is perceived as a valuable tool by patients [13, 14] and that patients would recommend patch testing to others [13]. Also in our study patients with positive DPT were actually more satisfied with the procedure than the ones with negative results, although this was not statistically different.

It was interesting to see that many patients actually felt more reassured after DPT and this is most certainly related to other perceived advantages, such as better information about the drugs to take or not to take and being more certain about the diagnosis. This was also shown recently for food challenges in children in a study where a decrease in parental anxiety was documented even in the group with a positive test result [15].

This is an important point as a recent study including patients from one of the participating centres (France) found out that even after going through an extensive diagnostic protocol with negative results, some patients and prescribing physicians still fear another reaction and prefer to keep on avoiding the drug [16].

The very high level of satisfaction and the number of patients who thought that the test was important and useful can be influenced and partially explained by the fact that we only test patients who agree to be tested. It is, however, important to note that the use of a self-questionnaire, without the intervention of a clinician, done within 15 days after the test, allows patients to feel free to report their real feelings (not the one a priori, but the one after the test and the fear of the test) and this is an advantage of the study.

Other strong points of the study that we would like to emphasize are: (1) the involvement of children and adults, which allows us to conclude that parents approve the use of this methodology for the study of reactions in their children, and (2) the fact that a quarter of the patients actually reacted, meaning that we have both considerations: those who reacted and those who did not.

The inclusion of patients from 3 different European centres in diverse geographic locations gives us the perspective of patients who probably have different ways of thinking and this contributes to the validation of the results.

However, it must be said that these patients did not represent the general population but are the ones who come into our centres for drug hypersensitivity evaluation and therefore those we test. Other possible drawbacks of the study are the application of a nonvalidated questionnaire and a potential bias induced by the investigators and the design of the study. Nevertheless, it is difficult to imagine that the same bias was present in 3 different populations with different socio-cultural patterns and 3 different teams, and multicentre studies usually reduce such a bias. Moreover, the patients were free to respond and easily understood that their answer had no impact on the procedure since the study was performed at the end of the clinical investigation. Therefore, the risk to miss some disadvantages and disaffection is limited.

Conclusions

Most patients, in the 3 centres, were very satisfied with DPTs for diagnostic purposes. All except 2 patients would recommend the test, including those who reacted.

Future Investigation

A comparison with a group of patients submitted to DPT with alternative substances and patients submitted only to diagnostic skin tests would be interesting in order to better address the best practice according to the patients' point of view.

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