



Evaluation of drug provocation test–related anxiety in patients with drug hypersensitivity

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ABSTRACT

Background: Drug provocation tests (DPTs) are important in the treatment of patients with drug hypersensitivity (DH), but they carry certain hypersensitivity reaction risks, which lead to procedure-related concerns in patients.

Objective: To investigate DPT-related anxiety and its effect on long-term use of tested drugs.

Methods: The study included patients who underwent DPT from July 1, 2009, to July 1, 2012. After recording the patients' history and characteristics, a variety of psychiatric (Hospital Anxiety and Depression Scale, Panic and Agoraphobia Scale, and the Maudsley Obsessive-Compulsive Inventory) and quality-of-life (36-item Short Form Health Survey) tests were performed. DPT-related anxiety was also evaluated using a visual analog scale. The patients were questioned about whether they had used the tested drug within 1 year.

Results: A total of 126 patients were included in the study. According to the Hospital Anxiety and Depression Scale, 23.4% and 30.6% of the patients had depression and anxiety symptoms, respectively. The mean (SD) visual analog scale anxiety scores after a negative DPT result were lower than those before DPTs (2 [2.5] after vs 5.2 [3.4] before; $P < .001$). In the long term, 15.9% of the patients did not use the drug because of ongoing anxiety related to drug reactions, despite negative DPT results and symptoms indicated for use of the drug.

Conclusion: Our findings suggest that DPTs in themselves cause significant anxiety in patients with DH. Importantly, anxiety levels decreased after a negative test result. However, our results also suggested that a negative DPT result is not convincing enough for some patients to use the tested drug when needed in the future. Therefore, supporting strategies appear to be the most effective way to eliminate DH-related anxiety of patients.

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Introduction

Hypersensitivity reactions to drugs are a common problem for practicing allergists worldwide. In the treatment of patients with these reactions, drug provocation tests (DPTs) may be needed to either prove a diagnosis or find safe alternatives. However, these tests carry risks of hypersensitivity reaction redevelopment to varying degrees. Previous studies have found a certain level of anxiety or depression in patients with drug hypersensitivities (DHs), mainly related to past experience of symptoms ranging from mild to life-threatening reactions after consumption of drug.¹ As a

part of the routine approach, patients are informed about the risks of the DPTs, which could further increase their anxiety. Although anxiety related to DHs has been reported, to the best of our knowledge, anxiety related to DPTs in patients with DHs has not yet been studied.

After a negative DPT result, patients are told and expected to use the tested drug(s) whenever they are needed. However, in one of our previous studies,² we found an interesting low adherence to use of safe alternative drugs despite negative DPT results, which was also confirmed by another recent study.³ The main reason for this, as reported by the patients, was anxiety related to possibility of recurrence of the previous drug reactions.

In the present study, we primarily aimed to assess anxiety related to DPTs in patients with DH. The patients were also assessed for whether they had used the drug that tested negatively when necessary in the long term. We assessed for the presence of any

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symptoms of depression or anxiety disorders that might affect DPT-related anxiety and long-term use of the tested drug. We hypothesized that a negative DPT result would positively affect the patient's attitude toward use of the tested drug.

Methods

This prospective cohort included consecutive patients who were admitted with DH to our clinic and were drug tested (DPTs or skin tests) for DH from July 1, 2009, to July 1, 2012. Reactions considered related to DH were immediate reactions, including urticaria or angioedema, rhinitis, conjunctivitis, bronchospasm, throat tightness, gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal pain), anaphylaxis, and anaphylactic shock, to a prescribed drug.^{4,5} Patients who were 18 years or older, had a history of these reactions related to any drug use, were evaluated as having DH, and agreed to participate were enrolled in the study. The exclusion criteria were as follows: patients younger than 18 years, pregnancy, history of delayed hypersensitivity reactions, and refusal to participate in the study.

The local ethics committee at Ankara University, Turkey, approved the protocol. All participants gave their written informed consent before enrollment to the study.

Demographics and Disease Characteristics

Demographics and disease characteristics, such as age, sex, and history of drug allergy (ie, type of reaction, duration, and culprit drug[s]) and comorbid and physician-diagnosed psychiatric diseases were also recorded.

Tests Performed and Patient Management

A uniform drug allergy evaluation protocol was not used. Instead, usual management was provided by each physician specifically based on the history and patients' needs. Recommendations of the European Network for Drug Allergy were followed for the management of DH reactions.^{4–8}

After the initial assessment, the patients were tested for diagnostic purposes and/or to find safe alternatives, depending on their history and needs. For diagnosis, skin tests were performed if a skin testing material was available. Skin prick and intradermal tests were used to diagnose IgE-mediated drug reactions, such as urticaria, angioedema, anaphylaxis, dyspnea, and rhinitis. DPTs were performed if these test results were negative. DPTs were performed in the diagnosis of DH reactions to β -lactams, as well as for other drug classes, such as acetylsalicylic acid or nonsteroidal anti-inflammatory drugs (NSAIDs), non- β -lactam antibiotics, and local anesthetic agents. In addition, alternative analgesics (nimesulide or meloxicam) and antibiotics (macrolide) were tested in patients who had a history of analgesic and antibiotic hypersensitivity, respectively. DPTs were not performed in patients who had had a reaction within the last 4 to 6 weeks; those who used medication that could affect the test outcome, such as antihistamines and oral steroids; those with active signs of underlying disease, such as urticaria, uncontrolled asthma (forced expiratory volume in 1 second value <70% of predicted), uncontrolled cardiac, and renal or hepatic disease; and with current upper airway infection. DPTs were not performed in patients who had experienced severe reactions, such as toxic epidermal necrolysis, Stevens-Johnson syndrome, drug-induced hypersensitivity reactions, acute generalized exanthematous pustulosis, or manifestations of internal organ involvement, such as kidney or liver.

DPTs were performed in a single-blind, placebo-controlled design. Placebo and active drugs were tested on separate days. The placebo challenge consisted of the controlled administration of the divided doses of placebo (lactose) in similar dose intervals to those used with the active drug. If the placebo test result was negative,

the challenge with active drug consisted of administration of divided doses of the test drug within 1- to 2-hour intervals on a separate day. During the challenge procedure, blood pressure, forced expiratory volume in 1 second values, and skin, ocular, nasal, and bronchial reactions were monitored after each placebo or active drug dose was given. The patients were kept under medical observation for up to 2 hours after completing the test in case of a negative test result. Patients were monitored for 24 hours to detect delayed reactions. Test results were considered negative if no adverse reaction occurred after 24 hours. Test results were considered positive if any signs of hypersensitivity reaction, such as urticaria, angioedema, anaphylaxis or other rashes, were observed during or after the test. After a negative DPT result, patients were asked whether they would use this drug in the future.

Assessment of Depression or Anxiety Disorders Symptoms and Quality of Life

All patients initially underwent a serial assessment of standardized screening tests for symptoms of depression and anxiety disorders, including the Hospital Anxiety and Depression Scale (HADS), Panic and Agoraphobia Scale, and the Maudsley Obsessive-Compulsive Inventory. All test results were evaluated by a Psychiatrist. The cutoff points for the Turkish population of the tests are as follows: HADS, 10/11 for anxiety and 7/8 for depression⁹; the Panic and Agoraphobia Scale, 11/12¹⁰; and the Maudsley Obsessive-Compulsive Inventory, no cut-off score was calculated.¹¹ Quality of life was assessed with the Turkish version of 36-item Short-Form Health Survey (SF-36).

Assessment of Anxiety and DPT-Related Anxiety Levels

DH-related general anxiety was evaluated using the visual analog scale (VAS). In this analysis, 0 indicated no anxiety, whereas 10 indicated the highest anxiety level. DPT-related anxiety was also determined using the VAS before and after DPTs.

Assessment of Long-term Use of Drugs After Negative Test Results

Patients whose test results were negative for a certain drug were advised to use the test drug in the future if it was needed. After completing DPTs, the patients telephone a year later and asked whether they had used the tested drug, and, if not, the underlying reasons were questioned.

Statistical Analysis

Statistical analyses were performed using SPSS statistical software, version 15 (SPSS Inc, Chicago, Illinois). Variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov and Shapiro-Wilk tests) to determine whether data were normally distributed. Numeric values are expressed as mean (SD), whereas nominal values are given as number (percentage). The χ^2 test or Fisher exact test were used for the comparison of nominal values. Assessment of factors related to HADS and anxiety levels were performed using univariate analysis. The factors in the multivariate analysis were age, sex, severity of reaction, HADS score, SF-36 general health perception, VAS score before test with active drug. An overall $P < .05$ was considered to statistically significance.

Results

Demographics and Characteristics of the Study Group

One hundred twenty-six patients underwent evaluation in the present study. The challenge test result was positive in 3 patients (2 NSAIDs, 1 β -lactam), desensitization was indicated in 3 patients, and 2 patients underwent skin tests with general anesthetics. The remaining 118 patients with negative challenge test results, whose

Table 1

Demographics and disease characteristics of the patients with negative challenge test results

Variable	Finding ^a (n = 118)
Female/male	94/24 (79.7/20.3)
Age, mean (SD), y	37.7 (11.4)
Occupation	
Housewife	43 (36.4)
Clerk	20 (16.9)
Student	12 (10.2)
Retired	11 (9.3)
Others	32 (27.2)
Educational level	
Illiterate	2 (1.7)
Elementary education	38 (32.2)
High school	38 (32.2)
College	40 (33.9)
Underlying diseases	
Asthma	22 (18.6)
Chronic sinusitis	20 (16.9)
Chronic urticaria	13 (11)
Nasal polyps	6 (5.1)
Psychiatric disorders	14 (11.9)
Depression	12 (10.2)
Anxiety	2 (1.7)

^aData are presented as number (percentage) of patients unless otherwise indicated.

mean (SD) age was 37.7 (11.4) years (range, 18–60 years), were included in the study. There was a predominance of women in the study group (79.7%), and asthma and chronic sinusitis were the most common comorbid disorders. A total of 10.2% of the patients had depression, and 1.7% had physician-diagnosed anxiety. NSAIDs were the most common cause of hypersensitivity reactions, followed by β -lactam antibiotics (38.1% and 23.7%, respectively). The skin was the most commonly involved organ, with a frequency of urticaria with or without angioedema of 70.6% and 87.1% for NSAIDs and β -lactams, respectively (Tables 1 and 2).

Management of Patients With DH

Of the 118 patients with negative challenge test results, 109 (92.4%) underwent DPTs, 6 (5.1%) underwent skin tests and DPTs, and 3 (2.5%) underwent skin tests alone. Most DPTs were performed using NSAIDs (n = 41 [38.7%]) in the search for safe alternatives (Table 3).

Assessment of Anxiety and DPT-Related Anxiety Levels

The mean (SD) general VAS anxiety score was 9.5 (0.8) in all patients. Anxiety VAS scores were 8 and higher in 58.3% of patients. The main reason for this anxiety was the fear of recurrence of previous reactions (n = 90 [71.4%]) and fear of death (n = 19 [15.1%]).

The mean (SD) VAS anxiety scores after placebo on the first day were lower than those before placebo (first day: 3.3 [2.9] after placebo vs 5.2 [3.4] before placebo, $P < .001$). When there was a negative response to an active drug, anxiety levels decreased (second day: 2 [2.5] after active drug vs 3.9 [2.9] before active drug, $P < .001$). At the end of second day, the VAS scores were significantly lower than at the end of the first day (3.3 [2.9] vs 2 [2.5], $P < .001$). The mean VAS anxiety scores after negative test results were lower than those before DPTs (2 [2.5] after vs 5.2 [3.4] before, $P < .001$) (Fig 1).

The Relation Between Anxiety Related to DPT and Depression or Anxiety Disorder Symptoms

The summary of depression or anxiety disorder symptoms evaluated with screening tests before DPTs is given in Table 4. The most common symptoms were related to anxiety (30.6%) and obsessive compulsive disorders (27%).

Table 2

Drug hypersensitivity reaction characteristics of patients with negative challenge test results

Variable	Finding ^a
Culprit drugs	
Antibiotics	
β -lactams	28 (23.7)
Quinolones	4 (3.4)
Unknown	6 (5.1)
Aspirin or NSAIDs	45 (38.1)
Paracetamol	12 (10.2)
Others	23 (19.5)
Duration since the last drug reaction, median (range), mo	3 (1–60)
Immediate reactions to NSAIDs	
Urticaria or angioedema	24 (70.6)
Lower respiratory tract	6 (13.9)
Upper respiratory tract	10 (29.4)
Anaphylaxis	1 (2.9)
CVS	2 (5.9)
GIS	1 (2.9)
Neurologic	2 (5.9)
Immediate reactions to antibiotics	
Urticaria or angioedema	27 (87.1)
Lower respiratory tract	0
Upper respiratory tract	9 (29)
Anaphylaxis	4 (12.9)
CVS	2 (6.5)
GIS	4 (12.9)
Neurologic	3 (9.7)

Abbreviations: CVS, cardiovascular system; GIS, gastrointestinal system; NSAID, nonsteroidal anti-inflammatory drug.

^aData are presented as number (percentage) of patients unless otherwise indicated.

Overall, the DH-related general anxiety VAS score was positively correlated with VAS scores before and after testing with an active drug ($r = 0.55$, $P < .001$, $r = 0.372$, $P < .001$, respectively). No relation was found between all VAS scores on the first and second days for reason of test ($P > .05$).

The VAS anxiety scores of tests before and after placebo and active drug were related to anxiety symptoms as measured using HADS ($P = .02$, $P = .007$, $P = .001$, and $P = .001$, respectively). The VAS anxiety scores of tests before and after placebo and active drug were not related to symptoms of depression as measured using HADS ($P = .08$, $P = .09$, $P = .09$, and $P = .09$, respectively) or obsessive compulsive disorders.

Table 3

Types of drugs and reasons challenges were performed in patients with negative challenge test results

Drug	Tests for finding safe alternatives, n (%)	Test for diagnostic reason, n (%)
NSAIDs	41 (38.7)	3 (25.0)
Aspirin	NA	3 (25.0)
Nimesulide	5 (4.7)	NA
Meloxicam	36 (34.0)	NA
Paracetamol	2 (1.9)	2 (16.6)
Antibiotics		
β -lactams	NA	5 (41.7)
Amoxicillin and clavulanic acid	NA	4 (33.3)
Ampicillin and sulbactam	NA	1 (8.4)
Macrolides	28 (26.4)	NA
Clarithromycin	28 (26.4)	NA
Quinolones	6 (5.6)	NA
Levofloxacin	4 (3.7)	NA
Ciprofloxacin	2 (1.9)	NA
NSAIDs and macrolides	22 (20.8)	NA
Others	7 (6.6)	2 (16.7)
Total	106 (89.8)	12 (10.2)

Abbreviations: NA, not applicable; NSAIDs, nonsteroidal anti-inflammatory drugs.

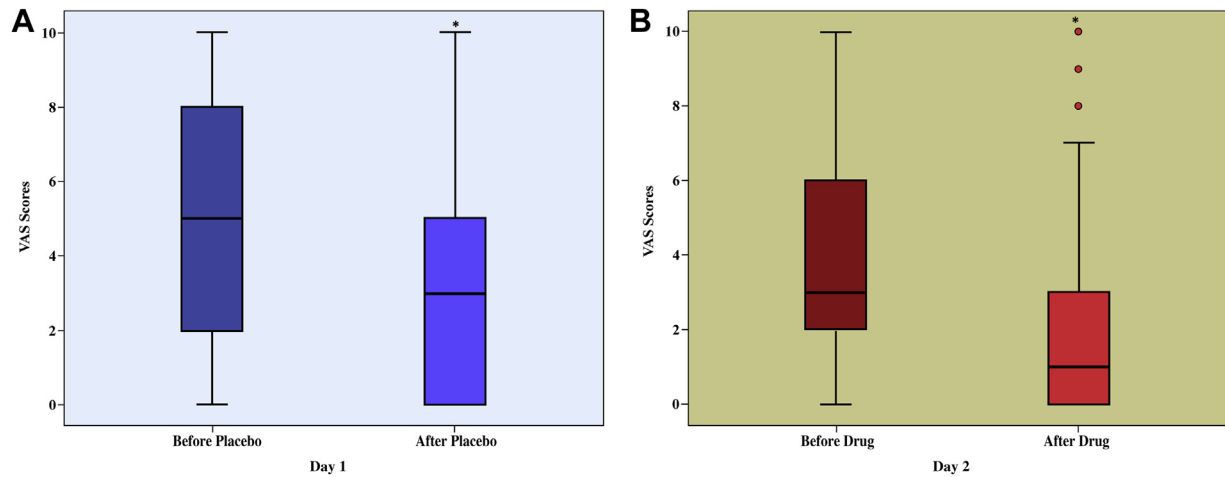


Figure 1. Mean visual analog scale (VAS) scores of the patients before and after placebo and active drug tests. Error bars indicate SDs. * $P < .001$.

Evaluation of Patients With Negative Test Results on the Behaviors of Long-term Drug Use

After negative DPT results, 69 patients (78.4%) reported that they had used the tested drug during the follow-up, 14 patients (15.9%) were undecided, and 5 patients (5.7%) declared that they would not use the tested drug. Forty-one of the 69 patients (59.4%) who were accessible by telephone who reported using the test drug after negative DPT results were contacted. Seventeen patients (24.6%) used the drug with no problems; immediate hypersensitivity reactions (urticaria and/or angioedema) developed in 5 patients (7.2%), 8 patients (11.6%) had not needed to use the drug, and 11 patients (15.9%) did not use the drug despite it being indicated. The main reason for this avoidance behavior was anxiety related to the possibility of recurrence of previous drug reactions. No significant relation was found between the previous test reason (ie, diagnostic or finding safe alternative) and long-term drug use ($P > .05$).

In the evaluation of factors that affected long-term drug use, no significant difference was found between those who used the drugs and those who did not in terms of age, sex, severity of reaction, HADS score, SF-36 general health perception score, and general VAS score ($P > .05$). However, the general health perception as evaluated using the SF-36 was impaired in 14 of the 16 patients who stated that they would not use the test drug in the future.

Discussion

The results of the current study indicate that DPTs caused significant anxiety in patients with DH who underwent these tests. The main reason for this anxiety was the possibility of recurrence of

previous drug reactions. Importantly, anxiety levels gradually decreased after each negative test result day. This result indicated that DPTs caused anxiety mainly related to the possibility of reaction risk during the test procedure. However, a negative test result led to a significant decrease in patients' anxiety. Importantly, patients with high DPT-related anxiety levels also had high anxiety scores in general, which reflects that underlying anxiety could have affected the patients' perception of the tests. However, the presence of any depressive obsessive-compulsive disorder symptoms did not affect this perception. Our results once again confirmed that, despite a negative DPT result, approximately 1 in 6 patients with DH would choose not to use a tested drug in the future despite it being indicated.

Adverse drug reactions may exert psychosocial effects on patients. Several studies found that patients who were allergic to drugs had more psychiatric disorders symptoms, such as hysteria, depression, anxiety, and somatization, than patients with allergic rhinitis and asthma.^{12–15} As an important tool in the management of DH reactions, DPTs in themselves carry some risks for the development of hypersensitivity reactions in this particular group of patients. In our clinical experience, we have observed that learning about risks of the tests during the informed consent procedure leads to concerns in some patients. In the present study, we documented that most patients had high anxiety levels before DPTs. Fear of the recurrence of previous reactions was the main cause of this anxiety. A finding that supported this was that anxiety scores significantly decreased each day after a negative test result. We may assume that patients feel more confident about the tests after a negative test result and feel less anxiety. Interestingly, the anxiety related to the active drug test day was lower than on the placebo day. In a previous study, anxiety trait and state values were reported high during testing, with a significant increase depending on whether the patients thought they had received a drug or a placebo.¹⁶ However, this was not the case in our study. The reason for this could be that the patients were not aware of what they had received on that particular test day because of the single-blind design of our DPTs. The test reason (ie, whether it was for diagnostic purposes or for finding a safe alternative) did not affect this outcome.

Compared with the general population of our country (4.7% for major depression and 7.3% for anxiety disorder^{17,18}), our study results suggest that common psychiatric disorders or symptoms of common psychiatric disorders were more prevalent in our patient group. Importantly, diagnosed depression was almost 3-fold higher than in the general population. However, considering the effect of underlying psychiatric status on DPT-related anxiety, we found no

Table 4
Screening of depression and anxiety disorder symptoms

Screen	Range	Mean (SD)	Patients with scores above the cutoff, n (%)
Hospital Anxiety Depression Scale			
Depression scale ^a	0–19	5.7 (3.9)	26 (23.4)
Anxiety scale ^b	0–20	7.6 (4.3)	34 (30.6)
Panic and Agoraphobia Scale ^c	0–36	8.4 (8.0)	30 (27)
Maudsley Obsessive-Compulsive Inventory	0–33	14.3 (6.9)	No cutoff

^aCutoff of 7/8.

^bCutoff of 10/11.

^cCutoff of 11/12.

association between the psychiatric test results and DPT-related anxiety levels. Nevertheless, the general anxiety level of the patients was significantly correlated with DPT-related anxiety. These data indicate that patients with high anxiety levels in general have the potential to be more anxious about DPTs. Therefore, screening for anxiety before DPTs could help to identify patients who may need support to overcome this. These patients might need to be given detailed information related to DPTs and more psychologic support by their physician to create a more positive test environment.

In patients with negative test challenge results (ie, demonstrated to tolerate the drug), the name of the drug is clearly discussed, and patients are told that they can use the drug in the event it is indicated. Previous studies have found a varying degree of use of the tested drug after a negative test result.^{2,19} In most cases, the reason for avoiding drug use was the fear of experiencing another reaction.^{3,19} Our results indicate that a large number of patients did not use the drug even though its safety was demonstrated by an allergy expert. Patients attributed their acts to anxiety, stating that their condition was significant in this respect. Therefore, education, psychologic support, and psychotherapy assume importance in the management of patients with drug allergy.

In conclusion, most patients who underwent DPTs had a significant amount of anxiety before the tests, which gradually decreased after negative test results. Importantly, this anxiety correlated with general anxiety due to DH. Thus, it is important to clarify factors that prevent the use of a tested drug by patients to reassure them about use of the tested drugs when needed in the future. Overall, our findings suggest that anxiety is an important inhibitory factor at each step of the management of DH reactions, such as during test procedures and/or long-term drug use after a negative test result. Therefore, supporting strategies mainly based on patients' needs and concerns appear the most effective way to eliminate patients' DH-based anxiety.

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