

The Psychological Relieving Effect of Drug Provocation Test in Drug Hypersensitivity

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Purpose: Drug hypersensitivity is an adverse drug reaction mediated by immunological mechanisms and is accompanied by a significant socioeconomic burden. The drug provocation test (DPT) is the gold standard for drug allergy diagnosis; however, a standardized protocol does not exist. This study aimed to investigate the effects of psychological relief from DPT in patients with drug hypersensitivity.

Patients and Methods: A total of 46 patients who had experienced drug hypersensitivity were administered DPT after admission to our clinic at Dong-A University Hospital and asked to complete the questionnaires before and after DPT. Anxiety and depressive symptom levels were assessed using the Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI)-II, respectively.

Results: There was a significant decrease in the BAI and BDI-II scores after DPT than before DPT, respectively (BAI: 10.22 ± 10.75 vs 7.26 ± 6.95 , $P=0.025$; BDI-II: 13.00 ± 7.92 vs 11.17 ± 7.80 , $P = 0.019$). Twenty-two patients with non-anaphylactic drug hypersensitivity showed a significant decrease in the BDI-II scores after DPT (11.50 ± 7.60 vs 9.50 ± 5.98 , $P = 0.009$), but not in the BAI scores (8.45 ± 7.41 vs 6.18 ± 4.58 , $P = 0.127$). However, there were no statistically significant differences in the BDI-II and BAI scores before and after DPT (BAI: 11.83 ± 13.05 vs 8.25 ± 8.56 , $P = 0.664$; BDI-II: 14.38 ± 8.11 vs 12.71 ± 9.01 , $P = 0.215$) in 24 patients with anaphylaxis.

Conclusion: DPT may reduce the psychological burden in patients with drug hypersensitivity, especially in those without anaphylaxis.

Keywords: drug hypersensitivity, diagnostic test, anxiety, depression

Introduction

Adverse drug reactions account for 3–6% of all hospital admissions and occur in 10–15% of hospitalized patients.^{1,2} Drug hypersensitivity reactions represent approximately one-third of all adverse drug reactions,³ and epidemiological studies have shown that approximately 7% of the population experience drug hypersensitivity reactions at least once in their lives.⁴ Drug hypersensitivity is considered a public health problem owing to the associated morbidity and socioeconomic costs worldwide.^{1–4} Patients with drug hypersensitivity experience a sensation of anxiety, fear, and tension, which can influence their quality of life and disrupt daily performance. Previously, studies have been conducted on the quality of life and psychology in patients with drug hypersensitivity,^{5–7} but many aspects remain to be elucidated. In addition, false drug allergy labels also cause many problems, including inappropriate drug prescriptions and a psychological burden of patients. In particular, approximately 90% of patients with penicillin allergy are falsely labelled, and penicillin allergy de-labeling has been carried out through drug provocation tests.^{8,9}

The drug provocation test (DPT) is the gold standard in a drug hypersensitivity workup and has the best sensitivity among all available diagnostic tools.¹⁰ DPT can be used to establish (or exclude) diagnosis, cross-reactivity, and safety of alternative drugs.^{10,11} We hypothesized that DPTs could reveal not only the culprit drugs, but also the safety of suspected or alternative drugs in patients with drug hypersensitivity, and would have the effect of psychological relief.

Patients and Methods

Patients and Materials

This study included 46 patients who had experienced drug hypersensitivity between May 2019 and January 2021 at Dong-A University Hospital. Drug hypersensitivity was patient's medical records and clinically diagnosed by two expert allergists based on a detailed history of reactions, including urticaria, angioedema, erythema, rhinitis, bronchospasm, laryngeal edema, hypoxemia, nausea, vomiting, abdominal pain, loss of consciousness, and hypotension after starting to take the drug. In addition, anaphylaxis was diagnosed based on the diagnostic criteria set forth in the 2011 World Allergy Organization anaphylaxis guidelines.¹² Study participants were investigated for clinical characteristics; underlying diseases, including psychiatric disorders, diabetes, hypertension, asthma, allergic rhinitis, atopic dermatitis, chronic urticaria, and food allergy; and history of medications from a review of electronic medical records. Morning basal serum cortisol levels at 6AM were measured using an electrochemiluminescence immunoassay (SamKwang Medical Laboratories, Seoul, Korea) in the study participants on the day of DPT. The normal cortisol range at 6AM is 5–27 µg/dL.

This study was approved by the Institutional Review Board of Dong-A University Hospital (DAUHIRB-19-137), and met the principles of the Declaration of Helsinki. All study participants signed a written informed consent.

Drug Provocation Test

DPT was conducted at least 4 weeks after the hypersensitivity reaction. All patients stopped antihistamines and corticosteroids the week prior to the test. Prior to DPT implementation, all study subjects were given a detailed enough explanation of the purpose, method, and side events of DPT. DPTs were conducted using a single-blind placebo-controlled test. The test was started with the placebo (Lacidofil[®] cap; probiotic *Lactobacillus*) and was continued for three steps of drug challenge in the order of 25%, 50%, and 100% of the maximum single dose. Blood pressure, body temperature, heart rate, respiratory rate, and O₂ saturation were measured. General conditions, including skin, ocular, nasal, and respiratory reactions were carefully inspected before the test, and were monitored every 30 min during the test by a trained nurse or physician. The patients were kept under medical observation for up to 4 h after completing the test. The DPT results were considered positive if any signs of hypersensitivity reactions were observed during or after the test, and considered negative if no adverse reactions occurred. All DPTs for alternatives and suspected drugs, as well as culprit drugs, were conducted in accordance with the patients' consent. DPTs were performed with up to two drugs per day.

Questionnaires

All patients were asked to complete the questionnaires before and after the DPT. Anxiety and depressive symptom levels were assessed using the Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI)-II, respectively.

Beck Anxiety Inventory (BAI)

The BAI is a 21-item questionnaire that analyzes the severity of anxiety symptoms occurring over a period of 1 week or more. The study participants rated symptoms of anxiety on a four-point scale for the previous week, with higher scores indicating greater anxiety and total scores ranging from 0 to 63. The total scores were classified as minimal anxiety (0–7), mild anxiety (8–15), moderate anxiety (16–25), and severe anxiety (26–63).¹³ A Korean version of the BAI, which was verified for its reliability and validity in 1997, was used in this study, and a score of 22 or more indicated the presence of anxiety symptoms.¹⁴

Beck Depression Inventory (BDI)-II

BDI-II is a 21-item inventory that assesses depressive symptoms and their severities. The study participants were rated on a four-point scale with the summation scores ranging from 0 to 63. The total scores were classified as minimal depression (0–13), mild depression (14–19), moderate depression (20–28), and severe depression (29–63).¹⁵ Higher total scores indicate higher levels of depression. A Korean version of the BDI-II, which was verified for its reliability and validity in 2011,¹⁶ was used and a score of 17 or more was considered to indicate the presence of depressive symptoms.¹⁷

Statistical Analysis

Statistical analyses were performed using IBM SPSS version 22 for Windows (IBM SPSS Inc., Chicago, IL, USA). Categorical variables are described as frequencies and proportions, and continuous variables are presented as mean \pm standard deviation and absolute numbers. Statistical significance was assessed using Student's *t*-test, paired *t*-test, Mann-Whitney test, or Wilcoxon test for continuous variables, and Pearson's chi-squared test or Fisher's exact test for categorical variables. Paired *t*-test or Wilcoxon signed rank test was used for analysis of scores of BAI and BDI-II before and after DPTs in every comparison. Multiple logistic regression analysis was used to identify the predictive factors for psychological relief after DPTs. $P < 0.05$ was considered statistically significant.

Results

Demographic and Clinical Characteristics of the Study Participants

A total of 46 patients with drug hypersensitivity participated in this prospective study. Twenty-five patients (54.3%) were women, and the mean age was 46.76 ± 12.57 years (Table 1). Two patients (4.3%) had psychiatric disorders, including panic disorder ($n=1$) and post-traumatic stress disorder (PTSD) due to a car accident ($n=1$). The most common comorbidity was allergic rhinitis (26.1%). Immediate hypersensitivity (anaphylaxis, $n=24$; urticaria and/or angioedema,

Table 1 Demographic and Clinical Characteristics of the Study Participants

Characteristics	Total (n=46)	Anaphylaxis (n=24)	Non-Anaphylaxis (n=22)	P
Female	25 (54.3)	11 (45.8)	14 (63.6)	0.226
Age*, years (18–84)	46.76 ± 12.57	49.92 ± 11.48	43.32 ± 13.05	0.075
Psychiatric disorder	2 (4.3)	1 (4.2)	1 (4.5)	0.950
Diabetes	5 (10.7)	1 (4.2)	4 (18.2)	0.127
Hypertension	10 (21.7)	6 (25.0)	4 (18.2)	0.575
Bronchial asthma	4 (8.7)	1 (4.2)	3 (13.6)	0.255
Allergic rhinitis	12 (26.1)	3 (12.5)	9 (40.9)	0.028
Atopic dermatitis	1 (2.2)	0 (0.0)	1 (4.5)	0.291
Chronic urticaria	2 (4.3)	2 (8.3)	0 (0.0)	0.166
Food allergy	7 (15.2)	2 (8.3)	5 (22.7)	0.175
Serum cortisol*, $\mu\text{g/dL}$	10.54 ± 6.32	10.38 ± 5.00	10.93 ± 7.88	0.790
Time interval between hypersensitivity reaction and DPT*, months (1–240)	18.15 ± 46.53	12.54 ± 48.52	24.27 ± 44.55	0.399
Culprit drugs				
Antibiotics	19 (41.3)	15 (62.5)	4 (18.2)	0.002
NSAIDs	26 (56.5)	10 (41.7)	16 (72.7)	0.034
H2-blocker	4 (8.7)	2 (8.3)	2 (9.1)	0.927
Muscle-relaxant	3 (6.5)	3 (12.5)	0 (0.0)	0.086
Other drugs	12 (26.1)	3 (12.5)	9 (40.9)	0.028
Purpose of DPT				
Identifying a culprit drug	15 (32.6)	5 (20.8)	10 (45.5)	0.075
Exclusion of a suspected drug	24 (52.2)	12 (50.0)	12 (54.5)	0.758
Confirming safe alternatives	46 (100.0)	24 (100.0)	22 (100.0)	

Note: *Data are presented as mean \pm SD.

Abbreviations: DPT, drug provocation test; NSAID, non-steroidal anti-inflammatory drug.

n=13; others, n=3) was observed in 40 patients (87.0%) and delayed hypersensitivity in 6 patients (13%). Nineteen patients (41.3%) reported a history of hypersensitivity reactions to antibiotics, 26 (56.5%) to nonsteroidal anti-inflammatory drugs (NSAIDs), 4 (8.7%) to H2-blocker, 3 (6.5%) to muscle relaxants, and 6 (13.0%) to both antibiotic and NSAIDs. Fifteen patients (32.6%) underwent DPTs to confirm a culprit drug, 24 (52.2%) to exclude a suspected drug, and all study participants underwent DPTs to seek safe alternatives. The average number of DPTs was 5.3 (range, 2–10). There was no reaction to the placebo drug challenge.

Positive results were confirmed in 9 patients who underwent DPTs to identify the culprit drug, 2 to exclude a suspected drug, and 9 to confirm safe alternatives. A total of 20 patients with positive result were confirmed drug hypersensitivity by DPT. The serum cortisol levels of all study participants were below the normal range, and the mean serum cortisol level was $10.54 \pm 6.32 \mu\text{g/dL}$.

Questionnaires of BAI and BDI-II Before and After DPT

In the study participants, the anxiety level before DPTs was minimal in 25 patients (54.3%), mild in 12 (26.1%), moderate in 4 (8.7%), and severe in 5 (10.9%). Depression levels before DPTs were minimal in 26 patients (56.5%), mild in 9 (19.6%), moderate in 9 (19.6%), and severe in 2 (4.3%) according to the BDI-II. Five patients had anxiety symptoms according to the BAI (≥ 22) before DPT, and two had anxiety symptoms after DPT. The number of patients with depressive symptoms according to the BDI-II (≥ 17) was 16 and 8 before and after DPT, respectively.

The total BAI and BDI-II scores of the study participants before DPT were 10.22 ± 10.75 and 13.00 ± 7.92 , respectively. After DPT, the total scores of the BAI and BDI-II were 7.26 ± 6.95 and 11.17 ± 7.80 , respectively. There was a statistically significant decrease in the scores before and after BAI ($P=0.025$) and BDI-II ($P=0.019$) (Figure 1A and B).

The scores of BAI and BDI-II before and after DPTs were not significantly different between in patients who were confirmed drug hypersensitivity by DPTs and in patients who were suspected drug hypersensitivity (Figure 2). However, the scores were significantly decreased after DPTs in both patients who were confirmed drug hypersensitivity by DPTs (BAI: 11.75 ± 9.08 vs 8.20 ± 6.63 , $P=0.001$; BDI-II: 13.70 ± 7.35 vs 11.70 ± 6.70 , $P=0.003$) (Figure 3A and B) and not (BAI: 9.04 ± 11.92 vs 6.54 ± 7.23 , $P=0.004$; BDI-II: 12.46 ± 8.43 vs 10.77 ± 8.66 , $P<0.001$) (Figure 3C and D).

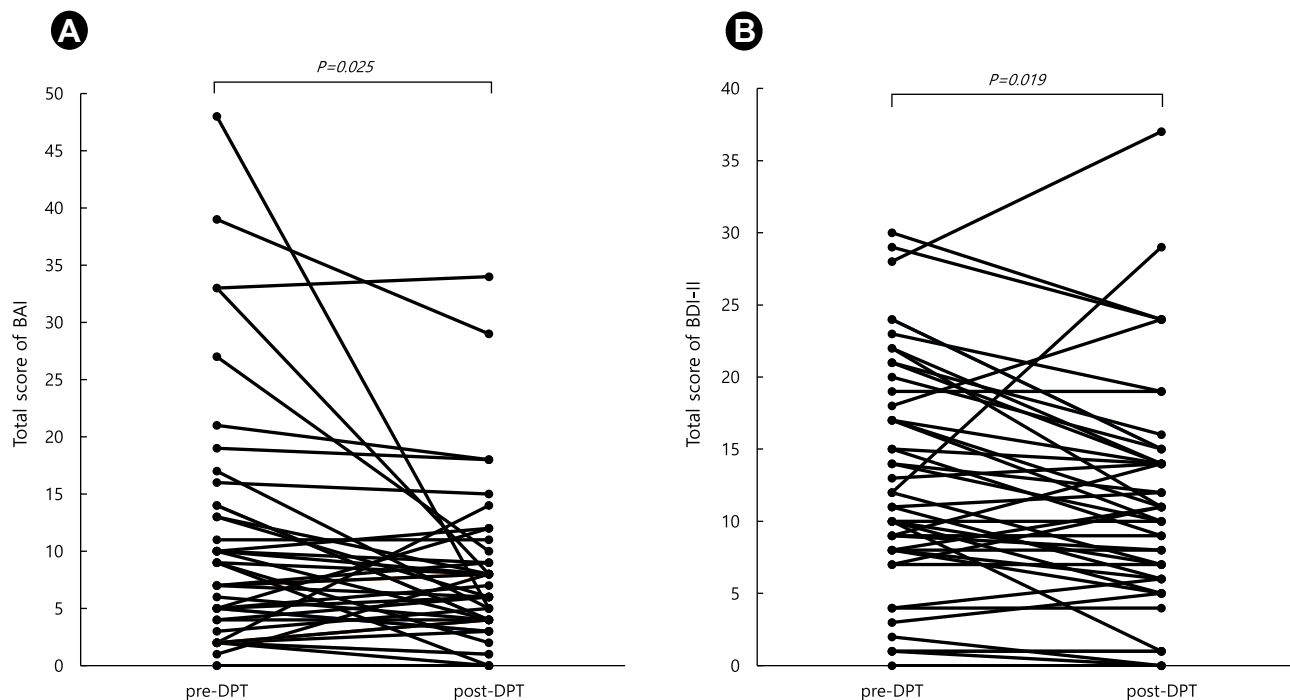


Figure 1 Comparison of the BAI (A) and BDI-II (B) scores before and after DPT in the study participants.

Abbreviations: BAI, Beck Anxiety Inventory; BDI-II, Beck Depression Inventory-II; DPT, drug provocation test.

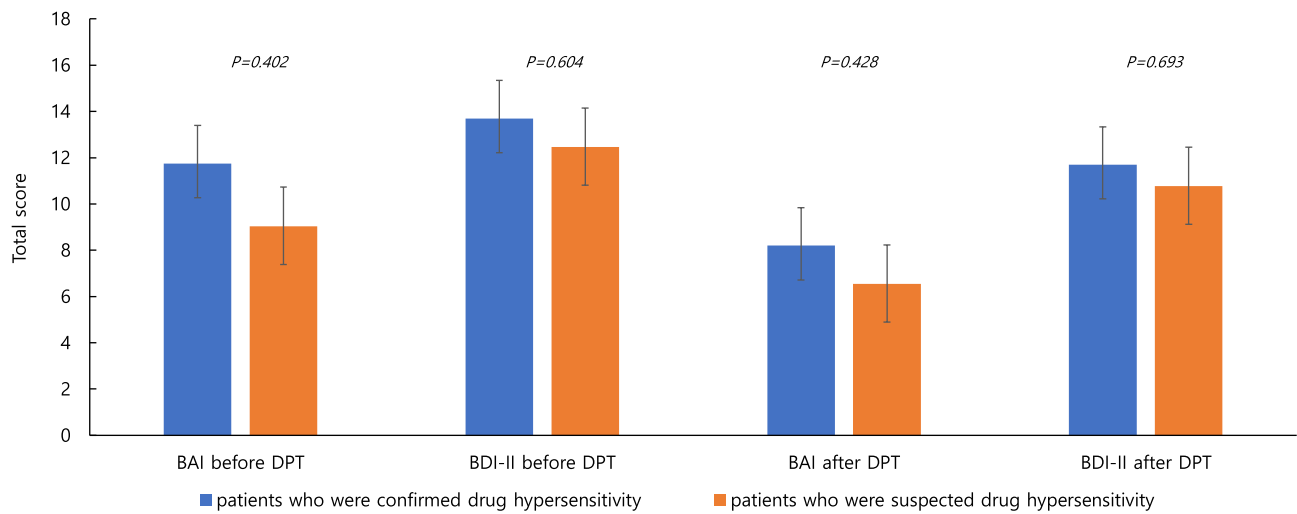


Figure 2 Comparison of the BAI and BDI-II scores before and after DPTs between in the confirmed drug hypersensitivity group and in the suspected drug hypersensitivity group.

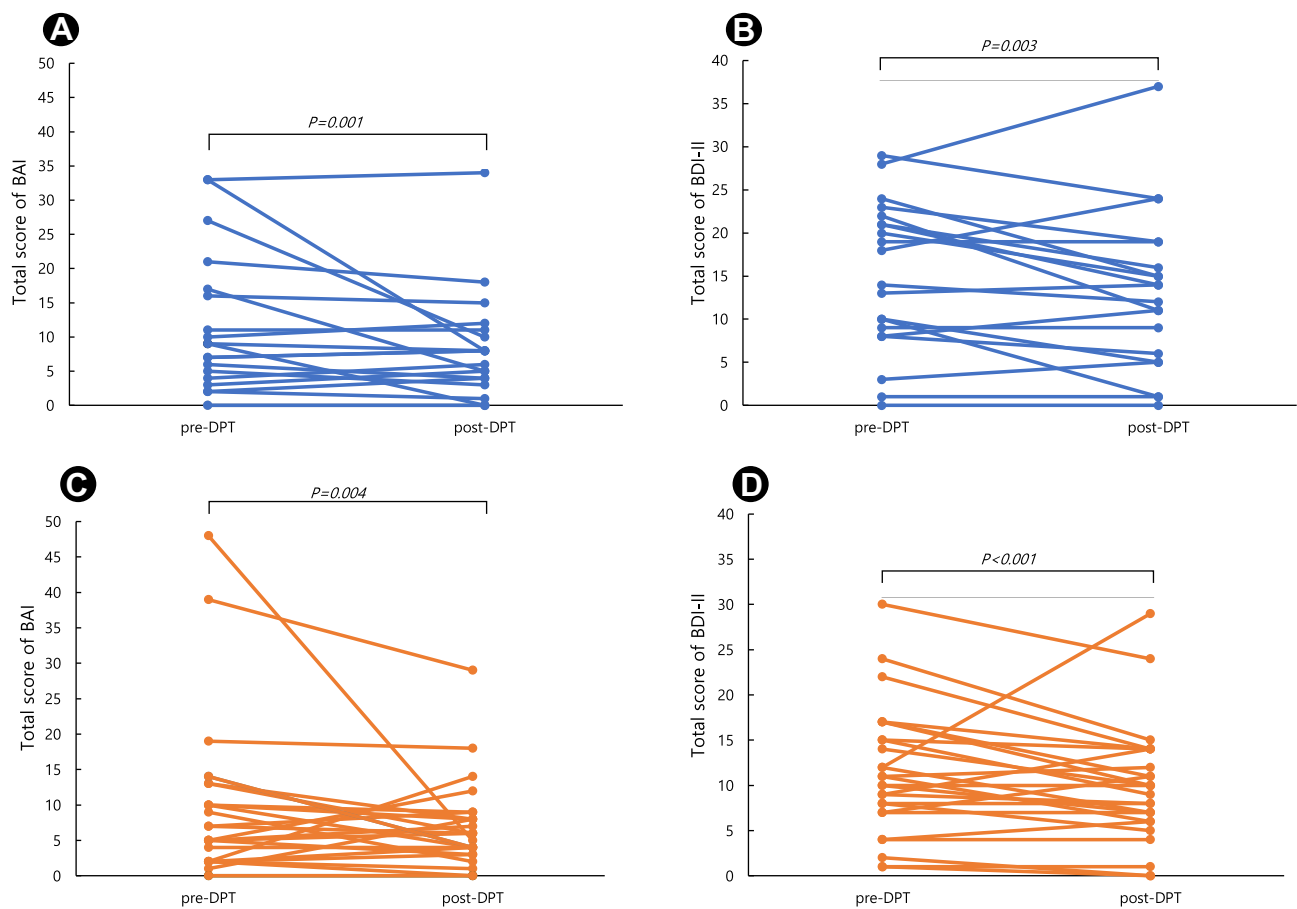


Figure 3 Comparison of the BAI and BDI-II scores before and after DPTs according to confirmation of drug hypersensitivity by DPT or not. The BAI (A) and BDI-II (B) scores before and after DPT in the confirmed drug hypersensitivity group (blue lines) (n=20). The BAI (C) and BDI-II (D) scores before and after DPT in the suspected drug hypersensitivity group (orange lines) (n=26).

Abbreviations: BAI, Beck Anxiety Inventory; BDI-II, Beck Depression Inventory-II; DPT, drug provocation test.

Comparison of Clinical Characteristics and the Scores of BAI and BDI-II According to Severity of the Hypersensitivity Reaction

In the present study, 22 patients experienced non-anaphylactic hypersensitivity reactions and 24 experienced anaphylaxis (Table 1). There were no significant differences in sex (63.6% vs 45.8%, $P=0.226$) and age (43.32 ± 13.05 years vs 49.92 ± 11.48 years, $P=0.075$) between the non-anaphylaxis and anaphylaxis groups. There was a significantly higher proportion of patients with allergic rhinitis in the non-anaphylaxis group than in the anaphylaxis group (40.9% vs 12.5%, $P=0.028$); other concomitant diseases, including psychiatric disorders, diabetes, hypertension, asthma, atopic dermatitis, chronic urticaria, and food allergies were not significantly different between the two groups. There was no significant difference in the serum cortisol level between the two groups (10.93 ± 7.88 $\mu\text{g/dL}$ vs 10.38 ± 5.00 $\mu\text{g/dL}$, $P=0.790$). Antibiotics were the most frequent causative drugs in the anaphylactic group than in the non-anaphylaxis group (62.5% vs 18.2%, $P=0.002$) and NSAIDs were significantly more frequent causative drugs in the non-anaphylaxis group than in the anaphylaxis group (72.7% vs 41.7%, $P=0.034$).

We compared the BAI and BDI-II scores according to the severity of hypersensitivity reactions. The BAI and BDI-II scores before DPT were lower in the non-anaphylaxis group than in the anaphylaxis group (BAI: 8.45 ± 7.41 vs 11.83 ± 13.05 , $P=0.282$; BDI-II: 11.50 ± 7.60 vs 14.38 ± 8.11 , $P=0.222$), but the differences were not statistically significant. In the non-anaphylaxis group, the BAI score did not change significantly after DPT (8.45 ± 7.41 vs 6.18 ± 4.58 , $P=0.127$) (Figure 4A), and the BDI-II score significantly decreased after DPT (11.50 ± 7.60 vs 9.50 ± 5.98 , $P=0.009$) (Figure 4B). In the anaphylaxis group, the BAI and BDI-II scores did not change significantly after DPT (BAI: 11.83 ± 13.05 vs 8.25 ± 8.55 , $P=0.664$; BDI-II: 14.38 ± 8.11 vs 12.71 ± 9.01 , $P=0.215$) (Figure 4C and D).

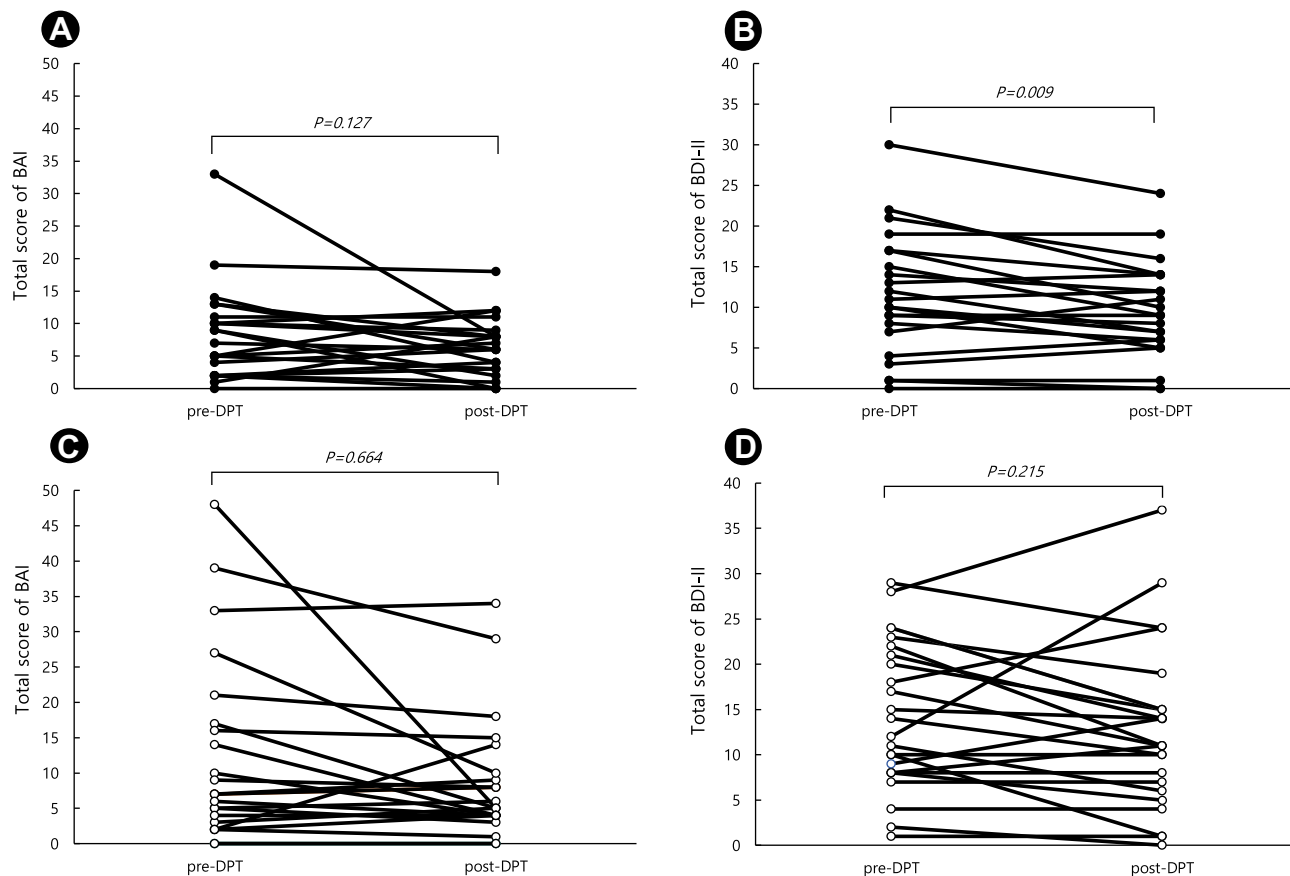


Figure 4 Comparison of the BAI and BDI-II scores before and after DPT according to the severity of drug hypersensitivity reaction. The BAI (A) and BDI-II (B) scores before and after DPT in the non-anaphylaxis group (black dots and lines) ($n=22$). The BAI (C) and BDI-II (D) scores before and after DPT in the anaphylaxis group (blank dots and lines) ($n=24$).

Abbreviations: BAI, Beck Anxiety Inventory; BDI-II, Beck Depression Inventory-II; DPT, drug provocation test.

Table 2 Predictive Factors for the Decrease in the BAI and BDI-II Scores After DPT in the Study Participants Using Univariate Logistic Regression

	BAI			BDI-II		
	OR	CI	P	OR	CI	P
Female	2.167	0.674–6.962	0.194	1.500	0.472–4.771	0.492
Age	0.996	0.952–1.042	0.870	0.972	0.927–1.019	0.237
Bronchial asthma	0.955	0.123–7.408	0.965	0.792	0.102–6.151	0.823
Allergic rhinitis	1.482	0.394–5.579	0.560	3.176	0.734–13.749	0.122
Food allergy	0.950	0.207–4.350	0.947	0.773	0.168–3.546	0.740
Time interval between hypersensitivity reaction and DPT, months	0.995	0.982–1.009	0.478	1.013	0.992–1.035	0.220
Anaphylaxis	0.769	0.244–2.427	0.654	1.061	0.335–3.357	0.920
Antibiotics	1.587	0.490–5.138	0.441	0.833	0.258–2.688	0.760
NSAIDs	0.313	0.094–1.041	0.058	0.875	0.258–2.688	0.821
H2-blocker	0.290	0.028–3.013	0.300	0.792	0.102–6.151	0.823
Muscle-relaxant	0.955	0.123–7.408	0.965	2.609	0.251–27.113	0.422
Other drugs	0.375	0.095–1.482	0.162	1.179	0.313–4.442	0.808
Confirmation of drug hypersensitivity by DPT	1.750	0.537–5.701	0.353	1.286	0.395–4.188	0.677
BAI score before the DPT	1.107	1.010–1.213	0.030	1.017	0.991–1.157	0.083
BDI-II score before the DPT	1.128	1.029–1.238	0.010	1.113	1.017–1.218	0.020

Abbreviations: OR, odds ratio; CI, confidence interval; DPT, drug provocation test; NSAID, non-steroidal anti-inflammatory drug; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory.

Predictive Factors for Psychological Relief of DPT

The predictive factors for decreased BAI and BDI-II scores after DPT were investigated using a logistic regression analysis. Using univariate logistic regression analysis, pre-DPT BAI scores (OR: 1.107, CI: 1.010–1.213, $P=0.030$), and pre-DPT BDI-II scores (OR: 1.128, CI: 1.029–1.238, $P=0.010$) were significant predictive factors for decreased BAI scores after DPT. The pre-DPT BDI-II score (OR: 1.113, CI: 1.017–1.218, $P=0.020$) was the only significant predictive factor for a decrease in the BDI-II score after DPT (Table 2). In multivariate logistic regression, NSAIDs as the culprit drug (OR: 0.197, CI: 0.042–0.923, $P=0.039$) was the only predictive factor for a decrease in the BAI score after DPT, and there was no significant predictive factor for a decrease in the BDI-II scores after DPT.

Discussion

Drug hypersensitivity has been known to cause an increase in the psychological burden in patients with allergic diseases, such as asthma, atopic dermatitis, allergic rhinitis, and food allergies.^{18–20} Because of the unpredictable nature and potential severity of drug hypersensitivity, patients with drug hypersensitivity may have a great psychological burden. This study was conducted on the psychological characteristics of 115 patients with suspected drug allergies.⁶ Both the groups of patients with confirmed drug allergies and those with excluded drug allergies had more psychological disturbances than the healthy controls. Similar findings were reported in patients with a history of drug hypersensitivity reactions who had high levels of anxiety, regardless of whether the results of diagnostic tests were positive or negative.⁷ However, there is no information on whether performing DPT has beneficial psychological effects in patients with drug hypersensitivity. In the present study, both the BAI and BDI-II scores significantly decreased after DPT, and these were

noted irrespective of confirmation of drug hypersensitivity by DPT. DPT may have a psychological relieving effect on both of patient who were confirmed drug hypersensitivity and patients who were suspected drug hypersensitivity.

The severity of drug reactions is associated with the level of psychological distress in patients with drug hypersensitivity. The anaphylactic group had higher BAI and BDI-II scores than the non-anaphylactic group, although these differences were not statistically significant in this study. In contrast, the BDI-II scores significantly decreased after DPT in the non-anaphylaxis group, whereas the anaphylaxis group showed no significant change in the BAI and BDI-II scores after DPT. Patients with mild drug reactions may experience a greater psychological relieving effect of DPT, whereas those who have experienced severe drug reactions, such as anaphylaxis, feel a lower psychological relieving effect of DPT. The history of severe reactions seems to play a major role in the psychological burden, as reported in previous studies on patients with allergic diseases.^{21,22} In a multicenter study of 203 patients who experienced anaphylaxis in Korea, 84 (41.4%) patients with PTSD were evaluated, and they showed increased anxiety and depression levels, especially those with more severe PTSD.²² Life-threatening reactions, such as anaphylaxis can also induce major psychological stress in patients with drug hypersensitivity.

Patients with NSAIDs hypersensitivity showed less improvement in the BAI scores. Unlike antibiotics, NSAIDs can be easily purchased without a prescription in Korea, which might lead to sustained psychological burden in patients with drug hypersensitivity. In addition, all patients with asthma and several patients with allergic rhinitis (73.3%) had NSAIDs hypersensitivity in the current study. A significant number of patients with hypersensitivity to NSAIDs are presumed to have NSAIDs-exacerbated respiratory disease, and these underlying diseases could have influenced the sustained psychological burden in the study participants, as reported in other studies.^{23–25} The pre-DPT BAI and BDI-II scores may be predictive factors for the reduction in psychological burden after DPT in the present study. However, anaphylaxis (the group with higher pre-DPT BAI and BDI-II scores than the non-anaphylaxis group) was not a significant factor in reducing depression and anxiety levels after DPT. In drug hypersensitivity, the psychological burden is thought to be affected by several complex factors, and further research is needed.

The present study had some limitations. First, the total number of participants was small. Second, as most of the surveys were completed within 2–3 days, the time interval between the pre- and post-survey questionnaires was relatively short. This short-term interval between the surveys and DPT may have influenced the results because of the psychological burden of the DPT itself. A previous study on the association between anxiety and/or depression and the reaction to placebo challenges conducted a survey before the drug challenge test and reported a strong association between the positivity of the Hospital Anxiety and Depression Scale questionnaire and a placebo-induced reaction.²⁶ However, in the present study, all DPTs were performed under rigorous surveillance conditions with emergency resuscitation equipment to manage adverse reactions under well-trained and experienced staff, and there was no reaction to the placebo challenge in the present study. In addition, the serum cortisol levels of all study participants were below the normal range. Therefore, the psychological burden on the study participants was not thought to have had a significant relationship with the execution of the DPT itself.

Conclusion

DPT alleviates psychological burden in patients who were suspected drug hypersensitivity as well as patients with drug hypersensitivity. Patients with anaphylaxis have a greater psychological burden than those with non-anaphylactic hypersensitivity reactions, and the psychological relief effect of DPT may be more significant in patients without anaphylaxis. A more detailed and large-scale study is required in the future.

Abbreviations

DPT, drug provocation test; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds ratio; CI, confidence interval; PTSD, post-traumatic stress disorder.

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Disclosure

The authors report no conflicts of interest in this work.

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