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THE EFFECTS OF DISTRACTION ON SYMPTOMS DURING DRUG PROVOCATION TEST

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Abstract

Background. *Some patients may have psychosomatic complaints due to their previous experiences during the drug hypersensitivity reaction. Worry about being hurt due to an administered drug is termed nocebo effect, which is the opposite of the placebo effect. In our study, we investigated the effect of distraction on symptoms during drug provocation test.*

Methods. *Our study included 112 patients who underwent DPTs for alternative purposes in our clinic. Previous hypersensitivity reactions of all the patients had objective signs. Patients were divided into two groups for the DPT. Sixty-three patients were kept busy during the test, performing tasks such as filling questionnaires, arranging files in alphabetical and numerical order, and doing archiving (Group 1). Forty-nine patients did not perform any tasks during the test (Group 2). Reactions that occurred during the test were recorded.*

Results. *During the DPT, 5 patients in Group 1 (5/63, 7.9%) and 17 patients in Group 2 (17/49, 34.7%), i.e. a total of 22 patients (22/112, 19.6%), had a reaction. There was a statistically significant difference between Group 1 and Group 2 according to the frequency of the reaction development.*

Conclusions. *Patient psychosomatic complaints during DPTs are proportional to their association with previous allergic reactions. In order to prevent such reactions, it may be beneficial to keep the patients busy with an activity in order to distract them during the test.*

Keywords: adverse effect, drug hypersensitivity, drug provocation test

Introduction

Drug hypersensitivity reactions constitute 5.0-10.0% of adverse drug reactions (ADR) [1]. Risk factors include age, gender, genetic polymorphism, some viral infections, and drug-related factors. Drug hypersensitivity typically occurs in young and middle-aged adults, and is more common in women than men. In addition to the genetic polymorphism found in human leukocyte antigen (HLA), the risk of drug-related immunologic reaction development is higher in some viral infections such as human immunodeficiency virus (HIV) and Epstein Barr Virus (EBV). Allergic reactions are more likely to occur when the drug is administered via topical, intramuscular, or the intravenous route compared to its oral use. A more serious reaction may occur especially following intravenous administration. Prolonged high doses or frequent doses are more likely to lead to hypersensitivity reactions than a large single dose. In addition, large macromolecular drugs or drugs that haptenate appear to have greater risk for development of hypersensitivity reactions [1-6].

A thorough anamnesis and physical examination is essential for determination of necessary diagnostic tests. Whenever they are obtainable, skin tests can be performed together with laboratory tests and the drug provocation tests (DPTs) [7,8,9].

DPTs are considered to be the gold standard to establish or exclude the diagnosis of drug hypersensitivity

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reactions. It can be applied as a single dose or in increasing multiple doses depending on the suspected drug and severity of the reaction. Placebo can be used whenever the symptoms of the reaction are subjective or the test results are suspicious. Oral administration is the preferred route in practical applications, but some clinics use the same route that caused the reaction. The European Network for Drug Allergy (ENDA) outlined 4 main indications for DPTs, namely: 1- excluding drug allergy in patients whose symptoms are inconsistent with hypersensitivity reaction; 2- confirmation of diagnosis in patients whose anamnesis is consistent with hypersensitivity reaction but in whom sensitivity could not be demonstrated with tests; 3- for an alternative treatment option using a drug that is structurally different than the drug to which the patient is sensitive; and 4- demonstration of absence of cross-reaction when there is a need to use a drug that is structurally similar to the drug to which the patient is sensitive [10-13].

DPTs can yield subjective symptoms as well as objective signs. Some patients may have psychosomatic complaints due to their previous experiences during the drug hypersensitivity reaction. Patients worried about being hurt due to an administered drug suffer from the so called nocebo effect, which is opposite of the placebo effect. These have more frequent subjective complaints (itching, nausea, headache, and not feeling well etc.) but may also have objective findings, but with less frequency (urticaria, rash, and tachycardia etc.) [14].

In our study, we investigated the effect of distraction on symptoms during drug provocation test.

Method

Our study included 112 patients who underwent DPTs for alternative purposes in our clinic between August 2014 and July 2015. Previous hypersensitivity reactions of all the patients had objective signs. First of all, patients were informed about the possible reactions that may occur during the test, and verbal and written consent was obtained from patients. DPT application was performed at least 4 weeks after the last experienced drug allergy reaction. Antihistamines were discontinued 7 days before and β blocker agents and ACE inhibitors were discontinued 1 day before the testing. Patients were evaluated clinically by physical examination prior to testing. Types of previously developed drug hypersensitivity reactions were recorded based on patients' statements (urticaria, anaphylaxis, laryngeal edema, bronchospasm, rhinoconjuctivitis, maculo-papular exanthema). For the DPT, patients were hospitalized and an intravenous line was placed. The tests were performed under the supervision of doctors and nurses in an environment where emergency intervention could be made. Each patient received a single type of drug application on a single day. Patients were divided into two groups for the DPT. Sixty-three patients were kept busy during the test, performing tasks such as verbal and written filling questionnaires, arranging files in alphabetical and numerical order, and doing archiving (Group 1). Forty-nine patients did not perform any tasks during the test (Group 2). Regardless of the route of administration of the previous drug that caused reaction, all provocations were performed via oral route except for prilocaine. For prilocaine and β-lactam drugs, skin tests were performed in the first place, and provocation was performed if the skin test was negative. Provocation with prilocaine was performed via subcutaneous route with 0.1 cc and 1 cc of the drug. Oral provocation tests were performed with 1/4 and 3/4 of the single dose of the drug. If there was no reaction during the follow up, then the single daily dose of the drug was administered. Intervals between the doses were adjusted to 1 hour, and before administration of each new dose, the patients were reevaluated. After the last dose application of the DPT (in which the full daily dose was achieved), patients were followed up for at least 4 hours. Reactions that occurred during the test were recorded.

Results

The study included 112 patients: 76 were women (67.9%) and 36 were men (32.1%) and the mean age was 41.8 years (19-68). Most of the patients had their previous drug hypersensitivity reaction with antibiotics and NSAID use, and the most frequent reaction was urticaria-angioedema (70.0%). During the DPT, 5 patients in Group 1 (5/63, 7.9%) and 17 patients in Group 2 (17/49, 34.7%), a total of 22 patients (22/112, 19.6%), had a reaction. There was a statistically significant difference between Group 1 and Group 2 according to the frequency of the reaction development (Pearson Chi-Square p=0.000). The frequency of reaction development was higher in women but the difference was not statistically significant (21.1% vs. 16.7%, p = 0.585) (Table I).

Table I. Demographical and clinical properties (Group 1: Patients who were kept busy during the DPT; Group 2: Patients who were not given any tasks during the DPT).

Total number of patients	112
Age range	19-68 yrs
Mean age	41.8yrs
Female/Male ratio	76/36
Number of patients who developed reaction (% of total)	22 (19.6%)
Number of patients in Group 1 who developed reaction	5 (7.9%)
Number of patients in Group 2 who developed reaction	17 (34.7%)
Female/male ratio in patients developing reaction (%)	16/6 (21.1%/16.7%)

The majority of the symptoms were subjective (17/112, 15.17%), including itchiness, nausea, feeling unwell, headache, and abdominal pain. Patients who showed objective findings (5/112, 4.46%) had urticaria, rash, and bronchospasm. The objective findings were present in 2 patients from Group 1 (3.2%) and in 3 patients from Group 2 (6.1%), while subjective symptoms were present in 3 patients form Group 1 (4.8%) and in 14 patients from Group 2 (28.6%) (Table II).

Table II. Types of reactions that developed during DPT.

	Group 1	Group 2
Urticaria/ angioedema	1	2
Maculopapular rash	1	-
Bronchospasm	-	1
Generalized itching	3	7
Nonspecific symptoms	-	7

During drug provocation test, no reaction was observed with paracetamol and quinolone, while the observed reaction rates were 40.0% for β-lactam, 31.6% for NSAID, 20.09% for prilocaine, 12.1% for macrolide, and 16.7% for other drugs (Table III).

Table III. Drug classes that were used during DPT.

Drug class	Patients number	Positive results n (%)
Macrolides	33	4 (12.1)
Quinolones	2	0
β-lactam	5	2 (40.0)
NSAID	38	12 (31.6)
Paracetamol	12	0
Prilocaine	10	2 (20.09)
Others	12	2 (16.7)

Reaction development times were less than 1 hour in 2 patients (9.1%), 1-4 hours in 19 patients (86.4%), more than 4 hours in 1 patient (4.5%), most frequently occurred between 1-4 hours.

Discussion

Adverse drug reactions (ADR) are classified into two groups, predictable reactions (Type A) and unpredictable reactions (Type B). Type A reactions are frequent, dose-dependent, related to the pharmacological effect of the drug, and preventable or reversible. On the other hand, Type B reactions are rare, independent of the dose, usually not related to the pharmacological effect of the drug, and mediated immunologically [15]. Drug hypersensitivity is considered to belong to the unpredictable reactions category, and it involves immunologically mediated hypersensitivity reactions that show different clinical presentations with various mechanisms [16]. Drug allergy affects the patient's quality of life, causing delays in treatment, inadequate treatment with alternative drugs, and even death. Therefore, people who have drug allergy should be consulted by allergists [17].

The gold standard test for the diagnosis of drug hypersensitivity reaction is drug provocation tests. As it can be applied to selected cases for either diagnosis or excluding the condition after determination of risk/benefit ratio, it can also be performed for the alternative treatment option that meets the demands of the patient. If the original symptoms recur during DPT, the test is regarded as positive. However, if the original symptoms are subjective and if the patient re-experiences them during the test, placebo application is needed. If the placebo yields a negative result, it is recommended to continue DPT with the previous dosage [18]. People who have had a previous experience with adverse drug effects have been shown to exhibit anxiety and concerns about similar reaction again during the test [19,20]. In contrast to the placebo, the anxiety of being harmed during the use of a drug is defined as the nocebo effect. Studies that are performed with the use of placebo have reported varying rates of the nocebo effect (27.0%, 3.0%) [14,21]. In our study, we investigated whether distraction during drug provocation test had any effect on the test results. Sixty-three patients were kept busy during the test by giving them tasks such as verbal and written filling questionnaires, arranging files in alphabetical and numerical order, and doing archiving, which distracted them from the test (Group 1), while 49 patients were not given any tasks during DPT (Group 2). We did not use placebo before starting the test and we performed drug provocation tests with active drugs that were meant to be used for alternative purposes. We observed reactions in 22 of the 112 patients (19.6%) during DPT. In 5 (4.5%) of these patients, objective findings were observed that were consistent with the original symptoms, and DPT was ended in these patients with positive results, and the patients were given medical treatment. However, 17 (15.2%) patients had subjective symptoms that were inconsistent with the original symptoms, occurring mostly between 1-4 hours. During DPT, there were objective findings in 2 patients from Group 1 and in 3 patients from Group 2, while subjective complaints were present in 3 patients from Group 1 and in 14 patients from Group 2. There was a statistically significant difference between Group 1 and Group 2 with regards to the frequency of reaction development. The frequency of reaction development was higher in women but the difference was not statistically significant. Patients with subjective complaints most frequently had itchiness, headache, nausea, abdominal pain, and felt unwell.

In conclusion, patient anxiety levels and psychosomatic complaints during DPTs are proportional to their association with previous hypersensitivity reactions. Due to these kinds of reactions, which are also known as the nocebo effect and sometimes mimic a true allergic reaction, some patients refuse to continue with the test. In order to prevent such reactions, it may be beneficial to keep the patients busy with an activity to distract them during the test.

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