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ORIGINAL ARTICLE

Determinants of nocebo effect during oral drug provocation tests

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Abstract
Background: A ''nocebo'' effect is defined as troublesome symptoms after the administration of placebo. The aim of this study was to determine characteristics of nocebo responses and related factors.
Methods: Patients with a reliable history of drug-induced hypersensitivity reactions subjected to placebo-controlled oral drug provocation tests and reacted to placebo, were consecutively included in this case–control study. Controls consisted of the randomly selected subjects who had a history of drug hypersensitivity reaction but did not react to placebo. A structured questionnaire was performed by an allergy specialist.
Results: There were 137 subjects (mean age: 43.10 ± 12.65 years), with nocebo and 91 subjects (42.38 ± 12.18 years) without any reaction to placebo. Most nocebo reactions (71.5%, $n = 98$) were classified as subjective, with local pruritus as the most common finding. A minority of nocebo reactions (11.7%, $n = 16$) were objective as cutaneous reactions including flushing and urticaria. Factors related with nocebo risks were university graduation (OR: 2.96, 95% CI: 1.27–6.93, $p = 0.012$) and non-atopy (OR: 2.12, 95% CI: 1.02–4.40, $p = 0.043$). In terms of the time of first and last historical reaction to drugs, each 1-unit (a month) increase in first reaction time (OR: 1.008, 95% CI: 1.00–1.02, $p = 0.001$) and last reaction time (OR: 1.019, 95% CI: 1.01–1.03, $p < 0.001$) were associated with increased nocebo risk.
Conclusion: In conclusion, subjects with high education, non-atopy, and older drug hypersensitivity reactions history seem to be more likely to experience nocebo effect during oral drug provocation tests. These risk factors should be considered and managed accordingly to complete the drug provocation procedure successfully.

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Introduction

The nocebo response or effect is defined as a negative and unpleasant response to the placebo, which is an inactive substance or a procedure.[1] Nocebo was first defined in 1961 and since then more and more attention has been paid to this topic, because it is common, distressing, and results in wasted medication.[2,3]

Placebo-controlled oral challenge is an essential step in the management of drug allergy by aiming to find safe alternatives for patients with a history of drug-related hypersensitivity reactions. The procedure always involves blind administration of a placebo preceding administration of increasing doses of an alternative drug. In this context, it is obvious to differentiate bothersome symptoms provoked by placebo from those provoked by active drug. However, a limited number of studies have been focused on nocebo effect during placebo-controlled oral drug provocation tests in patients with hypersensitivity reactions to drugs.[4,5] According to these studies the nocebo effect was common in drug allergy practice, but there was a lack of information regarding factors associated with nocebo effect in this group since there were no control subjects without placebo responses.

We have been performing single-blind placebo-controlled drug provocation tests in our university hospital for 15 years.[6–8] By using this background experience, in this case–control prospective study, we aimed to assess the characteristics of nocebo effect and to document demographic and clinical factors affecting nocebo response among patients who underwent placebo-controlled oral provocation tests by comparing those who experienced or did not experience a negative response to placebo. Several factors associated with nocebo response in different clinical situations, none in drug allergy, have been defined previously.[2,3] It will be helpful to determine the factors associated with nocebo response in patients with drug hypersensitivity reactions because this information will lead to good collaboration in advance between the attending physician and the patient who is candidate for drug provocation test in order to prevent unnecessary medical visits, waste of medications, and unnecessary alternative drugs.

Methods

Subjects

The case–control study was carried out in a prospective manner in our allergy department located in a large tertiary clinic for adult patients in Ankara, Turkey. Between 2005 and 2012, 137 patients with a reliable history of drug-induced hypersensitivity reactions including urticaria, angio-oedema, generalised pruritus, rhinitis, acute bronchospasm, laryngeal oedema, and anaphylaxis who had been subjected to placebo-controlled oral drug provocation tests and had reacted to placebo with objective and or subjective symptoms were consecutively enrolled in the study.

After enrolment of nocebo cases, based on the statistical evaluation, 91 patients were selected as control group in order to reach a sample size of 228 which provides 75% power to detect an effect size (W) of 0.1752 using a 1 degree of freedom Chi-Square Test with a significance level (alpha) of 0.05000.[9] The controls were randomly selected among patients who admitted to our department with a reliable history of drug-induced hypersensitivity reaction and subjected to placebo-controlled oral drug provocation tests but did not react to placebo challenge during 2012. Age–gender was matched to the nocebo subjects to account for potential confounding effects by age and gender.

The reliability of drug hypersensitivity was evaluated based on the patients' detailed anamnesis and/or documentations from emergency care units, hospitalisation or involved physicians. Subjects with symptoms attributable to known side effects or severe non-immediate reactions such as Toxic Epidermal Necrolysis (TEN), and Steven–Johnson Syndrome (SJS) were not included. Since drug provocation tests were part of the routine management, the patients were informed about the tests and a written signed informed consent was obtained prior to the challenges. The Ethical Committee of our faculty approves the oral challenge with placebo as part of the routine procedures.

Drug provocation tests

Drug provocation tests were designed in a single-blind placebo-controlled oral drug challenge. The challenge protocol consisted of oral administration of the drug with increasing doses, as described in our previous studies.[6–8] On two consecutive days, one and three fourths of divided doses of placebo and the active drugs were given at 1-h intervals. Active drugs were mainly antibiotics or analgesics that were tested for finding safe alternatives. Placebo challenge consisted of the controlled administration of the divided doses of placebo tablets or capsules (lactose) in similar dose intervals with the active drug. The challenges were performed at our outpatients' clinic under continuous medical supervision and with emergency care equipment available. During the challenge procedure, blood pressure and FEV1 values as well as skin, ocular, nasal, and bronchial reactions were monitored every hour after each placebo or active drug dose was given. Patients were followed up to 24 h to detect a delayed reaction for both placebo and active drug. In case of no reaction at the end of 24 h, patients were regarded as placebo non-reactive or related drug tolerant.

Questionnaire

A face-to-face interview was performed by a specialist in clinical immunology and allergy. A specially designed questionnaire developed by the authors was used to evaluate nocebo effect among patients who reacted to placebo or not. The questionnaire consisted of questions about the patients' demographics including age, gender, occupation, and educational status, family history of drug allergy, accompanying doctor diagnosed allergic or non-allergic diseases such as asthma, rhinitis, cardiovascular or gastrointestinal diseases, and psychiatric disorders. Additional items concerning clinical characteristics of previous drug reactions including time of first and last drug reaction before admission to hospital, the classes of the drugs involved in the reactions such as antibiotics, analgesics, local and general anaesthetics, muscle relaxants, radio contrast media, emergency room visit, and hospitalisation related with these