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The nocebo effect during oral challenge in subjects with adverse drug reactions

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Key words

Drug challenge, adverse drug reaction, nocebo effect

Summary

Background: *Nocebo effect is the occurrence of troublesome symptoms after the administration of inert substances. It can be easily studied during blind oral challenges for drug reactions, which always involve the administration of a placebo.* ***Methods:*** *We collected data about nocebo effect in outpatients undergoing oral drug challenge. Patients with previous documented adverse reactions to drugs underwent an oral challenge with alternative drugs to identify the compounds that can be safely used. The challenges involved the administration of a placebo before the active drugs and were performed under medical supervision.* ***Results:*** *Four hundred and thirty-five patients (18-68 yrs, 68% female) underwent the oral drug challenge. Most of them (52%) had a previous reaction with antibiotics and non-steroidal antinflammatory drugs. The reported reactions were urticaria (and/or angioedema), respiratory complaints, generalized itching and non-specific symptoms. A nocebo effect was seen in 13 patients (3%), (10 female). The majority of the observed effects were subjective (malaise, itching, abdominal pain). No special demographic or clinical characteristic could be identified in the nocebo reactors. Ten/13 patients had an abnormal result at the hospital anxiety depression questionnaire.* ***Conclusion:*** *Nocebo effect was not negligible in this procedure, although less frequent than previously reported.*

Introduction

The "placebo effect" is defined as the beneficial action, based on patient's expectation, exerted by an inert substance on the symptoms of a disease. Of note, in recent years an increasing attention has been devoted to the power of sham medications in clinical practice (1, 2), and the use of placebo has been extensively discussed (3, 4). By contrary, the "nocebo effect" is the occurrence of troublesome symptoms after the administration of inert substances (5). The nocebo response is usually subjective (e.g. nausea, headache, itching, feelings of cold or warmth), but it may also be objective (e.g. rush, urticaria, vomiting, tachycardia, changes in blood pressure). Similarly to the placebo effect, the nocebo effect is influenced by several factors such as patient's expectation, previous experiences, setting, appearance of the drug.

In some cases of adverse reactions to drugs (ADR), the only reasonable way to manage the problem is to identify the alternative drugs which can be used safely. This is usually done by means of a single-dose or an incremental oral challenge with the alternative drug (6, 7). In this case, the blind use of a placebo is mandatory in order to rule out the possible psychosomatic reactions.

Patients with ADR undergoing an oral drug challenge represent an ideal model to study the nocebo effect. We prospectively evaluated the occurrence and characteristics of the nocebo effects in patients with previous adverse drug reactions, seen in a 5-year period at our Allergy Unit in an hospital setting.

Methods

Consecutive outpatients seen at our Allergy Unit (Department of Internal Medicine, Sant'Orsola Hospital, Brescia), undergoing an oral challenge with drugs were evaluated concerning the occurrence of nocebo effects. The patients with indication to the oral challenge were those with reported urticaria/angioedema, generalized itching, respiratory symptoms (cough, chest tightness, wheezing) or laryngeal oedema after the use of a given drug. Patients with a history of anaphylaxis, Stevens-Johnson syndrome or other severe skin reactions to drugs were not admitted to the challenge. Those patients with major systemic diseases (insulin-dependant diabetes, arrhythmias, severe uncontrolled asthma or systemic autoimmune diseases) were excluded as well.

The clinical ADR history was evaluated by trained allergists, based on the documentation from GPs or from emergency care units. ADRs had to have occurred within 24 hours from the intake of a single drug. In the case of subjective symptoms (e.g. itching, malaise, headache), the symptoms had to be present at least in two occasions, with the same drug and with the same time of onset.

All patients underwent these following procedures before the oral challenge test: detailed clinical history, physical exam, electrocardiogram, signed and informed consent, and they had to be symptom free since at least one week. A peripheral intravenous access was positioned, and arterial blood pressure and oxygen saturation were constantly monitored during the challenge. The challenges were performed under continuous medical supervision and with emergency care equipment immediately available. An Ethical Committee approval was not required as the procedure is considered part of the routine procedures used in the hospital.

The oral challenge involved the administration of one (or more) drug(s), different in structure from those suspected to have caused ADRs, irrespective of the mechanism. In fact, aim of the challenge is to identify for each patient a drug to be taken safely if needed (8). Drugs were given in capsules containing either different amounts of the active principle (between 1/10 and 1 of a therapeutic dose), or talcum. All capsules were packed by specialized personnel of the Internal Medicine Department. The challenges were single-blinded and the placebo always preceded the administration of the active drug(s), but the patients were not informed of the presence of the placebo in the procedure. Patients were observed for at least eight hours after each administration, and any possible problem/symptom was recorded by the attending physician.

The Hospital Anxiety and Depression (HAD)(9) questionnaire was administered to those patients who reacted to the administration of the placebo (nocebo effect). The questionnaire is a self-screening scale for depression and anxiety and is a reliable tool for detecting those states in the setting of an hospital outpatient clinic. The anxiety and depression subscales also measure the severity of the emotional disorder. The range of HAD is: 0-7 = normal; 8-10 = borderline; 11-21 = abnormal.

Results

Four hundred and thirty-five patients underwent the oral drug challenge between 2002 and 2007. Their demographic characteristics are summarized in table 1. Most of them (52%) had a previous reaction with antibiotics (38% beta-lactams), followed by non-steroidal antinflammatory drugs (NSAIDs) (41%), whereas a minority of patients had ADRs with diverse other drugs (e.g. anesthetic agents, chemotherapy agents, antispastics, glucocorticosteroids). The reported ADRs were urticaria (and/or angioedema) in 86% of patients, followed by respiratory complaints, generalized itching and other non-specific symptoms as tachycardia, headache and generic malaise (Table 2).

A nocebo effect (untoward reaction after placebo) was seen in 13 patients (3%), 10 of whose were female. The characteristics of the nocebo reactions are summarized in table 3. The majority of the observed effects were subjective (malaise, itching, abdominal pain), whereas in few occasion objective symptoms were reported. Placebo reactors did not differ from those who had no reaction concerning demographic and clinical characteristics (including the type of previous reaction and atopic status). In particular, the coexistence of atopic status (rhinoconjuctivitis, asthma,atopic dermatitis, food allergy and/or positivity of aeroallergens or food allergens) was low (2 cases;

Table 1 - Demographic and clinical data of the patients

Total number of patients	435
Age range	18-68 yrs
Mean age	39.7 yrs
Male/Female ratio	139/296 (F: 68%)
Patients reacting to placebo (%)	13 (3%)
M/F ratio reacting to placebo	3/10
Mean age of patients reacting to placebo	35.4 yrs

Table 2 - Clinical characteristics and frequency of the drug reactions reported in the clinical history (435 patients). Some patients had more than one symptom

Description	N	%
Urticaria, angioedema or both	374	86.1
Respiratory symptoms (rhinitis, wheeze, chest tightness, dyspnea, shortness of breath)	89	20.4
Laryngeal oedema	6	1.4
Generalized itching	55	12.6
Nonspecific (malaise, headache, tachycardia)	42	9.6

Table 3 - Clinical symptoms and signs of the reactions to placebo (most patients had multiple symptoms/signs at the same time)

Itching	9
Nausea	5
Abdominal pain	4
Headache	2
Dyspnea/cough	3
Tachycardia/bradycardia	5
Erythema/rash/urticaria	2
Gneralised malaise	6
Anxiety	8
Laryngeal obstruction subjective sensation	2
Eye vision alterations (not documented)	1

about 20%) and similar to the rate recorded in non-reactors (12/422). Also, there was no apparent correlation between the severity of the previous drug reaction and the onset of nocebo effect. In addition, we found that 3/13 patients (2 female) had a frankly abnormal result at the HAD questionnaire and 7/13 (6 female) had a borderline result.

Discussion

The effects of substances without pharmacological actions are well known in medical practice, and the placebo effect is a matter of fact (1, 10). The clinical aspects of the opposite phenomenon (nocebo effect) has been extensively considered as well, since also the nocebo effect may be of relevance in many clinical trials (11). Patients with previous adverse reaction to drugs are particularly susceptible to the nocebo effect, since they had experienced previous side effects and, more or less consciously, expect new troublesome reactions. The blind oral challenge with alternative drugs is a good model to study this effect. There are, in fact, some studies in literature on this topic (8, 12), consistently showing that some untoward reaction to placebo occurs in about one quarter of the patients.

Our data confirm some of the already described facts, such as the well-known higher prevalence of female (13) and the subjective nature of the nocebo effect. On the other hand, in our patients the rate of nocebo effect was quite lower (3%) than in other similar articles where the occurrence was reported up to 21% (8). This is difficult to explain, although some hypotheses can be suggested, involving a different empathy of the medical personnel, the cultural differences among the patients studied, or the influence of the medical environment. None of these hypotheses could be experimentally verified in this context. Another possible explanation of the aforementioned discrepancy is that in the present study those patients with more severe reactions (e.g. anaphylaxis or exfoliative dermatitis) were not admitted to challenge. It can be hypothesized that patients who experienced a very severe reaction are more prone to develop a nocebo effect, as a result of their expectation. Despite this speculation, there is in literature no correlation between the severity of the previous drug reaction and the occurrence of the nocebo effect (8, 12). Finally, another interesting observation of our survey was that the majority of patients with the nocebo effect, had an abnormal result to the hospital anxiety-depression questionnaire, this suggesting and confirming the relevant weight of the psycho-emotional situation of the subject in determining the clinical reaction to placebo.

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