Original Article

Identifying Allergic Drug Reactions Through Placebo-Controlled Graded Challenges

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What is already known about this topic? Graded challenges are performed to exclude hypersensitivity reactions in patients with a low likelihood of drug allergy. Literature regarding optimal protocols with a defined number of steps and use of placebo is lacking.

What does this article add to our knowledge? This study suggests that graded challenges can safely be performed in 2 steps with the addition of placebo to reduce false-positive reactions, especially in females and in patients with multiple drug allergies.

How does this study impact current management guidelines? The addition of placebo to 2-step oral graded drug challenges should be considered to reduce false-positive challenge reactions, especially in female patients and patients with multiple drug allergies.

BACKGROUND: Graded challenges are performed to exclude hypersensitivity reactions in patients with a low likelihood of drug allergy. Literature regarding optimal protocols with a defined number of steps and use of placebo is lacking.
OBJECTIVE: To identify allergic drug reactions (ADRs) through a 3-step protocol composed of placebo followed by a 2-step graded drug challenge.
METHODS: We performed a 5-year retrospective chart review of all patients with historical ADRs who underwent single-blind, placebo-controlled graded drug challenges between October 2010 and November 2015 at an outpatient drug allergy clinic. Patients' demographic characteristics and description of historical reaction were obtained. Outcomes of challenges to drug versus placebo were compared by drug class.
RESULTS: Two hundred twenty-nine patients underwent at least 1 single-blind placebo-controlled graded challenge. The most commonly challenged drug class was beta-lactams (70.8%) followed by nonsteroidal anti-inflammatory drugs (17.5%). The reaction rate to drug and placebo was similar during beta-lactam challenges (9.4% vs 8.2%; $P = .9$) and during nonsteroidal anti-inflammatory drug challenges (14% vs 7%, $P = .5$), respectively. Only 10 patients (4.4%) had objective findings during drug challenges. Patients who reacted to placebo before beta-lactam challenges had an increased number of drug allergies (4.3 ± 1.0) compared with nonreactors (2.4 ± 0.1) and to beta-lactam reactors (3.3 ± 0.7) ($P = .002$). All placebo reactors were female (20 of 183 vs 0 of 46 males; $P = .02$).
CONCLUSIONS: Two-step graded challenges are safe in appropriately selected patients with a low risk of reaction. Placebo should be considered to reduce false-positive results, especially in females and in patients with multiple drug allergies. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;■:■-■)

Key words: *Graded challenge; Drug provocation test; Adverse drug reaction; Hypersensitivity reaction; Drug allergy; Placebo*

Graded challenges are performed to exclude hypersensitivity reactions in patients with a low likelihood of drug allergy.[1-9] They confirm that patients are not at an increased risk for future allergic drug reactions (ADRs) compared with the general population.[1-11] Previous studies of graded challenges in appropriately selected patients have demonstrated low reaction rates with predominantly mild and subjective symptoms.[9,12-16] One study reported a 16% subjective reaction rate with a 0.8% true reaction rate,[12] whereas other studies reported an overall reaction rate between 4.1% and 12%.[9,13,17]

Despite the extensive use of graded challenges for the evaluation of ADRs, evidence-based guidelines regarding optimal protocols are lacking.[8] A study published in 1992 of patients with historical penicillin reactions and subsequent negative skin testing used a 2-step active challenge composed of a subcutaneous test dose of 5 mg of penicillin followed by a full therapeutic dose.[17] Other challenges reported in the literature range from

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This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
Conflicts of interest: The authors declare that they have no relevant conflicts of interest.
Received for publication June 11, 2016; revised September 17, 2016; accepted for publication September 28, 2016.
Available online ■■
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2213-2198

http://dx.doi.org/10.1016/j.jaip.2016.09.041

Abbreviations used
ADR- Allergic drug reaction
NSAID- Nonsteroidal anti-inflammatory drug

administration of single therapeutic doses to multiple doses over several days with variable use of placebo.[9,12-16,18] Concern exists that challenges composed of more than 4 steps may lead to an induction of tolerance.[6] A recent non−placebo-controlled study demonstrated that a 2-step graded challenge is as safe as a 3- or 4-step graded challenge with a reaction rate of 11% versus 12%, respectively.[9] However, the absence of placebo during this study raises the possibility of potential false-positive reactions, especially because most reactions were subjective.

Although placebo has been used in previous studies, the protocols for the drug challenges in these studies were not well described and consisted of a varying number of steps.[12-15,19] To our knowledge, only 1 small placebo-controlled study was conducted in the United States, which comprised 21 challenges ranging from 1 to 6 steps with a median of 3 steps (interquartile range, 2-4).[12] In Lombardi et al's study[15] of 435 Italian patients, placebo was administered before capsules containing various amounts of the active drug ranging from 10% to 100% of the full therapeutic dose with an unclear number of cumulative doses administered.[15] Aun et al's[13] Brazilian study of single-blind, placebo-controlled challenges consisted of 1 to 2 doses of placebo followed by increasing doses of the suspected causal drug once every 20 minutes until a full therapeutic dose was reached; no description of the total number of doses is provided.[13] Although Passalacqua et al[19] describe the use of 1 or 2 doses of placebo before a single-dose oral challenge composed of 10% of the therapeutic dose, the patient population included patients with well-documented ADRs, including laryngeal edema and anaphylaxis, who were being challenged to an alternative drug given their high risk of reaction.[19] Therefore, this patient population differs substantially from patients with low likelihood of drug allergy deemed appropriate for graded challenges.

There is a lack of literature on well-defined protocols for placebo-controlled graded challenges. Our objective was to evaluate a 3-step protocol composed of placebo followed by a 2-step graded drug challenge to identify ADRs.

METHODS

We performed a 5-year retrospective chart review of all patients with a reported history of drug allergy who underwent an outpatient oral graded drug challenge between October 2010 and November 2015 at a drug allergy clinic affiliated with a single, tertiary-care academic center. This study was approved by the Institutional Review Board at Montefiore Medical Center/Albert Einstein College of Medicine.

Patients selected for challenges had a low-risk history of hypersensitivity reaction determined by history and/or negative skin testing. Patients with a history consistent with aspirin-exacerbated respiratory disease were excluded from nonsteroidal anti-inflammatory drug (NSAID) challenges. Patients with a history of severe non−IgE-mediated reactions were also excluded. Skin tests were performed when appropriate before challenges according to published guidelines.[8,20] Patients with skin testing positive for benzylpenicilloyl polylysine, penicillin G, piperacillin, or ampicillin but negative for cephalosporins underwent cephalexin graded challenges. In patients with positive cephalosporin skin testing but negative skin testing to penicillins, graded challenges to amoxicillin were subsequently performed. Informed consent was obtained before challenges.

All graded challenges were single-blind and placebo-controlled. Patients were informed that they would receive a placebo, but were unaware when it would be administered. All challenges were conducted as follows: patients first received a placebo in the form of berry-flavored yogurt with additional cherry-flavored pharmaceutical sweetener followed by a 30-minute observation period. A 2-step oral drug challenge was subsequently performed with 1/10th the therapeutic dose of the drug followed by 30 minutes of observation and subsequent administration of a full therapeutic dose of the drug (see Table E1 in this article's Online Repository at www.jaci-inpractice.org) followed by another 60 minutes of observation. The challenge drugs were liquid formulations, if available, or crushed pills mixed in the same yogurt and sweetener used to administer the placebo.

If a patient reported subjective symptoms during the challenge, the patient was informed that these symptoms may or may not be related to the substance given. Vital signs were rechecked and, if no change, the patient was reassured and offered the following options: (1) Receive treatment for the subjective symptoms (eg, antihistamines for pruritus) and stop the challenge; (2) Stop the challenge without treatment; or (3) Continue the challenge without any treatment as it would obscure any additional reactions and observe whether symptoms would change with the next dose. Patients with subjective symptoms to the challenge drug that resolved without intervention were deemed not to be allergic and were advised that they can take the medication they were challenged to in the future. Patients' demographic characteristics, description of historical reaction, total number of reported drug allergies, and outcomes of challenges were obtained from the electronic medical record. The severity of historical reaction was graded as either mild or severe on the basis of patient's description. Severe ADR refers to anaphylaxis, syncope, angioedema, bronchospasm, or severe rash with mucosal lesions. All other ADRs were considered mild and included the following: urticaria, rash, subjective throat symptom, or fever. If a patient reported more than 1 historical reaction to the same drug, the most severe reaction was recorded. Outcomes of challenges to placebo versus drug were compared for each class of medication. If a patient reacted to more than 1 drug challenge within the same drug class, the most severe reaction was recorded. Characteristics of patients who experienced an ADR to placebo or drug were also compared with those of patients who did not experience a reaction. Treatment of ADRs was reviewed. Patients were contacted by telephone to determine whether they had subsequently taken the drug to which they were challenged and whether any reactions occurred.

Statistical analysis

Baseline characteristics were compared among the 3 groups of patients: patients who reacted to drug, patients who reacted to placebo, and patients who did not react to either, for each medication class. The proportion of ADRs to medications during challenges was compared to ADRs to placebo using the McNemar test for correlated proportions. One-way ANOVA or Kruskal-Wallis rank test (if data were nonnormally distributed) were used for comparison of baseline characteristics. Categorical data were analyzed by chi-square test or Fisher exact test, as appropriate. If patients reacted to both drug and placebo during the same drug class challenge, their characteristics were presented among drug reactors. All summary