Original Article

Safety and Outcomes of Test Doses for the Evaluation of Adverse Drug Reactions: A 5-Year Retrospective Review

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What is already known about this topic? Although graded challenges are considered the criterion standard for evaluating adverse drug reactions, there are no evidence-based guidelines regarding the optimal number of steps.

What does this article add to our knowledge? This study specifically defined the term test dose and, in addition, demonstrated that 1- or 2-step test doses are safe.

How does this study impact current management guidelines? This study demonstrated that 1- or 2-step test doses are safe with a specific group of patients.

BACKGROUND: Graded challenges are the criterion standard for evaluating adverse drug reactions (ADR). Evidence-based guidelines regarding the optimal number of steps for challenges are lacking.

OBJECTIVE: To determine the safety and outcomes of 1- or 2-step test doses among patients with ADRs seen by the allergy/immunology consult service and to compare the outcomes of 1- or 2-step test doses with multistep challenges performed during the same time period.

METHODS: We conducted a retrospective chart review of all 1- or 2-step test doses and multistep challenges at a single academic center between 2008 and 2013. Patient demographics, symptoms of initial ADRs, and outcomes of test doses and multistep challenges were reviewed. ADRs were classified by type and were graded by severity. Outcomes of 1- or 2-step test doses were compared with multistep challenges.

RESULTS: We identified 456 patients who underwent 497 one- or 2-step test doses (mean age, 51 years; 67.5% female patients). The most common drugs that prompted test doses were β-lactams (62%). The majority of patients (n = 444 [89%]) did not experience any ADRs during test doses. ADRs that occurred during test doses (n = 53 [11%]) were most commonly non-immune-mediated (45%) or IgE-mediated (32%), with grade 1 or 2 severity (100%). Forty-nine percent of ADRs during test doses did not receive any treatment. The ADR rate during multistep challenges (10/82 [12%]) was similar to test doses.

CONCLUSION: One- or 2-step test doses were safe for evaluation of ADRs. Multistep challenges did not confer added safety. Furthermore, 1- or 2-step test doses did not raise concern for induction of tolerance. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;2:768-74)

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

Graded challenges are the criterion standard for the evaluation of adverse drug reactions (ADR).[1-7] Challenges can exclude hypersensitivity in patients with a low-risk history and allow for the evaluation of cross-reactivity of structurally related compounds among different drug classes.[2,3,8] Given that graded challenges are performed when a low likelihood of allergy exists, ADR rates observed during these challenges are low in the literature. One prior study demonstrated a 16% subjective reaction rate and 0.8% true reaction rate, whereas another study reported a reaction rate of 4.1%, which included 2 anaphylactic reactions.[9,10] Graded challenges are not recommended if the patient's history was consistent with a severe non-IgE–mediated reaction, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, interstitial nephritis, hepatitis, or hemolytic anemia.[11,12]

Despite the widespread use of graded challenges for the evaluation of ADRs, there are no evidence-based guidelines that delineate the optimal number of steps. Test preparations and time intervals vary among published studies, largely based on provider preference.[7,9,13] Although the Joint Task Force on Practice Parameters provides an algorithm for management of drug hypersensitivity reactions (HSR), it does not provide specific guidance for performing graded challenges.[11] The Standards of Care Committee of the British Society for Allergy and Clinical Immunology's guidelines indicate that the starting dose for challenges may be as low as 10^{-9} of the therapeutic dose for parenteral challenges, with 2- to 10-fold increments until the therapeutic dose is reached.[12]

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Abbreviations used
ACE- Angiotensin-converting-enzyme inhibitor
ADR- Adverse drug reaction
HSR- Hypersensitivity reaction
NSAID- Nonsteroidal anti-inflammatory drug
SMX- Sulfamethoxazole
TMP- Trimethoprim

Without specific evidence provided in the practice parameters or published guidelines, some graded challenges lasted hours to days.[14,15] However, multistep graded challenges composed of 4 or more steps may induce tolerance (desensitization) through modifications of immune effector cells.[12] If temporary tolerance is induced by a multistep graded challenge, then there is concern that a reaction could occur with subsequent exposure to the drug, which would be less likely if the drug were tolerated without potential desensitization in a graded challenge composed of fewer steps. Therefore, we implemented a standardized 1- or 2-step test dose (limited-step graded challenge) and sought to determine the safety and outcomes of these test doses among patients referred for evaluation of ADRs. We also compared outcomes of 1- or 2-step test doses with multistep challenges performed during the same period of time.

METHODS

At our institution, a test dose or multistep challenge was only performed for the evaluation of ADRs with patients who met the following criteria: low-risk history of HSR without a severe non−IgE-mediated reaction, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, interstitial nephritis, hepatitis, or hemolytic anemia. If a patient's history was suggestive of an IgE-mediated HSR, then a test dose or multistep challenge was only considered if the ADR was distant (≥10 years ago) and mild (ie, no features of anaphylaxis). Skin testing, when available, was not required before performing a test dose or multistep challenge. However, specific guidelines that used nonirritating skin testing concentrations were followed when skin testing was performed before a test dose or challenge.[16-18] Furthermore, patients with confirmed aspirin-exacerbated respiratory disease did not undergo challenges to nonsteroidal anti-inflammatory drugs (NSAIDs).

An initial review of all graded challenges performed at our institution from July 2005 to April 2008 found that, among 52 challenges, 5 resulted in mild ADRs and there were no severe ADRs. Only 1 of the 5 ADRs was thought to likely be due to an IgE-mediated reaction to the drug. Furthermore, ADRs did not occur at doses lower than one-tenth of the total dose. Consequently, in May 2008, a standardized test dose was created in which patients would receive one-tenth of the full dose for a parenteral medication or one-fourth of a pill for an oral medication followed by the full dose after 60 minutes of observation. The term test dose defined challenges with 1 or 2 steps in contrast to a multistep challenge when there were more than 2 steps. Although this standardized protocol and terminology was recommended, there was no enforcement of its use. Some allergy/immunology physicians opted to administer a full dose, whereas others opted to proceed with a multistep challenge composed of 3 or 4 steps.

We performed a retrospective chart review of all the patients who underwent 1- or 2-step test doses and multistep challenges between May 2008 and May 2013 at a single academic center in consultation with the allergy/immunology service. Outpatients were identified by billing data by using the International Classification of Diseases, Ninth Revision, Clinical Modification codes for ADR or drug allergy (693.0, 708.0, E930-E947, and 995-995.3), in conjunction with Current Procedural Terminology codes for ingestion challenge tests (95075) and rapid desensitization (95180). Inpatients were identified by the allergy/immunology consultation log maintained by 1 allergy administrator and the allergy/immunology fellows.

Patient demographics, symptoms of initial ADR, the culprit drug, and outcomes of test doses and multistep challenges were obtained from the electronic medical record. Both the initial ADR and any ADR induced by a test dose or multistep challenge were independently classified and graded by 2 clinicians (M.I., A.B.), 1 of whom is a board-certified allergist/immunologist (A.B.). If discrepancies arose, then an independent third physician (K.G.B.) reviewed the ADR. Reaction classification followed our previously published schema (Figure 1).[19] The severity of the ADR was graded by using Ring's criteria, a standardized grading scale (Table I).[20] Because this grading system does not address angioedema, we classified this sign as grade 2. Treatment of ADRs also was reviewed. The outcomes of 1- or 2-step test doses were compared with multistep challenges. This study was approved by the institutional review board of Partners Human Research Committee.

Statistical analyses

Descriptive findings are presented as percentages and means ± SDs. Comparisons of 1- to 2-step test doses with 3- to 4-step challenges were performed by using the unpaired t test and the Fisher exact test to calculate 2-sided P values, with values $<.05$ considered statistically significant. All statistical analyses were performed by using SAS 9.4 software (SAS Institute, Cary, NC).

RESULTS

Patient characteristics

Between May 2008 and May 2013, we identified 456 patients who underwent 497 1- or 2-step test doses. Of these, 117 patients (23.5%) had 1-step test doses and 380 (76.5%) had 2-step test doses. The majority of patients were female patients (n = 308 [67.5%]) and white (n = 383 [84%]), with a mean age of 51.5 years (Table II).

Initial ADRs

The majority of drugs that prompted allergy/immunology referrals that resulted in test doses were antimicrobials (n = 377 [76%]), of which 81% (n = 306) were β-lactam antibiotics and 8% (n = 29) were fluoroquinolones. More test doses were completed for antimicrobials than for multistep challenges ($P <$ .001) Other drugs that prompted referral that resulted in test doses included NSAIDs (n = 60 [12%]), opioids (n = 11 [2.2%]), cardiovascular drugs (n = 11 [2.2%]), acetaminophen (n = 8 [1.6%]), and corticosteroids (n = 9 [1.8%]). More multistep challenges than test doses were completed for NSAIDs as well as simvastatin, clonazepam, diphenhydramine, milnacipran, esomeprazole, probenecid, tropicamide (ophthalmic), and phenylephrine (ophthalmic).

The majority (n = 259 [52.1%]) of initial ADRs that resulted in subsequent test dose or multistep challenge were classified as grade 1 severity. Thirty-four percent (n = 167) were classified as grade 2 severity. Only 2.2% (n = 11) were grade 3 severity and