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. © **2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;■:■-■)**

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

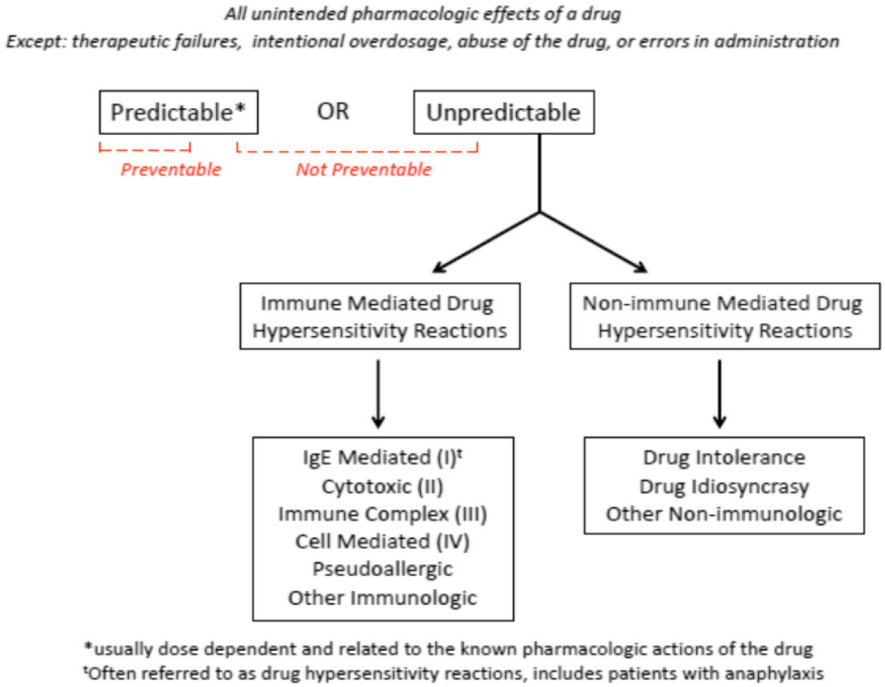


FIGURE 1. Classification of ADRs. ADRs were classified as either immune-mediated HSR, non–immune-mediated HSR, or unrelated (ie, ADRs in patients with chronic urticaria or when a test dose was used as a precautionary measure) (from Ref 16). ADRs that involved NSAIDs, nonspecific rashes, and bradykinin-mediated reactions were classified as other immunologic.

TABLE I. Classification for grading of hypersensitivity reactions*

Grade	Description
1	Presence of skin symptoms and/or mild fever reaction
2	Presence of measurable but non–life-threatening symptoms, including angioedema, cardiovascular reaction (tachycardia, hypotension), gastrointestinal disturbance (nausea), and respiratory disturbance (cough or difficulty in mechanical ventilation)
3	Presence of life-threatening reactions, including shock and spasm of smooth muscles (bronchi and uterus)
4	Cardiac arrest and/or respiratory arrest

*From Ref 20.

TABLE II. Demographics of patients for test dose and multistep challenge

	Test dose (n = 456)	Multistep (n = 74)	*P* value
Age (y), mean ± SD	51.5 ± 17.9	49.5 ± 16.4	.37
Female patients, no. (%)	308 (67.5)	56 (75.7)	.18
Race, no. (%)			
White	383 (84)	60 (81.1)	>.5
Hispanic	24 (5.3)	4 (5.4)	>.5
Black	16 (3.5)	4 (5.4)	>.5
Asian	16 (3.5)	3 (4.1)	>.5
Other or unknown	17 (3.7)	3 (4.1)	>.5

1.2% (n = 6) were grade 4 severity. Symptoms of ADR that were either unknown by the patient or unrelated to the test dose drug (n = 54 [11%]) were not graded by severity (Table III). Most initial ADRs were classified as IgE-mediated (n = 211 [42.5%]) or other immunologic (n = 129 [26%]).

Skin testing

Forty-seven percent (272/579) of all test doses and multistep challenges were preceded by skin testing, with the following frequencies for each drug class: penicillins 86% (221/257), first- and second-generation cephalosporins 65% (15/23), third- and fourth-generation cephalosporins 19% (5/26), fluoroquinolones 34% (11/32), macrolides 37.5% (6/16), corticosteroids 66.7% (6/9), and lincosamides 40% (2/5).

Safety and outcomes of test doses

ADRs were induced by 11% of test doses (n = 53) (Table IV). Female patients (n = 45, [84.9%]) were more likely to have ADRs during test doses than male patients (n = 8 [15.1%]). Seven ADRs occurred during 117 one-step test doses (6%), and 46 ADRs occurred during 380 two-step test doses (12%). Antimicrobials (n = 31 [58.5%]), NSAIDs (n = 11 [20.7%]), and opioids (n = 3 [5.7%]) were the drug classes most commonly associated with ADRs. Of the antimicrobials, β-lactams (23/31 [74.2%]) were most commonly associated with ADRs during test doses.

For the patients who developed ADRs during test doses (n = 53), their initial ADR was classified primarily as IgE-mediated (n = 24 [45.3%]) or other immunologic (n = 13 [24.5%]) with either grade 1 (n = 22 [41.5%]) or grade 2 (n = 28 [52.8%]) severity. No patients who developed an ADR during a test dose had an initial ADR with a severity of grade 3 or 4. The majority of ADRs during test doses were deemed to be non-immune-mediated (n = 24 [45.3%]) or IgE-mediated (n = 17 [32.1%]) with either grade 1 or 2 symptoms (n = 53 [100%]). Examples

TABLE III. Comparison of initial ADRs of patients with test dose and multistep challenge

	Test dose, no. (%) (n = 497)	Multistep, no. (%) (n = 82)	*P* value
Drug class			
Antimicrobials	377 (75.9)	25 (30.5)	<.001
β-lactams	306 (61.6)	12 (14.6)	<.001
Fluoroquinolones	29 (5.8)	3 (3.7)	>.5
TMP-SMX	14 (2.8)	0 (0)	.24
Macrolides	12 (2.4)	4 (4.9)	.26
Other	16 (3.2)	6 (7.3)	.11
NSAIDs	60 (12.1)	32 (39)	<.001
Opioids	11 (2.2)	0 (0)	.38
Acetaminophen	8 (1.6)	6 (7.3)	.008
Cardiovascular drugs	11 (2.2)	2 (2.4)	>.5
Statins	7 (1.4)	1 (1.2)	>.5
ACE inhibitors and/or ARBs	4 (.8)	1 (1.2)	>.5
Corticosteroids	9 (1.8)	0 (0)	>.5
Other	21 (4.2)	17 (20.7)	<.001
Initial ADR			
Classification			
IgE mediated	211 (42.5)	27 (32.9)	.11
Cytotoxic	0 (0)	0 (0)	>.5
Immune complex	6 (1.2)	0 (0)	>.5
Cell mediated	35 (7)	1 (1.2)	.046
Other immunologic	129 (26)	40 (48.8)	<.001
Pseudoallergic	7 (1.4)	1 (1.2)	>.5
Nonimmune mediated	32 (6.4)	7 (8.5)	.48
Other, unrelated or unknown	77 (15.5)	6 (7.3)	.06
Grade			
1	257 (51.7)	37 (45.1)	.29
2	168 (33.8)	40 (48.8)	.013
3	11 (2.2)	0 (0)	.38
4	6 (1.2)	1 (1.2)	>.5
Unknown	36 (7.2)	2 (2.4)	.15
Unrelated	19 (3.8)	2 (2.4)	>.5

ACE, Angiotensin-converting-enzyme inhibitor; *ARB*, angiotensin receptor blocker; *SMX*, sulfamethoxazole; *TMP*, trimethoprim.

of non-immune-mediated ADRs include localized tingling sensation, nausea, drowsiness, chills, dry throat, headache, and mild throat clearing, whereas examples of IgE-mediated reactions included hives (n = 5), pruritus (n = 6), and angioedema (n = 1). None of the ADRs during test doses were grade 3 or 4.

Approximately half of the patients with ADRs during test doses (49%) received no treatment, whereas the remainder of patients were treated with a combination of antihistamines (47%), H2-antagonists (7.5%), corticosteroids (7.5%), and short-acting β-agonists (1.9%). Three female patients received epinephrine. The first patient, an 11-year-old white girl, reported subjective throat tightness with mild dysphagia and dysphonia 30 minutes after a test dose to acetaminophen with codeine. She had normal vital signs with no hypoxemia and a normal examination. Her initial ADR was reported as serum sickness of grade 2 severity. The second patient, a 44-year-old African American woman, developed symptoms of pruritus, somnolence, throat tightness, dysphonia, and diffuse erythema 1 hour after a full dose of tramadol. Her initial ADR was non-immune-mediated, grade 2 severity with symptoms of fatigue, nausea, vomiting, dyspnea, and pruritus. The third patient, a 45-year-old white woman, developed dry throat, nausea, chills, and rigors 10 minutes after a test dose to azithromycin. The patient's initial ADR was a grade 2, IgE-mediated reaction with sore throat, dyspnea, wheezing, angioedema, and dizziness, which resolved with diphenhydramine. On extensive chart review of these ADRs during test doses, all 3 patients were hemodynamically stable, with no documented objective findings that necessitated the administration of epinephrine.

Safety and outcomes of multistep challenges

Between May 2008 and May 2013, 74 patients underwent 82 multistep challenges. Of these, 68 (82.9%) were 3-step and 14 (17.1%) were 4-step challenges. The majority of patients were female patients (n = 56 [75.7%]) and white (n = 60 [81.1%]), with a mean age of 49.5 years (Table II). NSAIDs (n = 32 [39%]) and antimicrobials (n = 25 [30.5%]) were the most common drugs that prompted a multistep challenge (Table III). The majority of initial ADRs that prompted multistep challenges were other immunologic (n = 40 [48.8%]) and IgE-mediated (n = 27 [32.9%]), with a severity of grade 1 (n = 37 [45.1%]) or grade 2 (n = 40 [48.8%]). Only 1 initial ADR was classified as grade 4 severity. During 82 multistep challenges, 10 ADRs occurred (12%), with the majority classified as IgE-mediated (n = 3 [30%]), non-immune-mediated drug HSR (n = 3 [30%]) or other immunologic (n = 2 [20%]), with a severity of either grade 1 (n = 6 [60%]) or grade 2 (n = 4 [40%]) (Table IV). The most common culprit drugs were antimicrobials (n = 3 [30%]), NSAIDs (n = 3 [30%]), and acetaminophen (n = 3 [30%]). The initial ADR for patients with ADRs during multistep challenges was classified as IgE-mediated (n = 5 [50%]), other immunologic (n = 2 [20%]), or unrelated (n = 2 [20%]), with either grade 1 (n = 3 [30%]) or grade 2 (n = 6 [60%]) severity. No patients with an ADR during a multistep challenge had an initial ADR with a severity of grade 3 or 4.

Comparison of test doses with multistep challenges

The frequency of ADR during test doses (11%) and multistep challenges (12%) was similar. ADRs during test doses and multistep challenges were similar for female patients (70% vs 85%; $P = .36$) and white patients (70% vs 81%; $P = .42$), with no difference in age (38.9 vs 48.4 years; $P = .13$). The grade of the ADR for test doses compared with multistep challenges was not different (Table IV).

DISCUSSION

This is one of the largest studies to assess the outcome of test doses and multistep challenges, and to demonstrate the comparable safety of both test doses and multistep challenges. A comprehensive review of 497 one- or 2-step test doses and 82 multistep challenges showed that the overwhelming majority did not result in ADRs. Furthermore, when ADRs did occur, they were mild, with most patients reporting non-immune-mediated reactions, such as headache, nausea, or drowsiness. The ADR rates of 11% for test doses and 12% for multistep challenges in our study fall between rates of 4.1% and 16% reported in prior studies.[9,10] Unlike other studies, no anaphylactic reactions occurred with test doses or multistep challenges, which underlies the importance of careful review and evaluation of a patient's drug allergy history before performing test doses or challenges.[10] Our findings, therefore, demonstrated that test doses are safe for

TABLE IV. Comparison of characteristics of patients who developed ADRs during 1- or 2-step test doses vs multistep challenges

	Test dose (n = 53)	Multistep (n = 10)	*P* value, *z*-score
Reaction rate, %	11	12	>.5
Age (y), mean ± SD	48.4 ± 17.6	38.9 ± 20.5	.13
Female patients, no. (%)	45 (84.9)	7 (70)	.36
Race, no. (%)			
White	43 (81.1)	7 (70)	.42
Hispanic	2 (3.8)	1 (10)	.41
Black	4 (7.5)	1 (10)	>.5
Asian	2 (3.8)	1 (10)	.41
Other and/or unknown	2 (3.8)	0 (0)	>.5
Drug class, no. (%)			
Antimicrobials	31 (58.5)	3 (30)	.17
β-lactams	23 (43.4)	3 (30)	>.5
Fluoroquinolones	2 (3.8)	0 (0)	>.5
Macrolides	2 (3.8)	0 (0)	>.5
Other	4 (7.5)	0 (0)	>.5
NSAIDs	11 (20.8)	3 (30)	>.5
Opioids	3 (5.7)	0 (0)	>.5
Acetaminophen	0 (0)	3 (30)	.003
Other*	8 (15.1)	1 (10)	>.5
Initial ADR, no. (%)			
Classification			
IgE-mediated	24 (45.3)	5 (50)	>.5
Cytotoxic	0 (0)	0 (0)	>.5
Immune complex	1 (1.9)	0 (0)	>.5
Cell-mediated	3 (5.7)	0 (0)	>.5
Other immunologic	13 (24.5)	2 (20)	>.5
Pseudoallergic	1 (1.9)	0 (0)	>.5
Non-immune-mediated	6 (11.3)	0 (0)	>.5
Unrelated and/or unknown	5 (9.4)	3 (30)	.11
Grade, no. (%)			
1	22 (41.5)	3 (30)	.73
2	28 (52.8)	6 (30)	.74
3	0 (0)	0 (0)	>.5
4	0 (0)	0 (0)	>.5
Unknown	3 (5.7)	1 (10)	>.5
Test dose or multistep ADR, no. (%)			
Classification			
IgE-mediated	17 (32.1)	3 (30)	>.5
Cytotoxic	0 (0)	0 (0)	>.5
Immune complex	0 (0)	0 (0)	>.5
Cell-mediated	1 (1.9)	0 (0)	>.5
Other immunologic	6 (11.3)	2 (20)	>.5
Pseudoallergic	1 (1.9)	0 (0)	>.5
Non-immune-mediated	24 (45.3)	3 (30)	.49
Other, unrelated or unknown	4 (7.5)	2 (20)	.24
Grade, no. (%)			
1	24 (45.3)	6 (60)	.5
2	29 (54.7)	4 (40)	.5
3	0 (0)	0 (0)	>.5
4	0 (0)	0 (0)	>.5

*Includes the following: simvastatin, clonazepam, diphenhydramine, milnacipran, esomeprazole, probenecid, tropicamide (ophthalmic), and phenylephrine (ophthalmic).

evaluation of ADRs and that multistep challenges do not confer additional safety.

Advantages of 1- or 2-step test doses over multistep challenges include the lack of concern for induction of tolerance or desensitization; the requirement for fewer resources, such as staffing and time; and the ability for inpatients to reach therapeutic dosing more rapidly. Prior studies also demonstrated that the vast majority of patients (>95%) who undergo graded

challenges find the testing to be useful and would recommend testing to others, whereas 91% were either satisfied or very satisfied with challenges irrespective of the results.[21] Given that multistep challenges have a similar ADR rate to test doses, providers can still elect to perform multistep challenges when caution is required, such as for patients with anxiety or multiple comorbid conditions.

There are limitations of test doses and multistep challenges. Although positive challenges can be considered conclusive in defining the presence of a drug HSR, delayed HSR may still occur as a result of a presumed negative test dose or multistep challenge.[22] Some non-immediate HSRs, for example, maculopapular exanthema, have been reported to occur only after several days of therapeutic dosing.[23,24] Therefore, it is imperative that patients are counseled after a presumed negative test dose or multistep challenge regarding the possibility of a delayed HSR. There are no validated or evidence-based diagnostic tools currently available to predict these types of ADRs.[19] Another limitation of test doses and multistep challenges is the inability of providers to guarantee that a previously reported mild ADR will not result in a more severe ADR when the patient receives the offending drug during a challenge. To mitigate this possibility, we suggest that only patients with a low-risk history of HSR be selected for test doses or multistep challenges, as they were in our study, in which no grade 3 or 4 ADRs occurred. We further recommend that test doses and multistep challenges only be performed under close supervision of a medical professional.

There is no clear distinction in the literature between the terms graded challenge, test dose, and drug provocation test.[3,7,12,25] Test doses are considered a subset of graded challenges and are defined as the administration of progressively increasing doses of a medication to verify that a patient does not experience an immediate ADR to a given drug. Based on the demonstrated safety of test doses in our study, we propose that a 1-step test dose be defined as the administration of the full dose of a medication followed by a specific time period (ie, 60 minutes) of observation, whereas a 2-step test dose be defined as one-tenth of the full dose for a parenteral medication or one-fourth of a pill for an oral medication, followed by administration of the full dose after a specific period of observation.

Our study has several limitations, including recall bias for the initial ADR, which prevented 11% of initial ADRs from being graded and 16% of ADRs from being classified given that the initial ADRs were either unknown or unrelated. Another limitation of our study is the inability to determine why some providers chose to perform a multistep challenge rather than the recommended 1- or 2-step test dose. The initial ADRs that prompted multistep challenges were more likely to be other immunologic (49% vs 26%), which likely reflects the higher likelihood of NSAIDs to prompt a multistep challenge. However, there was no significant difference in ADRs between the test dose and multistep challenge for NSAIDs or other immunologic reactions. The severity of the initial ADR does not seem to be the reason that a multistep challenge was chosen over a test dose because the majority of initial ADRs that prompted multistep challenges were of grade 1 or grade 2 severity (94%), with no grade 3 reactions and only one grade 4 reaction.

Another limitation is that our study did not use placebos, and, therefore, it is plausible that some reported ADRs were not related to the administered drug. In a previous study, of 600 patients with a history of ADR who underwent a blind oral challenge with administration of an inert substance or an active drug, the overall occurrence of a nocebo effect was 27%.[26] Finally, our study was performed at a single academic center, which may limit the generalizability of our results. In conclusion, 1- or 2-step test doses are safe in appropriately selected patients for the evaluation of ADRs. Although multistep challenges do not provide additional safety, they may be performed for specific patients. Despite minor limitations, test doses and multistep challenges should remain the criterion standard for the evaluation of ADRs.

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