Drug Provocation Tests in Patients with a History Suggesting an Immediate Drug Hypersensitivity Reaction

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Background: **Drug hypersensitivity reactions are common and can be life-threatening. Confirmation of the diagnosis should be rigorous and based on clinical history and a physical examination, possibly followed by skin tests and drug provocation tests.**

Objective: **To describe the outcome of drug provocation tests in evaluating patients with histories suggesting drug allergy.**

Design: **Retrospective analysis of clinic case series.**

Setting: **The department for drug allergy at a university hospital.**

Patients: **898 consecutive patients with suspected immediate drug allergy referred to the clinic between September 1996 and August 2001. Patients with severe skin reactions and those with positive results on skin tests for β-lactams were excluded.**

Intervention: **Single-blinded administration of increasing doses of the suspected drug, up to the usual daily dose, under strict hospital surveillance.**

Results: **1372 drug provocation tests were performed using various drugs, including β-lactams (30.3%), aspirin (14.5%), other nonsteroidal anti-inflammatory drugs (11.7%), paracetamol (8.9%), macrolides (7.4%), and quinolones (2.4%). There were 241 (17.6%) positive drug provocation test results. Drug provocation reproduced the same symptoms, albeit milder and of a shorter duration, in the following patients: 13 (5.4%) with a history of anaphylactic shock, 17 (7.0%) with a history of anaphylaxis without shock, 10 (4.1%) with a history of laryngeal edema, 19 (7.9%) with a history of bronchospasm, 160 (66.4%) with a history of urticaria, and 22 (9.1%) with a history of maculopapular eruption. All adverse reactions were completely reversed by prednisolone, H_1-antihistamines, and epinephrine as needed.**

Limitations: **Falsely negative results on drug provocation tests may have occurred because of loss of sensitization, rare cofactors not included in the diagnostic procedure, and tolerance induction during provocation.**

Conclusions: **Drug provocation tests in individuals with suspected drug allergy performed in carefully controlled settings can confirm drug hypersensitivity.**

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Drug hypersensitivity reactions may affect up to 5% of hospitalized patients and can be life-threatening (1). Various reactions have been described (1–3), including nonimmunologic reactions, IgE-mediated allergic reactions (immediate anaphylactic shock, generalized urticaria, angioedema, or bronchospasm), and nonimmediate allergic reactions. Nonimmediate reactions may occur several days after the drug administration and include urticaria, maculopapular eruptions, fixed drug eruptions, vasculitis, toxic epidermal necrolysis, the Stevens–Johnson syndrome, and drug reaction with eosinophilia and systemic symptoms.

The strategy used to confirm a suspected drug hypersensitivity should be rigorous and based on a clinical history in search of one or several responsible drugs (3–5). A definite diagnosis often requires drug provocation tests that must be performed in a hospital environment. A drug provocation test is the controlled administration of the drug to a patient with a history suggesting a drug allergy. This drug is either an alternative, structurally or pharmacologically related drug or the suspected drug itself. The European Network for Drug Allergy from the European Academy of Allergology and Clinical Immunology (6) recommends the use of drug provocation tests to confirm drug hypersensitivity reactions, although this is controversial and there are no U.S. guidelines on drug provocation tests. With the exception of some drugs, such as aspirin (7), cyclooxygenase-2 inhibitors (8), and β-lactams (9), the only available data come from small cohort studies on the results of drug provocation tests.

We performed this retrospective study to evaluate the outcomes of more than 1300 drug provocation tests performed on more than 800 patients with histories suggesting immediate drug allergy.

METHODS

Patients

We included in our study all patients who consulted at our allergy clinic (University Hospital of Montpellier, Montpellier, France) between September 1996 and August 2001 because of a history of immediate drug hypersensitivity. Their primary physicians referred them to the clinic for testing because they required the drugs in question. According to the referring doctors, all patients had sustained a reaction suggesting drug allergy within 24 hours of the last administration of the drug.

We included patients with a history of a drug hypersensitivity reaction (anaphylaxis, bronchospasm, rhinoconjunctivitis, laryngeal edema, urticaria, maculopapular eruption, or isolated generalized pruritus) documented by the referring physician, occurring within 24 hours after the last administration of the drug. Anaphylaxis was defined as a reaction suggesting allergy and affecting at least 2 different organs (for example, urticaria and conjunctivitis) with or

Context

Physicians face a difficult decision when patients need to take a drug to which they have had a possible hypersensitivity reaction.

Contribution

The authors gave the implicated drug or drugs to 898 patients referred for evaluation of possible drug hypersensitivity. Of 1372 tests performed, 17.6% confirmed hypersensitivity. None of the 241 positive test results involved a reaction that clinicians could not readily control with prednisolone, epinephrine, or antihistamine.

Implications

When administered by experienced clinicians in a carefully monitored setting, drug provocation tests are a safe method for confirming immediate hypersensitivity.

–The Editors

without hypotension. We excluded patients with noncompatible clinical symptoms and signs (different from the one described above, such as isolated gastrointestinal pains and headhaches), nonimmediate chronology (>24 hours after the last drug administration), symptoms disappearing without cessation of the suspected causal drug, and reactions occurring several days after the cessation of treatment. We also excluded the following patients: patients with chronic urticaria and latex and food allergy; patients who had experienced severe life-threatening skin reactions (including vasculitis, exfoliative dermatitis, toxic epidermal necrolysis or the Stevens–Johnson syndrome, drug reaction with eosinophilia and systemic symptoms, and acute generalized exanthematous pustulosis), drug-induced autoimmune disease (including systemic lupus erythematosus, pemphigus vulgaris, and bullous pemphigoid), specific organ hypersensitivity manifestations (including blood cytopenia, hepatitis, nephritis, and pneumonitis), aspirin-induced asthma, or cardiovascular disease (contraindicating epinephrine therapy); patients with anaphylaxis and positive and validated results on skin tests for the suspected drug (mainly β-lactams and muscle relaxants); patients declining the whole drug allergy evaluation; and pregnant women.

Drug Provocation Tests

At least 4 to 6 weeks after clinical symptoms of the suspected drug reaction resolved and at least 4 weeks from any illness, patients underwent a standardized evaluation at our clinic. This included a standardized questionnaire (11), skin tests for β-lactams (10), and drug provocation tests (6, 12). Patients were denied β-blockers and H_1-antihistamines for 2 and 5 days, respectively, before the drug provocation test. All tests for a single drug in a given patient occurred on the same day.

For β-lactams, a skin test that followed internationally validated procedures was performed first (4, 9, 10). Drug provocation tests with β-lactams were carried out only when skin test results were negative (6, 10). For all other drugs, skin tests were not performed (10).

The drug provocation tests consisted of ingesting (or injecting) increasing doses of the suspected causal drug (**Table 1**) once every 30 minutes until the usual daily dose was administered or symptoms of a drug reaction occurred. In most cases, we used the same route of administration as the patient had used when the allergic reaction had occurred; if oral formulation of an injectable drug was available and identical, we administered the drug orally. Administration was single-blinded and performed on the ward by a physician with full resuscitation back-up. Patients with a history of anaphylactic shock had intravenous catheters in place during the entire test.

Physicians and nursing staff were present and monitored both symptoms and cutaneous signs throughout the test. They also performed pulmonary function tests if bronchospasm was evident in the clinical history, and they monitored pulse and blood pressures.

The drug provocation test result was considered positive if any of the symptoms or signs of an immediate drug reaction described previously were documented (anaphylaxis, bronchospasm, rhinoconjunctivitis, laryngeal edema, urticaria, maculopapular eruption, or isolated generalized pruritus) up to 2 hours after the last dose was administered (3 hours for provocations to aspirin and other nonsteroidal anti-inflammatory drugs [NSAIDs]). The drug provocation test result was considered negative if no sign of drug hypersensitivity occurred after the usual daily dose had been administered. After a reaction without a decrease in blood pressure, 40 to 60 mg of prednisolone and 10 mg of loratadine or cetirizine were prescribed and given for the following 2 days. If anaphylaxis occurred, 0.25 μg of intramuscular epinephrine was injected in addition to prednisolone or antihistamine. The dose was repeated every 15 minutes if necessary, together with plasma expanders in cases of hypotension. After the last dose had been administered without a reaction occurring, the patient was kept under surveillance for 2 hours (3 hours after tests for allergy to aspirin and other NSAIDs).

In patients who received more than 1 drug during the hypersensitivity episode or claimed to have hypersensitivity reactions to more than 1 drug, other drug provocation tests were performed a few days to a few months later.

Because no alternative test for drug allergy exists and because patients need to take the drugs in question, our institutional policy and the ethical committee at our institution do not require that an ethics committee authorize the drug provocation test study. However, institutional policy does require the patient's written informed consent for us to perform the test and review a patient's records; we obtained consent in every case.

Table 1. **Sequence of Increasing Drug Dosage during Drug Provocation Tests***

Drug	Drug Class	Doses†	Route	Usual Daily Dose for Adults‡
Amoxicillin	Penicillin	1, 5, 25, 100, 500, 1000	Oral	1000–2000 mg
Ampicillin	Penicillin	1, 5, 25, 100, 500, 1000	Oral	2000 mg
Cloxacillin	Penicillin	1, 5, 25, 100, 500, 1000	Oral	2000 mg
Cefaclor	Cephalosporin	1, 5, 25, 125, 500	Oral	750 mg
Cefadroxil	Cephalosporin	1, 5, 25, 100, 500, 1000	Oral	2000 mg
Cefatrizine	Cephalosporin	1, 5, 25, 50, 250, 700	Oral	1000 mg
Cefazolin	Cephalosporin	1, 5, 25, 100, 500, 2000	Intravenous	1500–3000 mg
Cefuroxime	Cephalosporin	1, 5, 20, 80, 400	Oral	500 mg
Ceftazidine	Cephalosporin	1, 5, 25, 100, 500, 2000	Intravenous	3000 mg
Cefixime	Cephalosporin	1, 5, 25, 100, 225	Oral	400 mg
Ceftriaxone	Cephalosporin	1, 5, 25, 100, 500, 1000	Intravenous	1000–2000 mg
Diclofenac	NSAID	1, 5, 20, 80	Oral	100–150 mg
Ibuprofen	NSAID	1, 5, 20, 80, 150, 300	Oral	200–1200 mg
Ketoprofen	NSAID	1, 5, 20, 80	Oral	100–200 mg
Tiaprofenic acid	NSAID	1, 5, 20, 80, 200	Oral	300–400 mg
Meloxicam	NSAID	1, 3, 7.5	Oral	7.5–15 mg
Piroxicam	NSAID	1, 3, 6, 10	Oral	20 mg
Niflumic acid	NSAID	1, 5, 25, 125, 625	Oral	750–1000 mg
Aspirin	NSAID	1, 5, 20, 50, 100, 200, 500	Oral	500–3000 mg
Paracetamol	NSAID	1, 10, 50, 250, 500, 1000	Oral	500–4000 mg
Azithromycin	Macrolide	1, 5, 25, 75, 125, 250	Oral	500 mg
Clarithromycin	Macrolide	1, 5, 25, 100, 500, 1000	Oral	1500–2000 mg
Erythromycin	Macrolide	1, 5, 25, 100, 500, 1500	Oral	2000–3000 mg
Josamycin	Macrolide	1, 5, 25, 100, 500, 1000	Oral	1000–2000 mg
Roxithromycin	Macrolide	1, 5, 25, 100, 150	Oral	300 mg
Spiramycin	Macrolide	15 000, 75 000, 325 000, 750 000, 1 500 000, 4 500 000	Oral	6–9 mIU
Ciprofloxacin	Quinolone	1, 5, 25, 100, 500	Oral	500–1500 mg
Ofloxacin	Quinolone	2, 10, 50, 100, 200	Oral	400 mg
Pefloxacin	Quinolone	4, 20, 100, 200, 400	Oral	800 mg
Betamethasone	Steroid	0.2, 1, 2, 4	Oral	3–12 mg
Methylprednisolone	Steroid	1.6, 8, 16, 32	Oral	16–64 mg
Prednisolone	Steroid	2, 10, 20, 40	Oral	20–80 mg
Omeprazole	Proton-pump inhibitor	1, 5, 10, 20	Oral	20–40 mg
Pristinamycin	Synergistin	1, 5, 25, 100, 500, 1500	Oral	2000–3000 mg
Tetrazepam	Benzodiazepin	1, 2.5, 25, 50	Oral	50–100 mg
Any vaccine	Vaccine	0.1, 0.4, (0.5)	Subcutaneous	0.5 (1.0) mL
Lidocaine Articaine	Local anesthetic	0.1, 1, 2	Subcutaneous	1–3 mL

* NSAID = nonsteroidal anti-inflammatory drug.
† Ten times less than the first dose for anaphylactic shocks; same units as fifth column.
‡ According to the recommendations of the French Agency on Drug Safety (www.AFSSAPS.sante.fr).

Statistical Analysis

We calculated the median and interquartile ranges for age, sex, time lapse since the clinical history, and interval between the last administration of the drug. The Kruskal–Wallis and Mann–Whitney U tests, as well as StatView software (Abacus Concepts, Inc., Berkeley, California), were used for statistical comparisons between patients with positive drug provocation test results and those with negative drug provocation test results.

Role of the Funding Source

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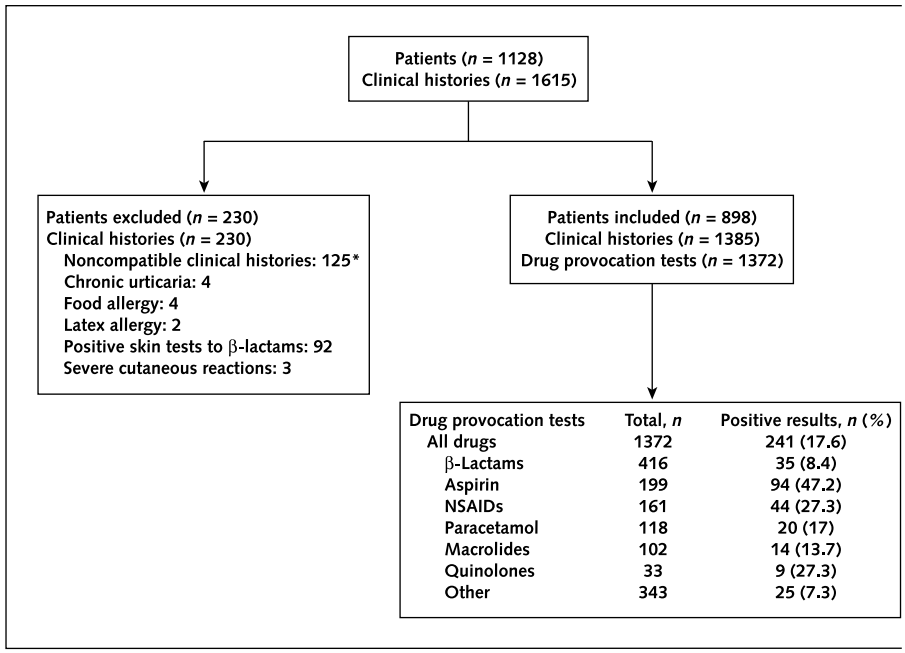
RESULTS

All Referred Patients

A total of 1128 patients were referred to our service with suspected drug allergy during the study period (**Figure**). Patients consisted of 772 women (68.4%) and 356 men (32.6%), among whom 144 were children (74 boys and 70 girls). Their ages ranged from 1 to 88 years (median, 39 years [interquartile range, 25 to 52 years]). There were 487 patients who had more than 1 suspected drug hypersensitivity reaction (1615 suspected reactions in 1128 patients), sometimes involving the same drug or the same drug class. We excluded 230 patients (accounting for suspected drug hypersensitivity reaction). A total of 1372 drug provocation tests covered the drugs suspected of causing an allergic reaction in the 898 patients. There were 1385 episodes of suspected reaction because some patients

Figure. **Flow chart of study patients and results of drug provocation tests.**



Drug provocation tests	Total, *n*	Positive results, *n* (%)
All drugs	1372	241 (17.6)
β-Lactams	416	35 (8.4)
Aspirin	199	94 (47.2)
NSAIDs	161	44 (27.3)
Paracetamol	118	20 (17)
Macrolides	102	14 (13.7)
Quinolones	33	9 (27.3)
Other	343	25 (7.3)

Some patients had more than 1 suspected drug hypersensitivity reaction (1615 suspected reactions in 1128 patients). *We excluded 15 patients with noncompatible clinical symptoms and signs (detailed in the text), 92 patients with a reaction occurring more than 24 hours after the last drug administration, and 18 patients with symptoms that disappeared while the patient continued to take the suspected drug. NSAID = nonsteroidal anti-inflammatory drug.

had not only more than 1 clinical history with different drugs but also more than 1 clinical history with the same drug. In these latter cases, we performed 1 drug provocation test for the drug in question.

Excluded Patients

A total of 230 patients (156 women and 74 men) were excluded. They each recalled 1 clinical history of drug hypersensitivity (**Figure**). Ages ranged from 1 to 56 years (median, 36 years [interquartile range, 26 to 53 years]), and 18 patients were children.

The main reason for their exclusion was a clinical history incompatible with an immediate drug hypersensitivity reaction (125 [54.3%] patients). Fifteen patients had incompatible clinical symptoms and signs. In 78 patients, the episode occurred too long after exposure to be consistent with an immediate hypersensitivity reaction. Eighteen patients had symptoms that resolved even though therapy with the suspected causal drug was continued, and 14 patients had reactions that occurred several days after treatment with the suspected drug was stopped.

Patients with a clinical history of β-lactam hypersensitivity reaction (92 [40.0%] patients) had positive results on skin tests for the relevant β-lactams (data not shown) and therefore did not have a drug provocation test.

Included Patients

The remaining 898 patients (616 women and 282 men), among whom 126 were children (58 girls and 68 boys), underwent 1372 drug provocation tests that were analyzed independently (**Table 2**).

The reasons given for referring the patient to our clinic, as stated by the referring doctors, were anaphylactic shock (64 [4.7%] patients), anaphylaxis without shock (57 [4.1%] patients), laryngeal edema (90 [6.6%] patients), bronchospasm (94 [6.9%] patients), urticaria (718 [52.3%] patients), and maculopapular eruption (300 [21.9%] patients). Other symptoms, such as faintness, conjunctivitis, fever, and isolated generalized pruritus, were present in 49 (4.4%) patients. Gastrointestinal symptoms (diarrhea, abdominal pains, sickness, and vomiting) were rare and generally associated with cutaneous eruptions (4 patients). The reactions had occurred 3 to 120 months (median, 12 months [interquartile range, 5 to 72 months]) before the drug provocation test. The time between the last administration of the suspected drug and the onset of symptoms was less than 1 hour for 448 (32.6%) patients.

We used the following drugs for the drug provocation tests: 416 (30.3%) β-lactams, 199 (14.5%) aspirin, 161 (11.7%) other NSAIDs, 118 (8.9%) paracetamol (acetaminophen), 102 (7.4%) macrolides, 33 (2.4%) quinolones, and 343 (25.0%) other drugs (including local anesthetics, vaccines, narcotics, and corticosteroids).

Results of the Drug Provocation Tests

There were 1131 (82.4%) negative drug provocation test results. Negative reactions occurred in 332 men (24.2% of the drug provocation tests) and 799 women age 2 to 88 years (median, 39 years [interquartile range, 24 to 52 years]). According to the referring doctor, some patients had severe reactions, including 43 episodes of anaphylactic

shock and 40 episodes of anaphylaxis without shock. In these test-negative cases, we attributed the symptoms to vagal faint (61%), nonspecific histamine release (37%), or food allergy (2%).

There were 241 (17.6%) positive drug provocation test results. These results occurred in 95 men and 146 women age 6 to 85 years (median, 41 years [interquartile range, 27 to 54 years]). They did not statistically significantly differ from the patients with negative drug provocation test results in terms of age, sex, or the time interval from the last administration of the drug to the onset of the allergic symptoms that led to referral to our clinic. In most cases, the clinical reactions during drug provocation tests reproduced the hypersensitivity reaction of the initial episode, including clinical symptoms and signs (which were milder in most cases) and chronology. Those who reacted, whether mildly or severely, were treated and had a rapid and good response. The predominant clinical syndrome in the patients with a positive drug provocation test result were anaphylactic shock (13 [5.4%] patients), anaphylaxis without shock (17 [7.0%] patients), laryngeal edema (10 [4.1%] patients), bronchospasm (19 [7.9%] patients), urticaria (160 [66.4%] patients), and maculopapular eruption (22 [9.1%] patients). The onset of the reaction in positive drug provocation test results was less than 1 hour for 123 (51%) patients, between 1 and 8 hours for 62 (26%) patients, between 8 and 12 hours for 28 (12%) patients, between 12 and 24 hours for 23 (9.5%) patients, and more than 24 hours for 5 (2%) patients. At the time of the suspected allergic reaction that led to referral to our clinic, these patients more often experienced an early reaction ($P < 0.001$), had more occurrences of anaphylaxis with and without hypotension and laryngeal edema, and had fewer occurrences of maculopapular eruptions compared with the patients with a negative drug provocation test results ($P < 0.001$) (**Table 2**).

Two drug provocation tests were performed on 325 patients, resulting in 49 (15%) patients with positive results. One hundred eight patients had 3 tests performed; 30 patients had 4 tests performed; 9 patients had 5 tests performed; and 2 patients had 6 and 7 tests performed, respectively. These tests resulted in 14 (13%), 5 (17%), 1, and 0 patients, respectively, with positive test results. No patient had more than 1 positive test result.

Table 2. **Characteristics of Patients with Positive Drug Provocation Test Results***

Patient Characteristic	Patients, *n*	Positive Drug Provocation Test Results, %
Sex		
Females	945	15.4
Males	427	22.2
Age		
≤18 y	144	15.9
18–65 y	986	17.7
≥65 y	242	17.8
Drug class		
β-lactam	416	8.4
Aspirin	199	47.2
NSAIDs	161	27.3
Paracetamol	118	17.0
Macrolides	102	13.7
Quinolones	33	27.3
Other†	343	7.3
Symptoms		
Anaphylactic shock	64	32.8
Anaphylaxis without shock	57	29.8
Laryngeal edema	90	27.8
Bronchospasm	94	20.2
Urticaria	718	17.8
Maculopapular eruption	300	10.3
Other‡	49	0
Chronology§		
≤1 h	448	24.8
1–8 h	184	24.5
8–12 h	556	12.2
12–24 h	184	9.2

* NSAID = nonsteroidal anti-inflammatory drug.
† Including local anesthetics, vaccines, narcotics, and corticosteroids.
‡ Other symptoms, such as faintness, conjunctivitis, fever, and generalized itching, without other features of anaphylaxis.
§ Denotes the time between last administration of drug and onset of symptoms.

DISCUSSION

The major result of this study is that confirmed drug hypersensitivity reactions occurred in less than one quarter of patients with a history suggesting possible drug allergy. A negative drug provocation test result is important to the patient with suspected drug allergy because nonhypersensitive patients do not need to avoid these drugs in the future. The clinical histories of the patients with positive drug provocation test results were more suggestive of drug hypersensitivity reactions than the clinical histories of the patients with negative drug provocation test results. Indeed, 64.7% of the former reactions occurred within the first 8 hours after the last intake of the drug (as compared with 42.7% for the latter) and 15.7% of those reactions were anaphylactic (as compared with 7.3%). However, on a single patient basis, relying on the history to prove drug hypersensitivity (or its absence) is not possible. Similarly, although the proportion of positive test results was higher for aspirin (47.2%), other NSAIDs (27.3%), and quinolones (27.3%) than for paracetamol (16.9%), macrolides (13.7%), and β-lactams (8.4%), this information is not helpful diagnostically in a particular patient. Therefore, a complete drug allergy work-up is required: a detailed clinical history and physical examination, followed by 1 or more skin tests and drug provocation tests (6). Other laboratory-based tests that could possibly replace drug provocation tests are being studied. The drug provocation test result may have been falsely negative in some patients with mild sensitivity or a long delay between drug hypersensitivity reaction and allergy evaluation (spontaneous desensitization). Because of this possibility, we enroll our patients

in a follow-up program; no patient has reported an allergic reaction to a drug that we had exonerated on the basis of a negative drug provocation result. If not included in the diagnostic procedure, important cofactors, such as exercise or sunlight, may sometimes explain the negative results (6). Tolerance induction during the provocation, although never documented in the literature, may also explain a false-negative result.

In our hands, drug provocation tests were effective and safe. With careful selection of patients, the progressive administration of the drug with a very small starting dose (**Table 1**), and strict medical surveillance, no positive reaction was too severe to respond promptly to treatment. We could reproduce the initial episode with the same chronology but with milder clinical symptoms and signs. Drug provocation tests are still serious and potentially dangerous procedures (6). Documenting the patient's personal details, medical history, and concomitant drug therapy and the availability of full resuscitation facilities during the tests are important. Generally, drug provocation tests with a suspected drug should not be performed on patients with severe comorbid illnesses (that is, underlying cardiac, hepatic, renal, or other diseases) (6). We excluded these patients from our present study, but exceptions may be permissible if the suspected drug is essential to the patient. Conversely, absolute contraindications to rechallenge with medication include patients who have had severe life-threatening reactions, such as vasculitis, the Stevens–Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, and organ involvement. Although very rare, these reactions, if reactivated, may not be controlled medically.

We excluded 230 patients. Among them, 125 patients had clinical histories that were not compatible with immediate drug hypersensitivity reactions (nonimmediate reaction, suspected drugs not stopped, chronology, and clinical symptoms and signs not compatible). To exclude hypersensitivity in a patient whose history does not suggest drug allergy, the European Academy of Allergology and Clinical Immunology (6) proposes drug provocation tests. Most patients excluded were so convinced that they were drug allergic that they underwent drug provocation tests (148 patients). The test results were all negative. Among patients excluded from the study were 92 patients who received a positive result on a skin test for β-lactams and later had drug provocation tests performed with other β-lactam alternatives. These test results were also negative (data not shown). These results demonstrate the utility of drug provocation tests in diagnosing suspected drug hypersensitivity reactions and in searching for appropriate alternative drugs.

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