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Retrospective Evaluation of Patients Undergoing Drug Provocation Tests

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Abstract

Objective: This study aims to evaluate the demographic characteristics of patients presenting with suspected drug allergies, identify the implicated drugs, classify the types of reactions observed, and assess the contribution of drug provocation tests in diagnosis.

Methods: A total of 47 patients who underwent drug provocation tests between January 2023 and December 2024 were retrospectively analyzed. Data on age, gender, suspected drugs, symptoms, onset time, and comorbidities were collected. Provocation tests were conducted in a controlled hospital setting, and necessary medical interventions were performed for positive reactions.

Results: Of the patients, 59.57% were female and 40.43% were male, with a mean age of 111.68 months. Antibiotics (61.70%) and NSAIDs (Non-Steroidal Anti-inflammatory Drugs) (23.40%) were the most implicated drug groups. Beta-lactam antibiotics were identified as the leading drug group. Among reactions, maculopapular rash (31.48%) and angioedema (27.78%) were the most common symptoms. Early reactions (48.33%) were observed more frequently, while delayed reactions accounted for 41.67%.

Conclusion: Drug provocation tests are reliable tools for evaluating low-risk drug allergy probabilities and preventing unnecessary labeling of allergies. This study provides valuable insights into the management and treatment of drug allergies in children.

Keywords: Drug hypersensitivity, drug provocation test, maculopapular rash, Urticaria

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İlaç Provakasyon Testi Yapılan Hastaların Retrospektif Değerlendirilmesi

Öz

Amaç: Bu çalışma, ilaç alerjisi şüphesiyle kliniğimize başvuran hastaların demografik özelliklerini değerlendirmeyi, sorumlu ilaçları belirlemeyi, gözlemlenen reaksiyon türlerini sınıflandırmayı ve ilaç provokasyon testlerinin tanıya katkısını analiz etmeyi amaçlamaktadır.

Yöntemler: Ocak 2023-Aralık 2024 tarihleri arasında ilaç alerjisi şüphesiyle başvuran ve ilaç provokasyon testi yapılan 47 hasta retrospektif olarak değerlendirildi. Hastaların yaş, cinsiyet, şüpheli ilaç, semptomlar, başlangıç zamanı ve eşlik eden hastalıklar gibi verileri kaydedildi. Provokasyon testleri kontrollü bir hastane ortamında gerçekleştirildi ve test pozitif bulunduğunda gerekli tıbbi müdahaleler yapıldı.

Bulgular: Hastaların %59,57'si kadın ve %40,43'ü erkek olup, yaş ortalaması 111,68 aydı. Şüpheli ilaç grupları arasında antibiyotikler (%61,70) ve NSAID'ler (Non-Steroid Anti enflamatuvar İlaçlar) (%23,40) öne çıktı. Beta-laktam antibiyotikler, en sık şüpheli ilaç grubu olarak belirlendi. Reaksiyonlar arasında makülopapüler döküntü (%31,48) ve anjiyoödem (%27,78) en yaygın görülen semptomlardı. Şüpheli ilaçlara karşı erken reaksiyonlar (%48,33) daha sık gözlemlenirken, geç reaksiyon oranı %41,67 olarak saptandı.

Sonuç: İlaç provokasyon testleri, düşük riskli ilaç alerjisi olasılıklarının değerlendirilmesinde ve yanlış alerji etiketlemesini önlemede güvenilir bir araçtır. Bu çalışma, çocuklarda ilaç alerjisinin yönetimi ve tedavisi için önemli veriler sunmaktadır.

Anahtar kelimeler: ilaç aşırı duyarlılığı, ilaç provakasyon testi, makülopapüler döküntü, ürtiker.

INTRODUCTION

With the increasing prevalence of medication use in recent years, drug allergies have emerged as a significant public health concern. It is estimated that approximately 3-5% of individuals presenting to outpatient clinics and 10-15% of hospitalized patients develop drug allergies[1]. Penicillin allergy, affecting about 10% of patients, is the most frequently reported drug allergy[2]. The diagnosis of penicillin allergy is often based on the assumption that a recent rash was caused by penicillin use, without further investigation[3]. Although the majority of reactions observed following the use of penicillin and related antibiotics are not true drug allergies, healthcare providers frequently prescribe less effective or more expensive alternatives[4-6]. This practice increases the risk of adverse events, promotes the proliferation of drug-resistant organisms, and contributes to a rise in Clostridium difficile infections[7,8].

Drug Provocation Test (DPT) refers to the controlled administration of a medication to diagnose immune-mediated or non-immune drug hypersensitivity. From a European perspective, DPT is often regarded as the "gold standard" for diagnosing drug hypersensitivity[9]. However, in the American context, this approach is defined as a graded challenge (or test dose), wherein a drug is administered cautiously to avoid triggering a severe reaction[10]. Patients who are incorrectly classified as allergic to certain drugs can often be shown to tolerate these medications through skin testing and drug provocation, leading to accurate diagnoses while reducing the costs and side effects associated with alternative therapies[11]. The provocative drug may be an alternative medication, a structurally or pharmacologically related drug, or the implicated drug itself[12]. A negative DPT result does not confirm future tolerance to the drug but only indicates that no hypersensitivity reaction occurred during provocation and at the maximum doses administered[13].

Clinically, drug hypersensitivity reactions (DHRs) are categorized into two groups: "immediate" and "delayed." Immediate reactions occur within 1–6 hours after drug administration and are characterized by typical symptoms of Ig E-mediated reactions, such as urticaria, angioedema, rhinitis, bronchospasm, or anaphylaxis. Delayed reactions, on the other hand, manifest after 1 hour to several days following drug administration and may involve the skin (e.g., delayed urticaria, maculopapular rashes, vasculitis, bullous eruptions) and/or internal organs (e.g., hepatitis, renal failure, anemia, neutropenia)[14]. Non-immediate, T-lymphocyte-mediated reactions typically present as maculopapular rashes days after drug intake[15]. In contrast, Ig E-mediated immediate reactions develop within the first hour and may present as urticaria, angioedema, rhinitis, bronchospasm, or, in rare cases, anaphylaxis[3,16].

Our study aims to evaluate the demographic characteristics of patients presenting to our clinic with suspected drug allergy, identify the implicated drugs, classify the types of drug reactions observed, and assess the contribution of provocation tests in the diagnosis of drug allergies.

METHODS

A total of 47 patients who presented to the Pediatric Allergy and Immunology Clinic of our hospital with suspected drug allergies and underwent drug provocation tests between January 2023 and December 2024 were included in this study. Patient medical records were reviewed retrospectively to collect data on age, gender, suspected drug, symptoms observed, time to symptom onset, history of comorbidities, prior drug allergy in the patient or family, drug-specific Ig E results (if available), eosinophil and total Ig E levels, and diagnostic evaluations. Reactions were classified as early (immediate) if they occurred within 1 hour after drug administration, or delayed if they developed at varying intervals from 1 hour to several days after the last drug dose[17].

Skin prick tests (SPT) and intradermal tests (IDT) were performed on patients using the suspected drug or clinically appropriate alternative medications. Subsequently, oral provocation tests were conducted with drugs deemed suitable for oral administration. Diagnostic tests were performed at least 6–8 weeks after the suspected drug reaction, and antihistamines were discontinued one week before testing.

In the SPT (Skin Prick Test), histamine (10 mg/mL) was used as the positive control, while 0.9% sterile saline served as the negative control. The test was initially conducted using the suspected drug or an alternative medication. If the DPT yielded a negative result, the implicated drug was subsequently administered intradermally in incrementally increasing doses with diluted concentrations. A positive result for the SPT or IDT was defined by the presence of a wheal and erythema measuring at least 3 mm larger than the negative control. In patients with a history of reactions to beta-lactam antibiotics, specific Ig E levels for penicillin, ampicillin, and amoxicillin were measured using the ImmunoCAP method, with values above 0.35 kUA/L considered positive.

Drug provocation tests, drug concentrations to be tested and their durations were organized according to the National Allergy and Clinical Immunology Society of Turkey Guidelines for Approach to Drug Hypersensitivity Reactions[17]. All drug provocation tests were performed in a hospital setting equipped for emergency interventions. Drug doses were administered at one-hour intervals, either until an allergic reaction occurred or until the single daily therapeutic dose, calculated based on the patient's body weight, was reached. The test was considered positive and terminated if any of the following symptoms were observed

during or after the provocation: skin reactions such as urticaria, angioedema, or maculopapular rash; cardiovascular symptoms such as tachycardia or hypotension; respiratory symptoms including cough, wheezing, or dyspnea; neurological symptoms such as confusion or syncope; or gastrointestinal symptoms including abdominal pain, vomiting, or diarrhea. Patients with positive reactions received appropriate medical treatment and were monitored until their symptoms resolved. Patients who completed the test without symptoms after ingesting the final dose were observed for at least two additional hours. A negative DPT result was recorded for those who exhibited no symptoms throughout the testing process.

The study was conducted with ethical approval obtained from the hospital's ethics committee, as per decision number 450 dated December 26, 2024.

Statistical Analysis

Descriptive data were presented as numbers and percentages for categorical variables, while continuous variables were summarized using minimum, maximum, and median values. The normality of the distribution of continuous variables was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests, supported by visual methods such as histograms and Q-Q plots.

RESULTS

In our study, 60 drug provocations performed on 47 patients were evaluated. The cohort included 28 females (59.57%) and 19 males (40.43%), with a mean age of 111.68 months (range: 8–204 months). Regarding comorbid conditions, nine patients (19.14%) had allergic rhinitis (AR), two patients (4.25%) had asthma, six patients (12.76%) had a combination of asthma and allergic rhinitis, two patients (4.25%) had atopic dermatitis (AD), one patient (2.13%) had angioedema, one patient (2.13%) had phenylketonuria, one patient (2.13%) had cerebral palsy, and one patient (2.13%) had a bone tumor. None of the patients had a documented history of drug allergy in their parents (Table 1).

Table I: Demographic characteristics of the patients

Mean age (months), median (min-max)		111.68 months (8-204)
Gender, n (%)	Female	28 (59.57)
	Male	19 (40.43)
Family history of drug allergy, n (%)	No	47 (100)
	Yes	0 (0)
Comorbidity, n (%)	AR	9 (19.4)
	Asthma+ AR	6 (12.76)
	Asthma	2 (4.25)
	AD	2 (4.25)
	Other*	4 (8.5)

*AR: Allergic rhinitis, AD: atopic dermatitis, * one angioedema, one phenylketonuria, one cerebral palsy, one bone tumour*

When the distribution of suspected allergenic drugs and cases of multiple drug allergy suspicion were evaluated, antibiotics were identified as the suspected drug group in 29 out of 47 patients (61.70%). Among these, 22 patients (46.8%) had reactions to amoxicillin-clavulanic acid, 12 (25.53%) to clarithromycin, five (10.63%) to ceftriaxone, three (6.38%) to cefuroxime, three (6.38%) to azithromycin, one (2.13%) to penicillin G, one (2.13%) to cephalexin, one (2.13%) to metronidazole, 1 (2.13%) to ampicillin-sulbactam, one (2.13%) to cefdinir, one (2.13%) to cefpodoxime, and one (2.13%) to cefixime. Additionally, 11 patients (23.4%) had reactions to paracetamol. Reactions associated with NSAIDs were identified in 11 patients (23.40%), including 8 (17.02%) with ibuprofen, one (2.13%) with nimesulide, one (2.13%) with dexketoprofen, and 1 (2.13%) with metamizole. Eight patients (17.02%) were suspected of having allergic reactions to local anesthetics, including five (10.63%) to articaine and three (6.38%) to lidocaine. Other suspected allergens included

nasal steroids in one patient (2.13%), chlorhexidine in one patient (2.13%), and oxolamine in one patient (2.13%). Perioperative drugs were suspected in two patients (4.25%), including sodium thiopental in one patient (2.13%), ketamine in one patient (2.13%), and midazolam in one patient (2.13%). Multiple drug allergy suspicion was present in 25 patients (53.19%) (Table 2).

Table II: Evaluation of suspected allergens

Drugs Group	Suspected Medicine	n (%)
Antibiotics (beta lactam)	Amoxicillin-clavulanic acid	22 (46.8)
	Ceftriaxone	5 (10.63)
	Cefuroxime	3 (6.38)
	Ampicillin-sulbactam	1 (2.13)
	Penicillin G	1 (2.13)
	Sephalexin	1 (2.13)
	Sefdinir	1 (2.13)
	Cefpodoxime	1 (2.13)
	Sefiksim	1 (2.13)
Other Antibiotics	Clarithromycin	12 (25.53)
	Azithromycin	3 (6.38)
	Metronidazole	1 (2.13)
	Paracetamol	11 (23.4)
NSAIDS	İbuprofen	8 (17.02)
	Nimesulide	1 (2.13)
	Dexketoprofen	1 (2.13)
	Metamizole	1 (2.13)
Local anaesthetic	Artikaine	5 (10.63)
	Lidocaine	3 (6.38)
	Nasal steroid	1 (2.13)
	Chlorhexidine	1 (2.13)
	Oxolamine	1 (2.13)
Perioperative Medicines	Sodium thiopental	1 (2.13)
	Ketamine	1 (2.13)
	Midazolam	1 (2.13)

NSAIDS: Nonsteroidal anti-inflammatory drugs

When examining the percentage distribution of agents used in drug provocation tests, azithromycin was identified as the most frequently used agent (12%). This was followed by amoxicillin-clavulanic acid (with its major and minor determinants) at 21.67% and mepivacaine at 10%. Other agents included clarithromycin (8.33%), nimesulide (8.33%), paracetamol (6.67%), midazolam (3.33%), fentanyl (3.33%), propofol (3.33%), lidocaine (3.33%), and rocuronium (3.33%). Less frequently used agents were cefuroxime (1.67%), clindamycin (1.67%), ibuprofen (1.67%), prilocaine (1.67%), and meloxicam (1.67%).

It was found that 30 patients (63.82%) had previously used the suspected allergenic drug. The median absolute eosinophil count among patients was $150 \times 10^3/\mu L$ (range: 0–530), and the median total Ig E level was 92 IU/mL (range: 4–519). Specific Ig E tests for penicillin, ampicillin, and amoxicillin were positive in one patient (2.13%).

When the onset time of symptoms following drug administration was evaluated, it was found that 29 reactions (48.33%) occurred within the first hour (early reactions), while 25 reactions (41.67%) developed after 1 hour (delayed reactions).

Analyzing the distribution of symptoms observed after drug administration, among 54 drug reactions, maculopapular rash was identified in 17 cases (31.48%), angioedema in 15 cases (27.78%), urticaria in 11 cases (20.37%), and anaphylaxis in 8 cases (14.81%). Stevens-Johnson syndrome (SJS), presenting with oral lesions and skin findings, was detected in one case (1.85%), pruritus in one case (1.85%), and gastrointestinal symptoms in one case (1.85%) (Table 3).

Table III: Findings in suspected drug allergy

Symptom	n (%)
Maculopapular rash	17 (31.48)
Angioedema	15 (27.78)
Urticaria	11 (20.37)
Anaphylaxis	8 (14.81)
Oral lesions and rash (SJS)	1 (1.85)
Itching	1 (1.85)
GIS findings	1 (1.85)

SJS: Steven-Johnson Syndrome, GIS: Gastrointestinal system

In 13 of the patients, a drug provocation test was performed for definitive diagnosis with amoxicillin clavulanic acid when the suspected agent was a penicillin group. In two of these patients, urticaria was observed during oral provocation and in one of them the test was terminated due to a positive IDT result. In our study, late reaction due to OPC (oral provocation tests) was observed in 3 patients. However, one of these patients was suspected to have a rash secondary to viral infection after provocation. Table 4 shows the agents used in the IPT performed in the patients, the purpose of using the agents (for diagnostic purposes or to determine alternative drugs) and the test results. It is indicated in brackets whether the drugs that caused reactions were used for diagnostic purposes or to determine alternative drugs.

Table IV: Agents used in DPT and test results

The drug used in IPT	N	For diagnostic purposes (n)	Alternative drug (n)	No reaction (n)	Reaction (n)
Azithromycin	12	1	11	11	1 (alternative)
Amoxicillin-clavulanic acid	13	12	1	9	4 (**diagnostic purposes**; 2 urticaria, 1 IDT positive, 1 late reaction)
Mepivacaine	6	0	6	6	0
Clarithromycin	5	0	5	4	1 (alternative-urticaria)
Nimesulide	5	0	5	4	1 (late reaction)
Paracetamol	4	3	1	4	0
Midazolam	2	1	1	2	0
Fentanyl	2	0	2	2	0
Propofol	2	0	2	2	0
Lidocaine	2	0	2	2	0
Rocuronium	2	0	2	2	0
Cefuroxime	1	0	1	1	0
Clindamycin	1	0	1	1	0
Ibuprofen	1	0	1	1	0
Prilocaine	1	0	1	1	0
Meloxicam	1	0	1	1	0

DPT: Drug provocation test, IDT: Intradermal test

DISCUSSION

In our study, 60 drug provocations performed on 47 patients were evaluated. Among the patients assessed for suspected drug allergy, the proportion of females (59.57%) was found to be higher than that of males (40.43%). Similarly, in the literature, Kont et al. reported that 51.3% of their patients with early-type drug reactions were female[18]. The mean age of our patients was 111.68 months, with a wide age range encompassing both children and adolescents. Regarding comorbid conditions, allergic rhinitis (19.4%) was the most frequently observed. In a study by Aydoğdu et al., 16.3% of patients with NSAID allergy were found to have concomitant allergic rhinitis[19].

In our cohort, 53.19% of patients had suspected multiple drug allergies. Kont et al. also reported a history of multiple drug allergies in 48.6% of their study population[18].

In childhood, antibiotics are the most common cause of adverse drug reactions, followed by NSAIDs and antiepileptics[20]. In our study, the distribution of suspected drugs revealed that antibiotics were implicated in 61.70% of cases, NSAIDs in 23.40%, local anesthetics in 17.02%, and perioperative drugs in 4.25%. A study by Tuğcu et al.[21] reported similar findings, with antibiotics accounting for 62%, NSAIDs for 16%, local anesthetics for 6%, and perioperative drugs (muscle relaxants and general anesthetics) for 2% of cases. However, the rate of local anesthetic allergy was higher in our study.

Beta-lactams (penicillins and cephalosporins) were identified as the most frequently suspected antibiotic group in our study (including patients with suspected multidrug allergy), accounting for 76.6% of cases. Among non-beta-lactam antibiotics, clarithromycin was the most commonly implicated drug, with a rate of 25.53%. In the study by Tuğcu et al., beta-lactams were also the most frequently

implicated antibiotics, including amoxicillin-clavulanate (41%), penicillin (25%), cephalosporins (16%), and ampicillin (7%)[21]. Similarly, clarithromycin, with an 8% rate, was the most commonly implicated non-beta-lactam antibiotic. In our study, the suspicion of allergy to clarithromycin among non-beta-lactam antibiotics was higher.

In the study by Kont et al., beta-lactam antibiotics (68.9%) and NSAIDs (51.3%) were reported as the most frequent causes of allergic reactions, with clarithromycin being the most commonly implicated non-beta-lactam antibiotic[18]. These findings are consistent with our results, highlighting a similar pattern of suspected drug allergies.

In our study, three patients experienced delayed reactions associated with oral provocation tests (OPC). However, in one of these cases, a post-provocation rash was suspected to be secondary to a viral infection. Caubet et al. evaluated 88 children with a history of late-onset urticarial and maculopapular rash due to β-lactam use, of whom eleven (13%) had a positive ID test. Six children (6.8%) had a positive oral DPT with β-lactams and mild skin eruptions, mostly as late reactions (after 7-12 hours). Four of the six children with a positive DPT also had positive ID test results with β-lactams[22].

In one patient, urticaria developed during the first dose of the IDT (a patient with a history of suspected allergy to amoxicillin-clavulanic acid, azithromycin, and clarithromycin). The drug provocation test with amoxicillin-clavulanic acid was terminated to establish a definitive diagnosis. In another patient, positivity was observed during the second dose of the IDT (a patient with a history of suspected allergy to amoxicillin-clavulanic acid), leading to the termination of the drug provocation test with amoxicillin-clavulanic acid.

When analyzing the distribution of symptoms, maculopapular rash was identified as the most common reaction (31.48%), followed by angioedema (27.78%), urticaria (20.37%), and anaphylaxis (14.81%). In the study by Tuğcu et al.[21], a history of anaphylaxis was reported in 31.3% of drug reactions. Skin findings were predominant, with urticaria observed in 79.3% and angioedema in 45% of patients. Respiratory symptoms were noted in 27.1% of reactions. In our study, skin findings were also more prevalent, and respiratory symptoms were not observed except in patients who experienced anaphylaxis.

The finding that symptoms in most of our patients (48.33%) began within the first hour following drug administration supports the prevalence of Ig E-mediated immune reactions. However, the presence of delayed reactions (41.67%) highlights the significant role of T-cell-mediated responses as well.

Another notable observation in this study is the absence of a history of drug allergy among the parents of any of the patients. This suggests that, beyond genetic predisposition, environmental and individual factors may play a more decisive role in the development of drug allergies.

In conclusion, this study provides valuable data on the evaluation and management of drug allergies in children. It demonstrates that drug provocation tests are a reliable tool, particularly for assessing low-risk drug allergy probabilities and preventing unnecessary allergy labeling.

Ethics Committee Approval: The study was conducted with ethical approval obtained from the hospital's ethics committee, as per decision number 450 dated December 26, 2024.

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