



# Review of patients with immediate-type drug reactions and test results: Retrospective study from the Malatya Province

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## ARTICLE INFO

### Keywords:

Drug hypersensitivity  
Skin test  
Drug provocation test

Received: Mar 04, 2022

Accepted: May 23, 2022

Available Online: 26.08.2022

### DOI:

[10.5455/annalsmedres.2022.03.086](https://doi.org/10.5455/annalsmedres.2022.03.086)

## Abstract

**Aim:** Drug hypersensitivity is an important issue encountered by clinicians during clinical practice in Turkey and in the world. Any drug used for diagnosis or treatment has the potential to cause hypersensitivity reactions. The aim of the present study was to review the distribution of drugs reported to cause hypersensitivity reactions and to determine the distribution of tests and test results among patients that presented to the adult allergy and immunology outpatient clinic with immediate-type drug hypersensitivity in the Malatya province.

**Materials and Methods:** The study included adult patients who were admitted with immediate-type drug hypersensitivity (allergic and/or non-allergic) between October 2017 and October 2020 and underwent testing for drugs. Age, sex, atopic diseases (asthma, allergic rhinitis, urticaria, eczema), culprit drug(s), drug reaction types, time of reaction onset, and skin and drug provocation test results were evaluated.

**Results:** Of the 107 patients included, 83 (77.6%) were female and 24 (22.4%) were male. The mean age was  $40.74 \pm 11.28$  years. There was a history of drug hypersensitivity to antibiotics in 44 patients (41.1%) and analgesics in 56 patients (52.3%). Urticaria and/or angioedema were the most common reactions to culprit drugs. Overall, 148 tests for drug hypersensitivity were performed, and the positivity rate was 6.1%.

**Conclusion:** Analgesics and antibiotics were the most common causative agents in patients presenting to allergy outpatient clinics with drug allergy, and reactions occurred even with alternative agents. Thus, patients reporting drug reactions should undergo drug tests before physicians recommend drugs.



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## Introduction

There is limited data about the true incidence of drug hypersensitivity reactions (DHRs) in the general population [1]. This may be because studies included select populations or specific reactions, solely relied on patient history without supporting diagnostic drug tests, and misreported rashes due to infection or adverse drug reactions such as drug allergy [1]. Epidemiological data suggest that the DHR prevalence is 1–6% among adults and relatively lower in children [2,3]. In a Turkish study, the immediate-type DHR prevalence was 3.6% [4].

DHRs are classified as “allergic” and “non-allergic” based on underlying mechanisms, and as immediate (acute) or non-immediate (delayed) based on symptom onset. The reaction mediated by immune mechanisms (IgE and T lymphocyte-mediated) is defined as “drug allergy”, whereas

the reaction mediated by non-immune mechanisms (mast cell/basophil degranulation or COX-1 enzyme inhibition) is defined as “non-allergic DHR” [5]. Immediate reactions occur within 1-6 hours after drug intake. Reactions such as urticaria, angioedema, rhinitis, conjunctivitis, bronchospasm, or anaphylaxis develop as a result of IgE-mediated or non-allergic mechanisms. Delayed reactions are generally observed beyond 24 hours and mostly develop through T cell-mediated mechanisms, e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome, and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome [5].

In a patient with a suspected drug allergy, diagnostic tests can be performed after a thorough evaluation, including anamnesis and physical examination, and a safe alternative drug can be offered to the patient [5-7]. Skin prick tests (SPTs), intradermal tests, and drug provocation tests (DPTs) are used in the diagnosis of drug allergy [2]. The European Network for Drug Allergy (ENDA) guideline is

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commonly used for skin test application, concentrations, and evaluation [8].

The aim of the present study was to assess the distribution of drugs reported to cause DHR and the distribution of tests and test results among patients admitted to the adult allergy and immunology outpatient clinic with immediate-type DHR in the Malatya province.

## Materials and Methods

### *Patient selection*

This was a retrospective data review conducted at the adult allergy and immunology outpatient clinic in Malatya Training and Research Hospital. The study included adult patients who were admitted with immediate-type DHR (allergic and/or non-allergic) between October 2017 and October 2020 and underwent testing for drug hypersensitivity. Age, sex, atopic diseases (asthma, allergic rhinitis, urticaria, eczema), culprit drug(s), drug reaction types, time of reaction onset, and skin and drug provocation test results were all evaluated.

### *Skin and drug provocation test protocols*

The drug tests were performed by the same trained nurse and doctor in accordance with the ENDA guidelines [8,9]. Written informed consent was obtained from all patients. Histamine (10 mg/mL) and sterile saline were used as positive and negative controls for the SPT, respectively. The test was considered positive when a wheal diameter at the test region was 3 mm greater than the negative control after 20 minutes. Intradermal test was performed in the case of a negative SPT. The intradermal test was considered positive if the wheal diameter increased by more than 3 mm.

The DPT was performed in patients with negative skin tests in settings where resuscitation and monitoring were readily available in case of serious reactions during the test. In patients with a history of severe reactions, a venous line was established before DPT. A comprehensive assessment was performed in all patients, including physical examination and pulmonary function tests (PEF and FEV1 measurement) with vital signs. In anxious patients, the testing procedure was initiated using a placebo. The drugs were administered at incremental doses (not exceeding the total daily therapeutic dose) at a minimum of 30-minute intervals under close monitoring by an experienced nurse. The test was considered positive and stopped if an objective symptom such as urticaria, angioedema, shortness of breath, hypotension, or nasal symptoms developed and a 15% decrease in PEF was detected. In the case of a positive test, the patient was treated and followed up until recovery of symptoms. The patient was kept under observation for at least 2 hours after the last dose was administered without a reaction. Patients without symptoms were considered to have negative results.

The drugs were classified as antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), local anesthetics, and miscellaneous (chemotherapeutics, vitamin preparations, corticosteroids, iron supplements, contrast agents, proton pump inhibitors [PPIs], and general anesthetics).

The study was approved by the Ethics Committee of Malatya Turgut Özal University, Medicine School (2022/27).

### *Statistical analysis*

All statistical analyses were performed using SPSS for Windows, version 26.0. (IBM Corp., Armonk, NY, USA). The results of the descriptive statistics are expressed as counts, percentages, and means  $\pm$  standard deviations. The chi-square test was used to compare categorical variables. A p-value of  $< 0.05$  was considered statistically significant.

## Results

### *Patient characteristics*

Of the 107 patients included, 83 (77.6%) were female and 24 (22.4%) were male. The mean age was  $40.74 \pm 11.28$  years (range: 18–73 years). When all patients were evaluated for DHR via anamnesis, the most common reaction was urticaria and/or angioedema in 80 patients (74.8%), followed by anaphylaxis in 18 patients (16.8%) and respiratory symptoms in 17 patients (15.9%). Eight patients (7.5%) experienced two distinct types of DHR at different times (e.g., urticaria and anaphylaxis; urticaria and respiratory symptoms). Table 1 shows the clinical characteristics of the patients.

### *Distribution of drugs with hypersensitivity reactions*

No significant difference was detected in the frequency of reactions to antibiotics, NSAIDs, local anesthetics, and miscellaneous group drugs between the female and male patients. In 56 patients (52.3% 56/107), there was a history of DHR with NSAIDs. Of these, 10 patients reported DHR with paracetamol. Ten patients had underlying asthma and were diagnosed with NSAID-exacerbated respiratory disease (NERD). Forty-four patients (41.1% 44/107) reported DHR with one or more groups of antibiotics. In cases in which an antibiotic group could be identified, beta-lactam antibiotics (penicillin and/or cephalosporin) were the most common causative agents (77.8% 21/27), followed by quinolones (14.8% 4/27), macrolides (11.1% 3/27), and ornidazole (7.4% 2/27). Eleven patients (10.3% 11/107) reported DHR with one of the drugs in the miscellaneous group (chemotherapeutics, vitamin preparations, corticosteroids, iron supplements, contrast agents, PPI, and general anesthetics), while 9 patients (8.4% 9/107) reported DHR with local anesthetics. In 18 patients, there was DHR with more than one drug group. The culprit drug was unknown in 8 patients (7.5% 8/107). Figure 1 shows the distribution of drugs with hypersensitivity reactions.

### *Distribution and results of drug tests*

Overall, 148 drug tests were performed on 107 patients admitted with immediate-type DHR. Twenty-eight patients underwent more than one test. We performed 102 (69%) oral provocation, 23 (15.5%) skin and subcutaneous provocation, 15 (10.1%) skin and oral provocation, and 8 (5.4%) skin tests. NSAIDs were administered in 54 tests (36.9%

**Table 1.** Clinical characteristics of patients.

	n (%)
Sex (n=107)	
Female	83 (77.6)
Male	24 (22.4)
Mean age, years ± SD	40.74 ± 11.28
Atopic disease (n=101)	
Asthma and/or allergic rhinitis	27 (26.7)
Urticaria and/or angioedema	8 (7.9)
Eczema	1 (1)
None	65 (64.4)
Duration of drug hypersensitivity (n=95)	
<1 years	23 (24.2)
1–5 years	45 (47.4)
>5 years	27 (28.4)
Reaction type (n=107)*	
Urticaria and/or angioedema	80 (74.8)
Anaphylaxis	18 (16.8)
Respiratory	17 (15.9)

SD: standard deviation. \*8 patients (7.5%) reported that they experienced two distinct types of drug reactions at different times.

54/148), antibiotics in 56 tests (37.8% 56/148), local anesthetics in 23 tests (15.5% 23/148), and miscellaneous drugs in 15 tests (10.1% 15/148). There were 9 (6.1%) positive test results. The provocation tests were positive in 3 patients tested with meloxicam, in 1 patient tested with nimesulide, in 1 patient tested with quinolone, in 1 patient tested with tetracycline, and in 1 patient tested with metronidazole. Skin tests were positive in 1 patient tested with a quinolone and in 1 patient tested with clindamycin. Table 2 shows the distribution and results of the drug tests.

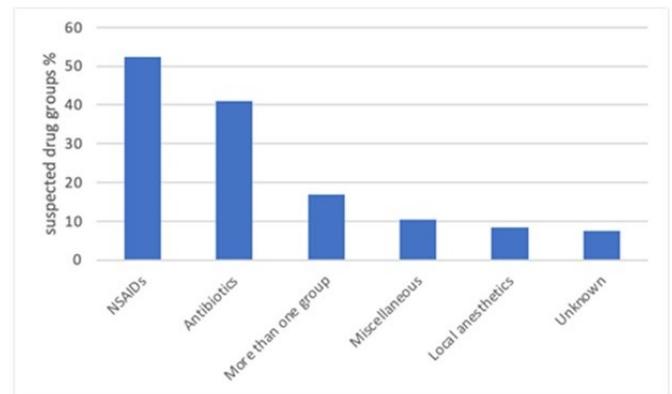
## Discussion

In this study, 148 drug tests were assessed in 107 patients who presented with immediate-type drug hypersensitivity. The most common causative drugs were NSAIDs and antibiotics, and the most common DHRs were urticaria and/or angioedema.

Drug allergy is more commonly reported in females than in males [10]. In a review of self-reported drug allergy assessing 126.306 participants, the frequency of self-reported drug allergy was found to be higher in female patients than in male patients [11]. A study in Turkey showed that drug allergy was eight times higher in women than in men [12]. In our study, drug hypersensitivity was 3.5-fold higher in women than in men, in agreement with the literature.

Beta-lactam antibiotics and NSAIDs are among the most common agents causing DHRs [13,14]. In a study in Turkey, beta-lactam antibiotics most frequently caused DHR (51.2%), followed by NSAIDs (41.5%) [4]. In our study, beta-lactam antibiotics and NSAIDs were most commonly reported in association with DHRs, in accordance with previous studies.

DHRs may manifest with different clinical presentations.

**Figure 1.** Distribution of drugs reported to cause immediate-type hypersensitivity reactions.

The most frequent reactions are cutaneous, such as urticaria and exanthems [2]. Urticaria was the most commonly described reaction in the anamnesis, according to a Turkish study by Celik et al. and a French study by Messaad et al [15,16]. In our study, urticaria and/or angioedema were the primary DHRs.

DPT is the gold standard for the diagnosis of DHRs developed through either immunological or non-immunological mechanisms, and it is defined as the controlled administration of the suspected drug. DPT can be performed to exclude hypersensitivity in patients with a history not suggesting a drug allergy, to find a safe alternative by exclud-

**Table 2.** Distribution of drug tests and administered drugs (n=148).

	n (%)
Distribution of drug tests	
Oral provocation	102 (69)
Skin test+ subcutaneous provocation	23 (15.5)
Skin test+ oral provocation	15 (10.1)
Skin test	8 (5.4)
Distribution of administered drugs	
Meloxicam	29 (19.6)
Paracetamol	23 (15.5)
Nimesulide	2 (1.4)
Macrolide	22 (14.9)
Quinolone	15 (10.1)
Clindamycin	11 (7.4)
Metronidazole	6 (4.1)
Tetracycline	2 (1.4)
Local anesthetics	23 (15.5)
Miscellaneous group	15 (10.1)
Test results	
Negative	139 (93.9)
Positive	9 (6.1)

Miscellaneous: chemotherapeutics, vitamin preparations, corticosteroids, iron supplements, contrast agents, general anesthetics, and PPIs.

ing cross-reactions in patients with drug allergy, or for anxious patients who decline to use drugs unless lack of drug hypersensitivity is proven [9]. In our study, 26 provocation tests were performed on patients who had a history of suspected allergic reactions to different drug groups and who refused to use the drug unless the absence of drug allergy was proven. In addition, all positive results (6.1%) were observed during tests performed to find a safe alternative. In a recent study, Damadoglu et al. reported a 5.45% positive result rate in tests performed for alternative agents [17].

A limitation of the present study was that we did not confirm each drug reaction with an oral provocation test. However, we attempted to improve the reliability of the information gathered via comprehensive anamnesis from the patients and past hospital reports.

### Conclusion

In conclusion, the most frequent causative agents of DHRs were analgesics and antibiotics in patients admitted with drug allergy to allergy clinics. However, it was difficult to identify the causative agent in most instances. Detailed history and physical examination followed by diagnostic tests were required in these patients. Drug reactions are still likely even with alternative agents. Thus, patients reporting drug reactions should be assessed in allergy and immunology clinics.

### Acknowledgement

The author would like to thank Nurse Esra Sarıgül for her contributions during the drug tests.

### Ethics approval

The study was approved by the Ethics Committee of Malatya Turgut Özal University, Medicine School (2022/27).

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