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RESEARCH ARTICLE

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Retrospective Evaluation of Immediate Drug Hypersensitivity Reactions: A Tertiary Care Single Center Experience

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ABSTRACT

Objective: Drug hypersensitivity reactions (DHRs) refer to unpredictable and dose-independent reactions to medications. The gold standard diagnostic method for drug allergies is the drug provocation testing. This study aimed to retrospectively evaluate the clinical characteristics, culprit drug classes, diagnostic approaches, and management strategies of DHRs.

Materials and Methods: Medical records of 260 patients evaluated for immediate drug hypersensitivity reactions during the defined study period, October 2023 - June 2025, were reviewed retrospectively. Demographic characteristics, suspected drugs, reaction patterns, severity grading, and oral challenge test results were analyzed.

Results: The study included 260 patients with 511 suspected drug reactions. The median age was 41.23± 12.94 (min: 18, max: 72) with a female predominance. Oral administration accounted for 82.7% of the responses, with nonsteroidal anti-inflammatory drugs being the most common culprit drug group (45.8%). In immediate reactions, skin symptoms were predominantly urticaria (91.2%) and angioedema (63.8%). Although anaphylaxis was frequently observed, epinephrine administration was disproportionately low.

Conclusion: A thorough evaluation of suspected DHRs is essential. Despite high suspicion rates, confirmation via diagnostic tests was low, emphasizing the need for referral to specialized clinics and appropriate diagnostics for accurate management. When full diagnostic work-up is not feasible, safe drug testing should at least be done, and patients should not be left without treatment.

Keywords: Drug hypersensitivity, drug allergy, anaphylaxis, NSAIDs, beta-lactam allergy, drug provocation testing, drug challenge

INTRODUCTION

Drug hypersensitivity reactions (DHRs) are unpredictable adverse drug reactions that develop through immune and non-immune mechanisms. These occur within 1-6 hours of drug ingestion (immediate reactions) with mild cutaneous eruptions to life-threatening anaphylaxis symptoms, or several hours to several days later (delayed reactions) primarily as rashes and severe cutaneous adverse reactions (1). Immune-mediated DHRs occur independently of dose and represent a major clinical and public health concern worldwide (1). Drug allergy frequency is screened using specific ICD codes in most studies; most do not differentiate between drug adverse effects (ADR) and allergic or hypersensitivity reactions (HSR). Although the true prevalence of drug allergy is largely unknown (2), due to estimates, self- reported drug allergy is substantially higher, approximately 8.3% (range across studies 0.7-38,5%) leading to widespread mislabeling and inappropriate avoidance of first-line therapies (3).

The diagnosis of DHRs is challenging and relies on a combination of detailed clinical history, skin testing, in vitro assays, and drug provocation testing (DPT), also called drug challenge (4), which remains the gold standard (5). However, access to standardized diagnostic testing is limited in many healthcare systems, leading to a reliance on clinical history alone. This practice contributes to overdi-

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agnosis, unnecessary drug avoidance, increased healthcare costs, antimicrobial resistance, and suboptimal patient outcomes (6).

Understanding real-world patterns of drug hypersensitivity, including demographic characteristics, clinical presentations, culprit drugs, diagnostic approaches, and management strategies, is essential for improving patient safety and optimizing prescribing practices. This study aims to evaluate the clinical characteristics of immediate DHRs, diagnostic modalities, and management approaches, encountered at a tertiary referral center.

MATERIAL and METHODS

Ethical Approval

All procedures involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the principles of the Declaration of Helsinki and its later amendments or comparable ethical standards. Ethical approval for this study was obtained from the Malatya Turgut Özal University Clinical Research Ethics Committee (approval date: 16 July 2025; decision no: E- 30785963-020-315732).

Study Populations

This retrospective study was conducted at the Allergy and Immunology Outpatient Clinic of Malatya Training and Research Hospital, with patient recruitment occurring between October 2023 and June 2025.

The inclusion criteria

* Diagnosed with immediate drug hypersensitivity by an allergy specialist;
** Aged >18 years, male or female

The exclusion criteria

* Patients with delayed-type hypersensitivity reactions

Patient Assessment

Patients diagnosed with drug hypersensitivity reactions were divided into two groups: immediate and late DHRs. Immediate DHRs were included. The reaction was examined in terms of the dose at which it occurred, accompanying symptoms, whether emergency care was sought, whether hospitalization and/or intensive care was required, history of anaphylaxis, and treatment data administered to the patient. The oral provocation testing results were obtained from the hospital information management system.

Statistical Analysis

Statistical analyses were performed using the SPSS software version 21.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were expressed as minimum, maximum, median, mean, standard deviation, and percentage, as appropriate.

RESULTS

The demographic and clinical characteristics of the study population are summarized in the relevant tables and figures. A total of 260 patients were included in the study, with a mean age of 41.23 ± 12.94 (min: 18 max: 72). Women (n=176, 67.7%) had a significant predominance in drug hypersensitivity reactions. Although most patients presented within the first year following the index reaction, a small number of delayed presentations were also observed. Oral administration was the primary route associated with hypersensitivity reactions (82.7%), followed by intravenous (11.2%) and intramuscular (6.2%) administration. This distribution, parallel to real-world prescription practices, indicates that acute drug hypersensitivity reactions are most commonly associated with drugs administered orally. Seventy-two (27.6%) patients developed a hypersensitivity reaction after the first dose of the drug (Figure 1). The most common chronic condition was hypertension (10.8%). In the comorbidity analysis, 41.5% of the patients had no underlying chronic disease. Drug hypersensitivity reactions can also occur in healthy individuals (Figure 2).

The main causes of hypersensitivity reactions were NSAIDs and beta-lactam antibiotics, respectively (Figures 3, 4). Among beta-lactams, penicillins were the most common. These rates are consistent with epidemiological data and demonstrate the continued predominance of these drug groups in immediate hypersensitivity reactions. Skin findings were the most frequently observed (Table I). Urticaria was seen in 91.2% of the patients, and angioedema in 63.8%. Respiratory and systemic findings were relatively less frequent, and included dyspnea (27.3%), hypotension (17.7%), uvular edema (5.0%), and syncope or near-syncope (8.5%).

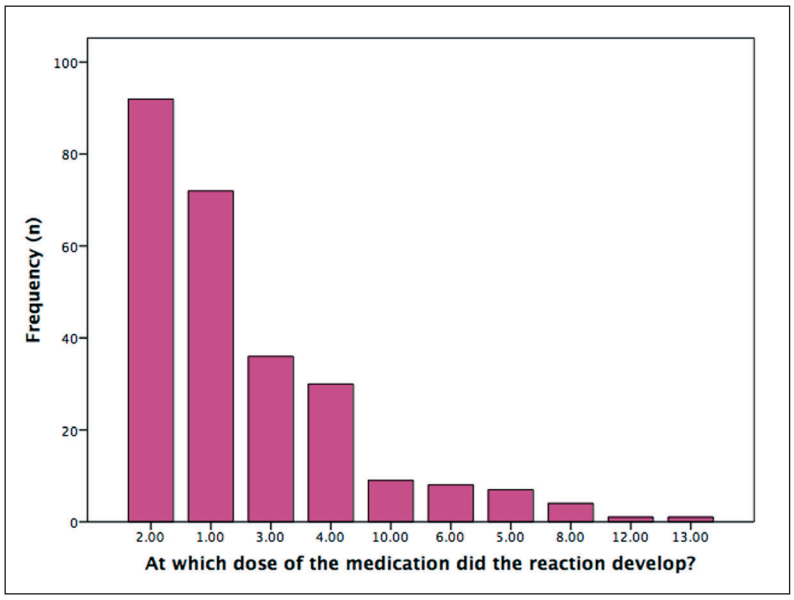

Figure 1: Distribution of patients according to the dose at which the hypersensitivity reaction developed.

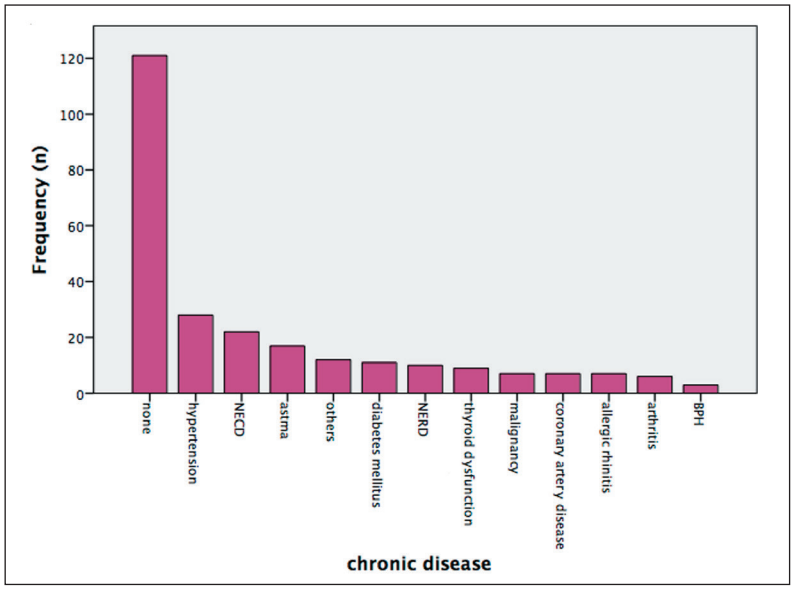

Figure 2: Prevalence of chronic diseases
NECD: *NSAID-exacerbated cutaneous disease,*
NERD: *NSAID-exacerbated respiratory disease,*
BPH: *benign prostatic hyperplasia.*

Table I: Clinical manifestation

	n (%)
Urticaria	237 (91.2)
Angioedema	166 (63.8)
Nause-vomiting	30 (11.5)
Dyspnea	71 (27.3)
Uvula edema	13 (5.0)
Hypotension	46 (17.7)
Near-syncope/ syncope	22 (8.5)
Anaphylaxis	87 (33.5)

Table II: Hospital admissions and treatments

	n (%)
Emergency service application	192 (73.8)
Antihistamine	231 (88.8)
Systemic steroid	186 (71.5)
Oxygen and bronchodilator therapy	68 (26.2)
Epinephrine	35 (13.5)
Hospitalization	14 (5.4)
Intensive care	6 (2.3)

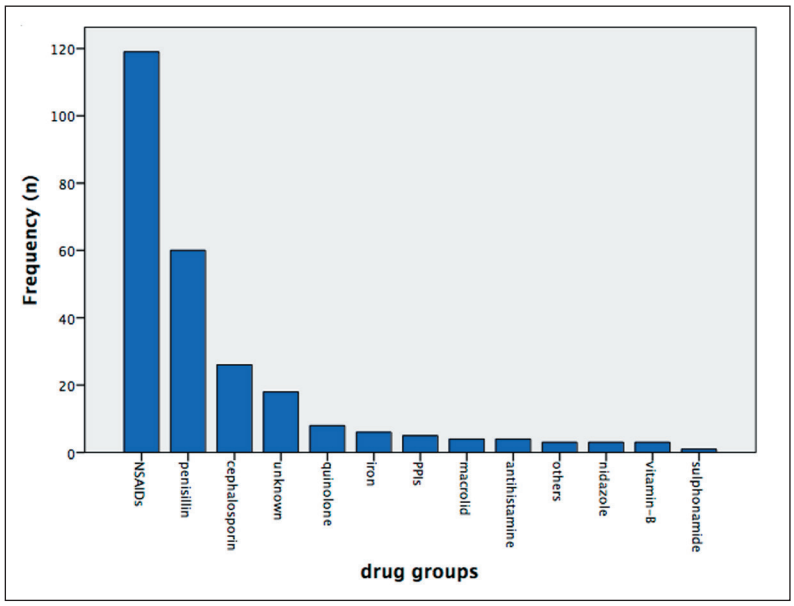

Figure 3: Frequency of drug hypersensitivity (in order)

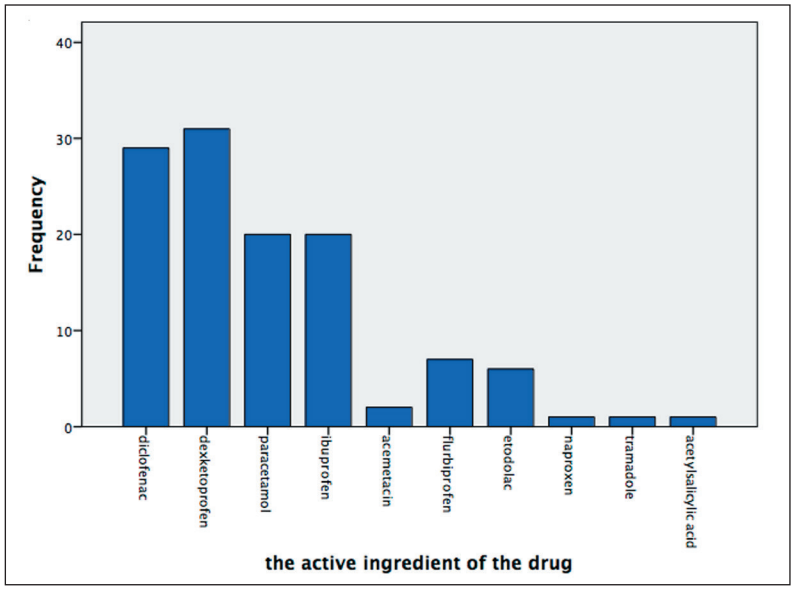

Figure 4: Frequency of nonsteroidal anti-inflammatory drug hypersensitivity (in order)

Anaphylaxis symptoms were present in 33.5% of the patients; approximately one-third developed a severe and potentially life-threatening clinical picture. Although most reactions manifested as skin involvement, systemic symptoms were not uncommon. Table II, summarizing hospitalizations and treatment interventions, shows that 73.8% of patients presented to the emergency department; antihistamines (88.8%) and systemic corticosteroids (71.5%) were the most frequently administered drugs during the initial intervention. Respiratory system involvement was significant in the patients. Oxygen and bronchodilator therapy was required in 26.2% of the cases. Anaphylaxis is a severe, life-threatening, systemic hypersensitivity reaction that develops rapidly after exposure to the suspected agent. It can be fatal if not diagnosed and treated promptly. Despite the high frequency of anaphylaxis, epinephrine was administered to only 13.5% of the patients. Hospitalization was required in 5.4% of the cases, and 2.3% required admission to the intensive care unit. These findings highlight a critical discrepancy between international anaphylaxis management guidelines and real-world clinical practice, particularly regarding the use of epinephrine.

Nevertheless, a substantial proportion of patients exhibit systemic involvement and anaphylaxis. Utilization of emergency department services is high, whereas epinephrine administration remains suboptimal. The high success rate in identifying tolerated alternative drugs underscores the clinical value of structured drug challenge protocols. No significant differences were observed with respect to sex, route of drug administration, presence of chronic disease, or causative drug classes among patients who experienced anaphylaxis. A critical aspect of the drug challenge protocol was the use of dosing steps below five, as higher-step protocols may induce desensitization. Accordingly, quarter, half, and full oral doses of the tablet were administered at 30-minute intervals. If no reaction occurred, the next dose was given. All patients were observed for at least 4 hours after the final dose.

Most antibiotic hypersensitivity reactions were attributed to beta-lactam antibiotics, primarily penicillins and cephalosporins; therefore, provocation testing was performed with non-beta-lactam antibiotics. In cases of NSAID hypersensitivity, weak partial or selective COX-2 inhibitors were selected based on the patient's allergy history, comorbidities, and/or the clinical urgency of use. Safe antibiotic testing was performed in 99 patients with clindamycin and ciprofloxacin and in 14 patients with clarithromycin. Among these patients, hypersensitivity reactions occurred in two patients receiving clarithromycin, five receiving ciprofloxacin, and one receiving clindamycin, manifesting as pruritus, erythema, and swelling (3.77%); three patients (1.41%) additionally developed concomitant angioedema. At least one tolerated alternative drug was successfully identified in the majority of patients.

Oral drug provocation testing was performed with paracetamol in 110 patients, nimesulide and meloxicam in 75 patients, and celecoxib in 45 patients. The test was discontinued due to the development of hypersensitivity reactions in three patients receiving nimesulide (0.98%), three receiving meloxicam (0.98%), and five receiving celecoxib and paracetamol (1.63%). Concomitant angioedema occurred in four patients (1.31%), and one patient (0.32%) developed shortness of breath and hypotension. Patients who developed isolated urticaria were treated with antihistamines, whereas systemic corticosteroids (1 mg/kg) were administered to those with accompanying angioedema. At least one tolerated alternative drug was successfully identified in the majority of the patients.

For patients who did not experience a hypersensitivity reaction during testing, a medication card was issued indicating tolerance to the tested drug as of the test date. Patients were informed that hypersensitivity reactions could still occur under certain conditions, such as drug interactions, viral infections, stress, or fever; therefore, they were advised to avoid using medications without medical supervision.

DISCUSSION

In this retrospective cohort, immediate drug hypersensitivity reactions predominantly affected middle-aged adults, with a clear female predominance. This sex distribution in adults is consistent with findings from previous large-scale epidemiological studies and may reflect both biological susceptibility and sex- related differences in healthcare utilization (7). The predominance of oral drug exposure further mirrors real-world prescribing practices and supports the observation that most immediate reactions occur following routine outpatient medication use.

In line with the current literature, NSAIDs and β-lactam antibiotics were identified as the leading triggers of hypersensitivity reactions in the present study (8,9). Among antibiotics, penicillin and cephalosporins were the most frequently implicated agents, reinforcing previous evidence that β-lactam allergy labels remain highly prevalent and are often inaccurate (10). In NSAID-related reactions, the predominance of cross-reactive phenotypes associated with COX-1 inhibition is consistent with current mechanistic models of NSAID hypersensitivity (11). Previous studies from Türkiye have demonstrated that diclofenac is among the most frequently prescribed and widely used NSAIDs in primary care after cold preparations (12). In accordance with these national prescribing patterns, our study revealed that hypersensitivity reactions were most frequently observed to diclofenac following dexketoprofen.

Cutaneous manifestations, particularly urticaria and angioedema, were the predominant clinical presentations, consistent with findings from several studies (10,13).

Anaphylaxis is a severe, life-threatening, systemic hypersensitivity reaction that occurs rapidly after exposure. It can be fatal if not diagnosed and treated promptly (14).

Approximately one-third of patients fulfilled the diagnostic criteria for anaphylaxis, underscoring that immediate drug hypersensitivity reactions cannot be regarded as benign conditions. Despite this substantial rate of anaphylaxis, epinephrine was administered to only a small proportion of patients. This observation is consistent with previous reports demonstrating the persistent underuse of epinephrine in emergency departments, even in clearly defined cases of anaphylaxis (14). In contrast, antihistamines and systemic corticosteroids were widely utilized, despite their lack of life-saving efficacy in anaphylaxis (15), highlighting a significant and ongoing gap between guideline recommendations and real-world clinical practice. Drug challenge enabled the identification of at least one tolerated alternative medication in the majority of patients. Nevertheless, breakthrough reactions during testing occurred in a small but clinically relevant proportion of cases, including angioedema and systemic symptoms. These findings emphasize that even alternative drugs selected based on chemical structure and pharmacological class are not entirely risk-free and that all drug testing procedures must be performed under close supervision by an allergy specialist in appropriately equipped clinical settings (4,16). In Türkiye, formal allergy specialization is obtained as a secondary specialty following training in internal medicine, chest diseases, or dermatology, after which mandatory public service is required, predominantly in the eastern regions of the country. Due to limitations such as the lack of dedicated testing facilities, inadequate emergency intervention infrastructure, insufficient staff training, and restricted access to intensive care support, some allergists may refrain from drug provocation testing, whereas others continue to conduct drug challenge under appropriate conditions.

Clinical recommendations for drug provocation testing

- A detailed drug allergy history should be obtained, including the culprit drug, time to reaction onset, clinical manifestations, need for medical treatment, and any prior tolerance.
- The reaction should be classified as IgE-mediated, immunological or nonimmunological, and its severity must be carefully assessed, as severe reactions require strict avoidance of the culprit drug and structurally related agents.
- Structurally similar drugs should generally be avoided, and alternative medications should be selected based on chemical dissimilarity, low risk of cross-reactivity, and appropriate pharmacological efficacy.
- The risk of cross-reactivity varies among drug classes and should be individually evaluated.
- Skin testing should be considered when available, particularly for suspected IgE-mediated reactions, and ideally performed 6 weeks to 12 months after the index reaction.
- When diagnostic uncertainty persists or when no suitable alternative exists, drug provocation testing should be performed under strict hospital supervision by experienced allergy specialists.
- Patients should be provided with a drug allergy or tolerance card and advised to avoid unsupervised medication use.

Although patients with suspected drug hypersensitivity are routinely referred to specialized drug allergy centers for diagnostic evaluation, a considerable proportion do not undergo testing. This is largely attributable to practical barriers such as long travel distances, financial constraints related to transportation, difficulty obtaining timely appointments through centralized hospital scheduling systems, and limited patient awareness regarding the potential severity of drug reactions. Physicians may choose to undertake a drug challenge by using medications that have a lower risk profile and a minimal likelihood of cross-reaction. The cornerstone of management in drug hypersensitivity remains strict avoidance of the culprit drug; whenever feasible, alternative agents with distinct chemical structures and low cross-reactivity potential should be selected.

Overreliance on patient-reported history alone is a major contributor to inaccurate drug allergy labeling and unnecessary lifelong drug avoidance, which may lead to suboptimal therapy, increased healthcare costs, and the use of broader spectrum or less effective medications.

This study has several strengths, including a relatively large sample size, the inclusion of both NSAID and antibiotic hypersensitivity reactions, and the real-world evaluation of drug challenge practices. However, the retrospective design is inherently subject to potential recall and documentation biases. In addition, the single-center

nature of the study limits the generalizability of the findings. The absence of advanced in vitro diagnostic testing and the lack of long-term follow-up after re-exposure represent further important limitations.

CONCLUSION

Drug hypersensitivity reactions represent a significant clinical problem with substantial implications for patient safety, therapeutic decision-making, and healthcare resource utilization. If suitable conditions exist, drug testing with an alternative medication is recommended to confirm tolerance. Importantly, hypersensitivity reactions may occur even with drugs from different pharmacological classes with low or no expected cross-reactivity. Therefore, all diagnostic drug-testing procedures must be performed under strict medical supervision in appropriately equipped clinical settings to ensure patient safety. Without such structured evaluation, patients may inadvertently be re-exposed to the unsafe or structurally similar drugs, placing them at risk for more severe hypersensitivity reactions, including anaphylaxis.

Author Contributions

The author (**Gulistan Alpagat**) confirm responsibility for the following: study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

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