Cumhuriyet Medical Journal, 45(3): 64-72, 2023
DOI: http://dx.doi.org/10.7197/cmj.1342682

Cumhuriyet Medical Journal

| cmj.cumhuriyet.edu.tr | Founded: 2004 Available online, ISSN:1305-0028 Publisher: Sivas Cumhuriyet Üniversitesi

Clinical Features of Drug Hypersensitivity and Factors Affecting Drug-Induced Anaphylaxis: Single Center Experience of the Tertiary University Hospital

Ceyda Tunakan Dalgıç[1,a]

[1]*Ege University Faculty of Medicine, Department of Internal Diseases, Allergy and Clinical Immunology, İzmir, Türkiye*

Research Article

History

Received: 14/08/2023
Accepted: 25/09/2023

ABSTRACT

Background-Aims: The prevalence and incidence of drug-induced hypersensitivity reactions (HSRs) are increasing worldwide. They are causing increasing morbidity and costs. Also, for physicians, they are one of the most challenging issues to manage. Understanding the etiology, prevalence, and triggering factors of drug-induced HSRs to treat and prevent them is important. Some literature data have shown the frequency of DHR to be approximately 2% in our country, however, to date, the eastern part of Central Anatolia has not been investigated for drug-induced HSRs particularly. In line with all this information, we aim to determine the frequency, etiology, and clinical features of drug hypersensitivity reactions (DHRs), and to evaluate the factors affecting drug-induced anaphylaxis among the patients admitted to the outpatient allergy clinic of the tertiary university hospital.

Materials-methods: In this retrospective cohort study, medical records of the 8295 patients who visited the allergy outpatient clinic of Sivas Cumhuriyet University Hospital from 2nd July 2018 to 10 December 2019 were retrospectively reviewed by the hospital data system using the ICD-code Y57.4 (adverse effects caused by pharmacological agents). The frequency, etiologies, demographic, and clinical features of the DHRs were evaluated.

Results: Among the 8295 patients who visited the allergy outpatient clinic of Sivas Cumhuriyet University Hospital, 159 patients with a mean age of 40,52± 14,85 years (129 female, 30 male) were evaluated with the diagnosis of DHRs. The frequency of DHRs among admissions was found to be approximately 2%. Accompanying allergic diseases included respiratory (17%), cutaneous (10%), venom (n=3), drug (7%), and food hypersensitivity (n=2). Multiple allergic diseases were detected in 20%. Eighty-six % (n=138) could recognize the culprit drug. The causes of drug hypersensitivity were non-steroidal anti-inflammatory drugs (NSAIDs) (27%), beta-lactams (16%), co-sensitization to beta-lactams and NSAIDs (8%), non-beta lactam antibiotics (8%), and other kinds of drugs (39%). Type 1 reaction occurred in 80%, type 4 in 21%, non-immune mediated in 7, and mixed type composed of type 1 and 4 in 9 patients. Anaphylaxis occurred in 46,5%. Fifteen% had grade 2, 22% had grade 3, and 4 had grade 4 anaphylactic reactions. Systematical assessment showed cutaneous symptoms in 93%, respiratory in 38%, cardiovascular in 29.5%, neurologic in 25%, and gastrointestinal in 11%. Allergy to NSAIDs (88,6 %) and beta-lactams (82,5%) were more frequent in type 1 reactions than in type 4 and mixed type reactions (p<0,001).

Discussion-conclusions: Drug-induced anaphylaxis was commonly grade 3, occurred by NSAIDs and beta-lactams, and presented with cutaneous symptoms. Although drug-induced HSRs generally occurred by NSAIDs and/or beta-lactams, drugs such as proton pump inhibitors and vitamins were the culprits in up to 40% of the cases. Particular attention should be paid to this group in the evaluation of drug-induced anaphylaxis. Healthcare providers and patients need to be informed more to avoid neglecting the diagnosis of DHRs, especially drug-induced anaphylaxis.

Keywords: Drug hypersensitivity, frequency, anaphylaxis, hypersensitivity reactions

İlaç Aşırı Duyarlılığının Klinik Özellikleri ve İlaç ile İndüklenen Anafilaksiyi Etkileyen Faktörler: Üçüncü Basamak Üniversite Hastanesi Tek Merkez Deneyimi

Süreç

Geliş: 14/08/2023
Kabul: 25/09/2023

ÖZ

Giriş- amaç: İlaca bağlı aşırı duyarlılık reaksiyonlarının (ADR) prevalansı ve insidansı dünya çapında artmaktadır. Artan morbiditeye ve maliyetlere neden oluyorlar. Ayrıca hekimler için yönetilmesi en zor konulardan biridir. İlaca bağlı HSR'lerin etiyolojisini, yaygınlığını ve tetikleyici faktörlerini anlamak, bunları tedavi etmek ve önlemek önemlidir. Bazı literatür verileri ülkemizde DHR sıklığının yaklaşık %2 olduğunu göstermektedir ancak bugüne kadar Orta Anadolu'nun doğu kısmı uyuşturucuya bağlı HSR açısından özellikle araştırılmamıştır. Bütün bu bilgiler doğrultusunda amacımız, üçüncü basamak bir üniversite hastanesi alerji polikliniğine başvuran hastalarda ilaç aşırı duyarlılığının sıklığını, etiyolojisini ve klinik özelliklerini belirlemek ve ilaç ile indüklenen anafilaksiyi etkileyen faktörleri değerlendirmektir.

Materyal-metodlar: Bu retrospektif kohort çalışmasında, Sivas Cumhuriyet Üniversitesi Hastanesi alerji polikliniğine 2 Temmuz 2018 - 10 Aralık 2019 tarihleri arasında başvuran 8295 hastanın tıbbi kayıtları geriye dönük olarak hastane veri sistemi tarafından ICD kodu Y57.4 (farmakolojik ajanların neden olduğu advers etkiler) kullanılarak incelendi. İlaç aşırı duyarlılık reaksiyonlarının (ADR) sıklığı, etiyolojileri, demografik ve klinik özellikleri değerlendirildi.

Bulgular: Sivas Cumhuriyet Üniversitesi Hastanesi alerji polikliniğine başvuran 8295 hastadan yaş ortalaması 40,52± 14,85 olan 159 hasta (129 kadın, 30 erkek) ilaç ile indüklenen aşırı duyarlılık reaksiyonu (İAR) tanısı ile değerlendirildi. Başvurular arasında IAR sıklığı yaklaşık %2 saptanmıştır. Eşlik eden alerjik hastalıklar arasında solunum (%17), deri (%10), venom (n=3), ilaç (%7) ve gıda (n=2) aşırı duyarlılığı yer almıştır. Çoklu alerjik hastalık tanısı %20'sinde saptandı. %86'sı (n=138) sorumlu ilacı tanıyabildi. İlaç alerjisinin nedenleri non-steroid anti-inflamatuar ilaçlar (NSAII'ler) (%27), beta-laktam antibiyotikler (%16), beta-laktamlara ve NSAII'lere eş zamanlı duyarlılık varlığı (%8), non-beta laktam antibiyotikler (%8) ve diğer tür ilaçlardı (%39). Hastaların %80'inde tip 1, %21'inde tip 4, 7'sinde non-immun aracılı ve 9'unda tip 1 ve 4'ten oluşan mikst tip reaksiyon görüldü. Anafilaksi %46,5 oranında meydana geldi. %15'inde derece 2, %22'sinde derece 3 ve 4'ünde derece 4 anafilaktik reaksiyon vardı. Sistematik değerlendirmeye göre %93 deri, %38 solunum, %29,5 kardiyovasküler, %25 nörolojik ve %11 gastrointestinal semptomlar gözlendi. NSAII'lere (% 88,6) ve beta-laktamlara (% 82,5) alerji, tip 1 reaksiyonlarda, tip 4 ve karma tip reaksiyonlara göre daha sıktı (p<0,001).

Tartışma ve sonuçlar: İlaç ile indüklenen anafilaksi genellikle 3. Derece idi, NSAII'ler ve beta-laktamlar tarafından meydana geliyordu ve kutanöz semptomlarla kendini göstermekteydi. İlaç ile indüklenen ADR'ler genellikle NSAII ve/veya beta-laktamlar tarafından meydana gelse de, vakaların %40'e varan kısmında proton pompası inhibitörleri ve vitaminler gibi ilaçlar suçludur. İlaç ile indüklenen anafilaksinin değerlendirilmesinde bu gruba özel dikkat gösterilmelidir. Özellikle ilaç ile indüklenen anafilaksi başta olmak üzere İAR tanısının ihmal edilmemesi için sağlık çalışanlarının ve hastaların daha fazla bilgilendirilmesi gerekmektedir.

Anahtar sözcükler*:* İlaç aşırı duyarlılığı, sıklık, anafilaksi, aşırı duyarlılık reaksiyonları

[a] *dr_ceydat@yahoo.com* *https://orcid.org/0000-0002-0318-3135*

How to Cite: Tunakan Dalgıç C (2023) Clinical Features of Drug Hypersensitivity and Factors Affecting Drug-Induced Anaphylaxis: Single Center Experience of the Tertiary University Hospital, Cumhuriyet Medical Journal, September 2023, 45(3): 64-72

Introduction

Drug hypersensitivity reactions usually develop unexpectedly and unpredictably with the use of drugs at normal therapeutic doses and are called adverse drug reactions. These reactions may develop non-immunologically (pseudoallergic/intolerance) or immunologically. True allergic (immunological) reactions are divided into early and late types; and are mediated by IgE and T cells, respectively. While conditions such as urticaria, angioedema, and anaphylaxis occur after contact with the drug and are included in the early-type drug hypersensitivity group; dermatitis, maculopapular exanthema, and severe cutaneous drug reactions are included in the delayed-type drug hypersensitivity reaction group [1].

Immunological drug hypersensitivity reactions should be diagnosed and treated promptly. For allergists and other physicians, drug allergies are one of the most difficult issues to manage in daily practice [2,3].

The prevalence and incidence of drug-induced hypersensitivity reactions are increasing worldwide. Drug-induced adverse reactions are among the important causes of increased morbidity and cost in hospitalized patients [2,3].

It is important to understand the etiology, prevalence, and triggering factors of drug-induced hypersensitivity reactions, to treat these patients correctly, prevent the recurrence of drug-induced hypersensitivity reactions, and develop prevention methods [1-3].

In various studies conducted in our country, the prevalence of self-reported DHR varies between 2.9% and 4.7% in students and adult male groups [4-6].

In addition, DHR frequency among outpatient clinic admissions was shown to be approximately 2% in a national multicenter study [7], but the northeast of our country was not examined on a regional basis. In particular, it is important to determine the frequency of drug hypersensitivity reactions seen in patients who applied to the allergy and clinical immunology outpatient clinic in Sivas province and to define the demographic and clinical characteristics of these patients, as they reflect the eastern part of Central Anatolia in Turkey.

In line with all this information, we aimed to investigate the frequency, the etiologies, the diversity of clinical presentations, the risk factors, and the treatments applied to the cases with DHRs admitted to the Cumhuriyet University Medical Faculty Hospital, Department of Chest Diseases, Allergy and Clinical Immunology outpatient clinics.

Material Method

The medical records of 8295 patients over the age of 16 who applied to the outpatient clinic of Sivas Cumhuriyet University Faculty of Medicine, Department of Chest Diseases, Division of Allergy and Clinical Immunology, between 2 July 2018 and 10 December 2019 due to DHRs were analyzed cross-sectionally and retrospectively through the hospital data system. 159 cases with Y57.4 ICD code (adverse effects caused by pharmacological agents) entry were included in our study.

At first, the frequency of DHRs among the admitted patients was evaluated, and then the history of drug reactions and demographic data were recorded using a detailed questionnaire. The patients' gender, age, presence of atopic disease, existing chronic diseases, drugs they use constantly, clinical features of DHRs (organ systems affected), culprit drug/drugs, the treatments applied in the case of DHRs, along with case report forms, were cross-sectionally and retrospectively obtained from hospital records.

DHRs are classified as immediate-type (urticaria, angioedema, bronchospasm, laryngeal edema, rhinitis, hypotension, and allergic shock) and delayed-type (maculopapular reactions and DRESS-Drug Reaction with Eosinophilia and Systemic Symptoms, fixed drug eruption,s contact dermatitis, vasculitic reactions, photosensitivity, as well as severe cutaneous drug reactions; Steven-Johnson syndrome, acute generalized exanthematous pustulosis, and toxic epidermal necrolysis) [1]. Drug-induced anaphylaxis was categorized into 4 grades according to the Mueller classification [8].

According to the Mueller classification of anaphylaxis; Grade 1 HSR defines mild skin reactions (such as urticaria, pruritus, malaise, and anxiety), grade 2; general systemic reactions (urticaria, itching, and anxiety, as well as generalized edema, chest pressure, wheezing, abdominal pain, nausea-vomiting, and dizziness), grade 3; severe systemic reactions (in addition to those listed previously, dyspnea, dysphagia, deepening of the voice and difficulty in speech, and confusion), and grade 4 defines allergic shock (in addition to those listed previously, drop in blood pressure, collapse, incontinence, loss of consciousness).

The atopic status of the patients was analyzed to investigate the presence of allergic diseases among the cohort with drug hypersensitivity and to compare the presence of atopy with the types of drug allergy. The atopic status of our cases was evaluated by quantitative skin tests. Skin tests were performed with ALK Alutard® allergen extracts, including inhalant, food, venom, and latex allergens. Histamine was used as a positive control, and normal saline was used as a negative control. Since it is not available in our laboratory, allergen-specific IgE values could not be evaluated.

After the evaluation of the atopic status of the patients, they are categorized into two main groups according to having only one type of allergic disease (for example, only respiratory/ cutaneous/ food/ venom/ drugs) and having≥2 types of allergic disease at the same time (for example, to have co-sensitivity to venom together with food at the same time, etc.)

Based on ENDA's recommendations, the cases were managed [9]; diagnostic drug tests could not be performed because the conditions could not be met, but oral drug provocation tests were performed with appropriate alternative drugs for the necessary patients.

Statistical Analysis

Statistical Analyses Values were expressed as frequency (number and percentage), and mean (range) as appropriate. Fisher's exact test and chi-square tests were used for 2 × 2 comparisons of categorical variables. Mann-Whitney U and KruskalWallis H test was used to compare numerical variables, where the numbers were <30. Statistical analyses were performed using the SPSS software package, version 23 (SPSS Inc., Chicago, IL, USA). Results with $p<0.05$ were evaluated as statistically significant.

Ethical Approval

Our study was approved by Sivas Cumhuriyet University, non-interventional clinical research ethics committee with the decision number 2020-01/01 dated January 15, 2020.

Results

1. Study Group and the Frequency of DHRs

Y57.4 ICD code (adverse effects caused by pharmacological agents) entry was detected in 159 cases out of 8295 applications during our study period, and the frequency of DHRs among allergy outpatient applications was found to be 2%.

2. Demographics and Characteristics of the Patients with DHRs

A total of 159 patients with a mean age of 40,52± 14,85 years (129 female, 30 male) were evaluated. Ninety- two (57%,n=92) had atopic diseases. Single-type allergic diseases included venom (n=3), drug (n=12), food (n=2), respiratory (n=27), and cutaneous allergies (n=16). Multiple allergic diseases were detected in 32 (20%) (*Figure 1*).

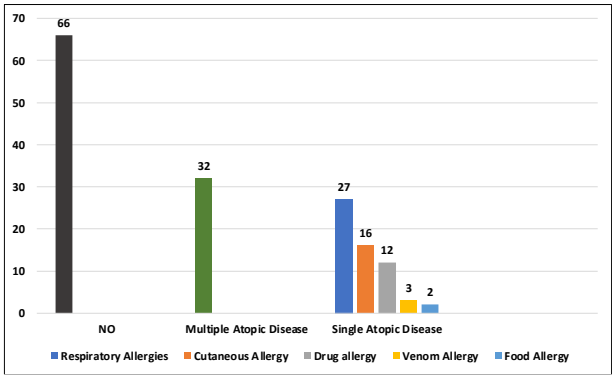

Figure 1. *Distribution of atopic diseases among patients with DHRs (shown as numbers)*

Ninety-three (58%, n=93) had a history of chronic diseases; of them, 13 had autoimmune diseases, and 7 had autoinflammatory diseases (8% and 4%, respectively). Seventy (44%) had chronic drug usage, and of them, 23 used anti-hypertensive drugs (%14) (Table 1).

Prick tests were assessed in 85 patients, of them 64 resulted negative. Twelve (n=12) had inhalant allergen sensitivity. Pollen and cockroach/house dust mite sensitivity were observed equally. 8 had polysensitization and only 1 had food sensitivity (*Figure 2*).

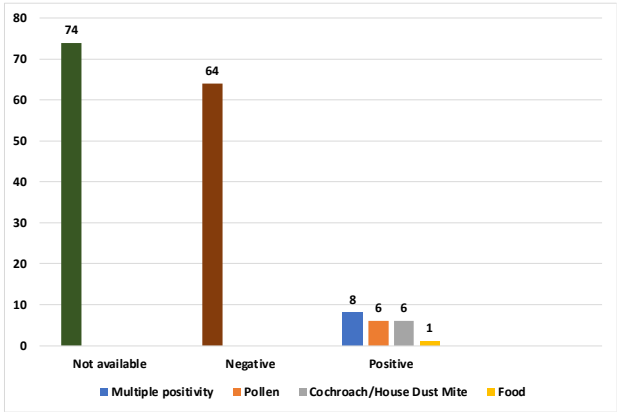

Figure 2. *Prick test results of the patients with DHRs (shown as numbers)*

Table 1. General characteristics of patients with DHRs

Variable	Number, %
Total number of patients	159
Age, mean±SD (years)	40,52± 14,85
Gender (female/male)	129/30
Chronic disease	93 (58%)
Chronic drug usage	70 (44%)
Anti-hypertensive drug usage	23 (14%)
Atopic disease	92 (57%)
Autoimmune disease	13 (8%)
Autoinflammatory disease	7 (4%)

3. Characteristics of the DHRs

Among 159, 138 (86%) could recognize the culprit drug (Table 2). The causes of drug hypersensitivity reactions were NSAIDs (n=44, 27%), beta-lactams (n=26, 16%), co-sensitization to beta-lactams and NSAIDs (n=14, 8%), antibiotics/ non-beta lactam antibiotics (n=13, 8%), and the other drugs (local and general anesthetics, proton pump inhibitors, vitamins, oral iron replacement therapy, disease-modifying anti-rheumatic drugs- DMARDs, antilipidemic, oral antimuscarinics, diuretics, oral anti-emetics, ACEI/ARBs, radiocontrast agents, antihistaminics, and oral anti-diabetics) (n=62, 39%) (*Figure 3*). In 127 (80%) of the DHRs, patients received the culprit drugs perorally.

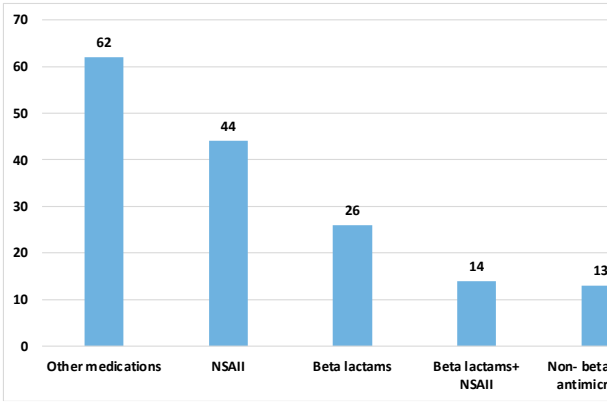

Figure 3. *The etiologies of DHRs (The frequencies of the culprit drugs are given as numbers).*

Type 1 reaction occurred in 116 (72%), type 4 occurred in 34 (21%), non-immune mediated occurred in 7, and mixed type composed of type 1 and 4 occurred in 9 patients. Among the drug-allergic patients, anaphylaxis occurred in 74 (46,5%). Among them, 24 (15%) had grade 2, 36 (22%) had grade 3, and 4 had grade 4 anaphylactic reactions (*Figure 4*).

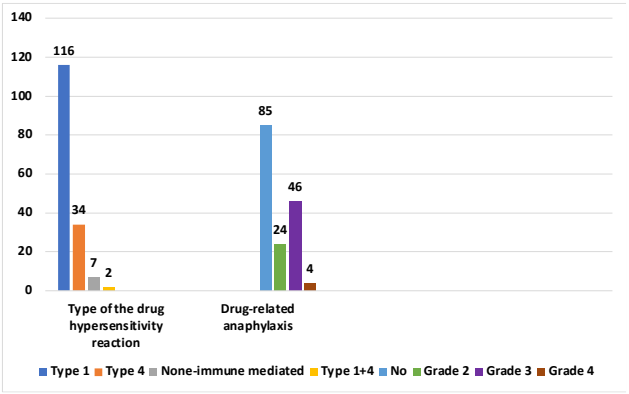

Figure 4. *Types of the DHRs and the distribution of the drug-induced anaphylaxis among our cohort (The frequencies are given as numbers).*

According to systematical assessment, cutaneous symptoms were observed in 148 (93%), respiratory in 61 (38%), cardiovascular in 47 (30%), neurological in 40 (25%), and gastrointestinal in 18 (11%) of all the patients (Table 2).

Table 2. Clinical characteristics and the treatment methods of DHR

Variable	Number, %
Recognition of the culprit drug	138 (86%)
Way of drug administration (po/pe)	127/32 (80%/20%)
Symptoms according to systematical assessment	
Mucocutaneous symptoms	148 (93%)
Respiratory symptoms	61 (38%)
Cardiovascular symptoms	47 (30%)
Neurological symptoms	40 (25%)
Gastrointestinal symptoms	18 (11%)
Hospitalization	8 (5%)
Drug-induced anaphylaxis	74 (46%)
Adrenalin administration	32 (20%)
Antihistaminic administration	153 (96%)
Corticosteroid administration	132 (83%)

(Abbreviations, po; peroral, pe; parenteral)

The local anesthetics and radiocontrast media drug skin tests were evaluated (n=17 and 7, respectively). The prick and intradermal tests were evaluated in line with the drug allergy guidelines (prick tests with the full concentration of the drug itself, and intradermal tests with the 1/100 and 1/10 dilutions of the drug, respectively). Histamine was used as positive and normal saline was used as negative controls. All of the drug skin tests with the local anesthetics and radiocontrast media resulted in negative.

When comparing the causes of drug hypersensitivity reactions with the atopic status; in the presence of concomitant atopic disease, beta-lactam sensitivity is observed and in the absence of atopic disease, sensitivity to antibiotics/ non-beta lactam antibiotics was observed (p=0,019) (Table 3).

When comparing the causes of drug allergy with the type of drug hypersensitivity, allergy to NSAIDs (88,5 %) and beta-lactams (82,5%) are more frequent in type 1 reactions than in type 4/mixed-type reactions (p<0,001) (Table 3).

While 100% of grade 4 anaphylactic reactions were observed within the first hour and grade 3 reactions were frequently within the first hour, the reactions that occurred after the 24th hour were completely grade 2 (p=0,043) (Table 3).

According to the systematical assessment, in the presence of beta-lactam allergy, respiratory symptoms were observed more frequently than the other types of drugs (p=0,018) (Table 3).

Table 3. The distribution of the frequencies according to the presence of atopic diseases, DHR types and grades, and the DHR-related symptoms is shown as based on the types of the culprit drugs.

Variables (n=159)	Atopic disease (+) (n=92)	Atopic disease (-) (n=67)		*P*
Beta-lactam allergy (n=40)	**77,5% (n= 31)**	22,5% (n=9)		0,019
Non-beta lactam antibiotics allergy (n=13)	38,5% (n=5)	**61,5% (n=8)**		
	Type 1 reactions (n=116)	**Type 4 reactions (n=34)**	**Mixed (Type 1+4) reactions (n=9)**	
NSAIDs allergy (n=44)	**88,5% (n=39)**	11,5% (n=5)	0	<0,001
Beta-lactam allergy (n=40)	**82,5% (n=33)**	17,5% (n=7)	0	
None-beta lactam antibiotics allergy (n=13) (n=13)	54% (n=7)	**46% (n=6)**	0	<0,05
Other kinds of drugs allergy (n=62)	60% (n=37)	25% (n=16)	**15% (n=9)**	
	Grade 2 (n=24)	**Grade 3 (n=46)**	**Grade 4 (n=4)**	
<1 hour (n=63)	27% (n=17)	66,7% (n=42)	**6,3% (n=4)**	0,043
1-24. hour (n=7)	43% (n=3)	57% (n=4)	0	
>24 hour (n=4)	**100% (n=4)**	0	0	
	Respiratory symptoms (+) (n=61)	**Respiratory symptoms (-) (n=98)**		
NSAIDs (n=44)	32% (n=14)	**68% (n=30)**		0,018
Beta-lactam antibiotics (n=40)	**58% (n=23)**	42% (n=17)		
None-beta lactam antibiotics (n=13)	15% (n=2)	**85% (n=11)**		
Other drugs (n=62)	36% (n=22)	**64% (n:40)**		

4. Management of the DHRs

Adrenalin injection was administered to 43% of the drug-induced anaphylaxis patients. These patients applied to emergency clinics and family practitioners to have the first step treatments of the drug HSRs. Especially, it is striking that only 43% of the anaphylaxis cases were treated with epinephrine administration. They were treated with antihistaminics and corticosteroid administrations. This result indirectly shows that the training of healthcare providers on the treatment of anaphylaxis is lacking.

Only 8 patients were hospitalized due to drug-induced anaphylaxis. As we observe in daily practice, antihistamines, and systemic corticosteroids (96% and 83%, respectively) were frequently administered in the case of drug hypersensitivity, with or without anaphylaxis (Table 2).

Discussion

In our study, drug hypersensitivity and drug-induced anaphylaxis cases admitted to the tertiary university hospital allergy outpatients in the north-

east of Turkey were analyzed retrospectively and the frequency was determined among applications from a single center. Our study did not include drug-induced adverse reactions, thus focusing on actual DHRs.

In the multicenter study of Çelik et al. in 2009-2010, the frequency of drug hypersensitivity was also found to be 2% in correlation with our study result [7]. Similar to the results by Çelik et al. from 11 centers across the country, the majority of the cases in which DHR was detected in our cohort were women, and respiratory and skin allergies or a combination of these accompanied the cases [7].

Consistent with the literature, NSAIDs were taken as the first-place culprits, followed by beta-lactams. In addition, immediate and grade 1 reactions (Mueller classification of anaphylaxis) are the most common and present with skin involvement. Non-immediate DHRs were relatively rare [10-12].

More than half of the cases had chronic systemic and/or accompanying atopic disease. The majority experienced DHRs on peroral treatments, with 46% describing drug-induced anaphylaxis, but <50% of them were administered adrenaline injections.

The lack of knowledge of physicians and health care providers, including allergists, in recognizing and treating anaphylaxis, prejudice about the side effects of adrenaline, and the presence of fear can be counted as the leading factors in the low rate of administration of adrenaline [13].

Besides, in general, while mucocutaneous manifestations are common, cardiovascular and neurologic symptoms are more common in grade 4 anaphylaxis. Although skin findings are frequently seen in the literature, consistent with our results, it should be kept in mind that anaphylaxis can occur without skin findings and even without cardiovascular collapse. In the absence of skin findings, the diagnosis of anaphylaxis becomes difficult, and the rate of adrenaline administration decreases in the absence of cardiovascular [13].

The diagnosis of anaphylaxis is mainly clinical. The most important point in diagnosis is awareness in primary care referral units. The first-line treatment for anaphylaxis is intramuscular (IM) adrenaline and it has no harm in anaphylaxis. Adrenaline administration also prevents prolonged and biphasic reactions.

In the event of an acute allergic reaction, the triggering agent should be removed first and then IM adrenaline should be administered by the caregivers and/or healthcare professionals. After this step, help should be called and the patient should lie flat and his/her feet should be lifted into the air. The required dose of adrenaline is 0.15 mg IM for children (<30 kg); and 0.3 mg IM for children (>30 kg) and adults. If necessary, IM adrenaline administration can be repeated at 5-10 minute intervals until help arrives [13].

After adrenaline administration, the patient should be monitored for vital signs. Vascular access should be established, intravenous fluid support (500-1000 cc bolus for adults, 10 mg/kg bolus for children and continued as needed), O2, inhaled B2 agonist, glucocorticoids and antihistaminics treatment should be applied when necessary [13].

As shown in our study, glucocorticoids and antihistaminics, which should be administered in the last step of the treatment of anaphylaxis, are applied in the first step with a frequency of almost 100%.

In addition, antihistaminics may not have life-saving effects but may have adverse cardiovascular effects (such as hypotension). They only have positive effects on cutaneous system findings.

Glucocorticoids are effective in preventing protracted signs and biphasic reactions. Their acute activities are limited, their effects begin later than adrenaline, and they have less positive cardiovascular effects. It should be kept in mind that they will have positive effects in the long-term treatments of anaphylaxis.

Cases known to be at risk (venom, food or drug allergies, etc.) should carry at least 2 adrenaline auto-injectors. Adrenaline auto-injector is the most important savior from fatal reactions, which should be preferred for long-term prophylaxis in these cases. Individualized treatment plans should be made for patients. Group activities can also eliminate judgments such as adrenaline side effects and fear of needles. Health professionals, nursery staff, and teachers should also be trained in anaphylaxis after graduation [13].

Safe alternative drugs were found for the cases presenting with DHRs. Diagnostic skin tests were performed only in local and general anesthetic drug allergies, due to the reasons physicians are more likely to use safe alternative drugs in inappropriate conditions to perform skin tests (lack of safe test areas, time limitation, inability to describe the culprit drug, or patients using drugs that affect the test technique, etc.)

In our center, cross-reactive NSAIDs are avoided. Anti-inflammatory treatments with

meloxicam/nimesulide (which preferentially inhibits the cyclo-oxygenase: COX-2 enzyme) were preferred as safe alternative drugs. In beta-lactam, allergic cases, oral provocation tests with macrolides were referred to as safe anti-microbial treatments, and DHRs were not observed in patients by the literature [14-17].

The most important limitation of our study is its retrospective design and the fact that the data is based on patients' statements. Confirmation/diagnostic tests or drug provocations have not been performed to reveal the culprit drug.

The main factors in the failure of drug diagnosis and provocation tests are the lack of allergy clinics with adequate safety, the long-term duration of the tests, and the lack of trained personnel (the preparation of the tests and the failure to provide appropriate treatment in case of an allergic reaction).

HSRs may develop during drug diagnosis and provocation tests. In these cases, the need for emergency assistance, advanced follow-up, environmental conditions to perform the first-line treatments, and trained personnel are required. Considering all these needs, if possible, performing a drug provocation test with an alternative drug is a more reliable and time-saving method.

All cases were managed with an alternative drug recommendation. For this reason, DHRs were classified as only immune/non-immune or immediate/delayed type.

However, in the literature, drug provocation tests showed low but different positivity rates between 4% and 27% [18-20]. Provocation tests are the gold standard in the diagnosis of true drug allergy and should be applied in the presence of safe conditions.

In conclusion, our study is remarkable in terms of the rarity of the actual DHR frequency among the cases admitted to the tertiary allergy immunology outpatient clinic in the Northeastern region of Turkey. When the demographic and clinical findings of these cases were examined, it was observed that the cases were frequently familiar with culprit drugs and approximately half of the cases had a history of anaphylaxis. However, the frequency of administration of adrenaline in cases of anaphylaxis was <50%. In addition, DHRs very rarely require hospitalization and can be treated on an outpatient basis. This result shows us that it is necessary to raise awareness before and after graduation about the diagnosis and treatment of anaphylaxis in emergency and primary health care services.

Conflict Of Interest

The authors have no conflict of interest to declare.

References

1. Wilkerson RG. Drug Hypersensitivity Reactions. Immunol Allergy Clin North Am. 2023 Aug;43(3):473-489.
2. Suh DC, Woodall BS, Shin SK, Hermes-De Santis ER. The clinical and economic impact of adverse drug reactions in hospitalized patients. Ann Pharmacother. 2000 Dec;34(12):1373-9.
3. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA. 1998 Apr 15;279(15):1200-5
4. Kalyoncu AF, Karakoca Y, Demir AU, Alpar R, Shehu V, Cöplü L, Sahin AA, Baris YI. Prevalence of asthma and allergic diseases in Turkish university students in Ankara. Allergol Immunopathol (Madr). 1996 Jul-Aug;24(4):152-7.
5. Bavbek S, Erkekol FÖ, Celik GE, Gönüllü I, Misirligil Z. Self-reported prevalence of hypersensitivity reactions against drugs among medical students: does awareness cause any difference? Pharmacoepidemiol Drug Saf. 2011 Feb;20(2):154-61.
6. Kurt E, Demir AU, Cadirci O. Immediate type drug hypersensitivity reactions and associated risk factors in an adult Turkish men population. Iran J Allergy Asthma Immunol. 2010 Dec;9(4):245-50.
7. Çelik GE, Karakaya G, Öztürk AB, Gelincik A, Abadoğlu O, Sin A, Damadoğlu E, Yılmaz İ, Demirtürk M, Dursun B, Özdemir SK, Çelikel S, Değirmenci P, Bozkurt B, Göksel Ö, Erkekol FÖ, Aydın Ö, Kavut AB, Kırmaz C, Kalpaklıoğlu F, Büyüköztürk S, Kalyoncu F. Drug allergy in tertiary care in Turkey: results of a national survey. The ADAPT study: adult drug allergy perception in Turkey. Allergol Immunopathol (Madr). 2014 Nov-Dec;42(6):573-9.
8. Mueller HL. Diagnosis and treatment of insect sensitivity. J Asthma Res. 1966 Jun;3(4):331-3.
9. Aberer W, Bircher A, Romano A, Blanca M, Campi P, Fernandez J, Brockow K, Pichler WJ, Demoly P; European Network for Drug Allergy (ENDA); EAACI interest group on

drug hypersensitivity. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. Allergy. 2003 Sep;58(9):854-63.
10. Demoly P, Gomes ER. Drug hypersensitivities: definition, epidemiology, and risk factors. Eur Ann Allergy Clin Immunol. 2005 Jun;37(6):202-6.
11. Gomes E, Cardoso MF, Praça F, Gomes L, Mariño E, Demoly P. Self-reported drug allergy in a general adult Portuguese population. Clin Exp Allergy. 2004 Oct;34(10):1597-601.
12. Dorner T, Lawrence K, Rieder A, Kunze M. Epidemiology of allergies in Austria. Results of the first Austrian allergy report. Wien Med Wochenschr. 2007;157(11-12):235-42.
13. Muraro A, Worm M, Alviani C, Cardona V, DunnGalvin A, Garvey LH, Riggioni C, de Silva D, Angier E, Arasi S, Bellou A, Beyer K, Bijlhout D, Bilò MB, Bindslev-Jensen C, Brockow K, Fernandez-Rivas M, Halken S, Jensen B, Khaleva E, Michaelis LJ, Oude Elberink HNG, Regent L, Sanchez A, Vlieg-Boerstra BJ, Roberts G; European Academy of Allergy and Clinical Immunology, Food Allergy, Anaphylaxis Guidelines Group. EAACI guidelines: Anaphylaxis (2021 update). Allergy. 2022 Feb;77(2):357-377.
14. Knowles SR, Drucker AM, Weber EA, Shear NH. Management options for patients with aspirin and nonsteroidal antiinflammatory drug sensitivity. Ann Pharmacother. 2007 Jul;41(7):1191-200.
15. Kowalski ML, Makowska J. Use of nonsteroidal anti-inflammatory drugs in patients with aspirin hypersensitivity: safety of cyclo-oxygenase-2 inhibitors. Treat Respir Med. 2006;5(6):399-406.
16. Kowalski ML, Makowska JS, Blanca M, Bavbek S, Bochenek G, Bousquet J, Bousquet P, Celik G, Demoly P, Gomes ER, Niżankowska-Mogilnicka E, Romano A, Sanchez-Borges M, Sanz M, Torres MJ, De Weck A, Szczeklik A, Brockow K. Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs)- classification, diagnosis and management: review of the EAACI/ENDA(#) and GA2LEN/HANNA*. Allergy. 2011 Jul;66(7):818-29.
17. Çelik GE, Erkekol FÖ, Aydın Ö, Demirel YS, Mısırlıgil Z. Are drug provocation tests still necessary to test the safety of COX-2 inhibitors in patients with cross-reactive NSAID hypersensitivity? Allergol Immunopathol (Madr). 2013 May-Jun;41(3):181-8.
18. Messaad D, Sahla H, Benahmed S, Godard P, Bousquet J, Demoly P. Drug provocation tests in patients with a history suggesting an immediate drug hypersensitivity reaction. Ann Intern Med. 2004 Jun 15;140(12):1001-6.
19. Na HR, Lee JM, Jung JW, Lee SY. The usefulness of drug provocation tests in children with a history of adverse drug reaction. Korean J Pediatr. 2011 Jul;54(7):304-9.
20. Aun MV, Bisaccioni C, Garro LS, Rodrigues AT, Tanno LK, Ensina LF, Kalil J, Motta AA, Giavina-Bianchi P. Outcomes and safety of drug provocation tests. Allergy Asthma Proc. 2011 Jul-Aug;32(4):301-6.