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Evaluation of the Potential Risk Factors for Drug-Induced Anaphylaxis in Adult Patients

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Keywords

Drug-induced anaphylaxis · Risk factors · Atopy · Tryptase · Total IgE

Abstract

Aim: To investigate the potential risk factors in patients who have experienced anaphylaxis from drugs. **Method:** The study included 281 adult patients (median age 40 years; 76.5% female) who experienced immediate types of hypersensitivity reaction to a drug. The patients were divided into an anaphylaxis group and a nonanaphylaxis group. The anaphylaxis group was diagnosed according to the criteria of the World Allergy Organization. Skin testing with culprit drugs was performed. In the nonanaphylaxis group, drug provocation tests were performed with culprit drugs, including aspirin or diclofenac, to determine nonsteroidal anti-inflammatory drug (NSAID) hypersensitivity. Atopy was determined by skin prick tests with the common inhalant allergens. Patients' demographics, clinical features, and baseline tryptase and total IgE levels were compared between the 2 groups. **Results:** The median interval between the last reaction in the patient's history and the study evaluation was 7

months (range 1–120 months). In 52.3% of the patients, reactions were defined as anaphylaxis. The most common culprit drugs were NSAIDs (56.9%) and β -lactams (34.7%). The culprit drugs were used parenterally in 13.2% of the patients. 34.9% of the patients had comorbid diseases and 24.6% used additional drugs, the most common being antihypertensives (10%). Atopy was determined in 28.8% and 28.1% of the patients were smokers. The median serum level of baseline tryptase and total IgE was 3.5 μ g/L and 77 kU/L, respectively. In 46.3% of the patients, skin tests with culprit drugs were positive and the positivity ratio was higher in the anaphylaxis group ($p = 0.002$). Anaphylaxis was more common in patients who were: hypertensive, atopic, using angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and received the culprit drug parenterally ($p = 0.034$, $p = 0.04$, $p = 0.03$, $p = 0.035$, $p = 0.013$, and $p < 0.001$). In the multivariate analysis, it was observed that the parenteral usage of the drug and the presence of atopy were significantly higher in the anaphylaxis group ($p < 0.001$, odds ratio [OR] = 20.05, confidence interval [CI] 4.75–88.64; $p =$

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0.012, OR = 2.1, CI 1.17–3.74). Age, smoking, family history, and serum levels of baseline tryptase and total IgE did not differ between groups. **Conclusion:** The parenteral route and atopy increase the risk of drug-induced anaphylaxis. IgE-mediated sensitivity to the culprit drug seems to facilitate anaphylaxis.

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Introduction

Anaphylaxis is a serious systemic hypersensitivity reaction (HR) with an acute onset and unpredictable course which occurs due to the sudden release of mediators from mast cells and basophils [1]. The American College of Allergy, Asthma and Immunology (ACAAI) Epidemiology of Anaphylaxis Working Group reported that a lifetime prevalence of anaphylaxis was between 0.05 and 2% [2]. Studies from the USA, Australia, and the UK indicate that the incidence of anaphylaxis has increased over the years [3–5]. The rate of mortality from anaphylaxis ranges from 2 to 20% [6]. Anaphylaxis can be induced by food, drugs, venom, or latex, or can be idiopathic. The most common causes of anaphylaxis in adult patients are medications and venom [7–10]. Amongst causative drugs, the most common triggering ones are nonsteroidal anti-inflammatory drugs (NSAIDs) and antibiotics [9–15]. It has been estimated that the incidence of drug-induced anaphylaxis and biphasic or resistant anaphylaxis are 0.04–3.1 and 10%, respectively [16–19]. Furthermore, drug use leads to more severe reactions than other causative agents. The most common reason for fatal anaphylaxis is medications, representing 58% of the cases [11, 20]. Several studies have investigated the risk factors for drug-induced anaphylaxis. Older age, intravenous administration, African-American ethnicity, and decreased platelet-activating factor acetylhydrolase activity are the factors associated with fatal drug-induced anaphylaxis [11, 21, 22]. Up to now, the role of atopy [13–15, 23, 24] and the basal serum tryptase level [25–29] in drug-induced anaphylaxis has remained controversial. Moreover, in a study investigating the HR to quinolone, the authors observed that a high total IgE level was associated with anaphylaxis [30].

It is important to try to decrease mortality and morbidity rates caused by anaphylaxis, and recurrence can be avoided by determining the triggers and risk factors. The aim of this study was to evaluate the potential risk factors in patients experiencing drug-induced anaphylaxis.

Methods

This cross-sectional study was conducted in the Adult Allergy and Immunology Clinics, Istanbul Training and Research Hospital and Istanbul University Faculty of Medicine in 2017. The study included patients >17 years of age who had experienced immediate-type HRs with any drug. We excluded patients who had: experienced nonimmediate-type HRs (such as Stevens-Johnson syndrome, toxic epidermal necrolysis, and DRESS syndrome), reactions that did not recover after discontinuation of the drug, a negative provocation test with culprit drugs, comorbid diseases involving uncontrolled hypertension, uncontrolled cardiac diseases, uncontrolled diabetes, uncontrolled asthma, malignancy, and those who did not give informed consent.

Drug HRs (DHRs) were classified as immediate DHRs which occurred within 24 h after NSAID administration, within 1 h for drugs other than NSAIDs after the last drug ingestion, and otherwise as nonimmediate DHRs [31, 32].

The patients who experienced immediate DHRs were divided into an anaphylaxis group and a nonanaphylaxis group. Anaphylaxis was diagnosed according to the World Allergy Organization (WAO) criteria [33]. Nonanaphylactic immediate DHRs consisted of itching, flushing, urticaria and/or angioedema, or acute rhinitis with or without dyspnea.

Allergologic Work-Up

Allergologic work-up was performed according to the Consensus Statement of the European Network of Drug Allergy [34]. Demographic data and clinical features were evaluated along with a detailed history. Skin prick tests (SPTs; undiluted, 1:100, or 1:10 dilutions of the drug depending on the severity of the reaction) on the volar side of forearm with the culprit drugs were performed on all patients, with the exception of drugs that induce a non-IgE-mediated mechanism involving a cross-reactive NSAID HR. The SPT with drugs available only in oral tablet form was performed by crushing the tablet and diluting the powder with saline to obtain a drug concentration of 1 mg/mL. Tests were considered positive if a wheal >3 mm in diameter was present after 20 min. If the results were negative, intradermal tests were performed with the culprit drugs in 3 incremental dilutions (1:1,000, 1:100, and 1:10) if they had a parenteral form. The intradermal tests were interpreted 20 min after the injection, and wheals >5 mm were considered positive [35, 36]. SPTs and intradermal testing with drugs were performed with the commercial forms of the drugs as described in the literature [31, 37].

In the nonanaphylaxis group, single-blind placebo-controlled drug provocation tests (SBPCDPTs) with culprit drugs were done if the SPT was negative. In NSAID-hypersensitive patients, SBPCDPTs with aspirin were performed to differentiate cross-reactive patients from selective responders. Patients with a history of severe anaphylaxis and those who did not accept reexposure were not provoked with the culprit drug.

Atopy was determined by SPTs with the most common inhalant allergens. Basal tryptase and total IgE levels were measured. Serum total IgE was determined using the ImmunoCAP system and serum tryptase by an enzyme immunoassay method.

Statistical Analysis

Descriptive statistics were used to evaluate demographic and clinical characteristics. They were described in percentages and

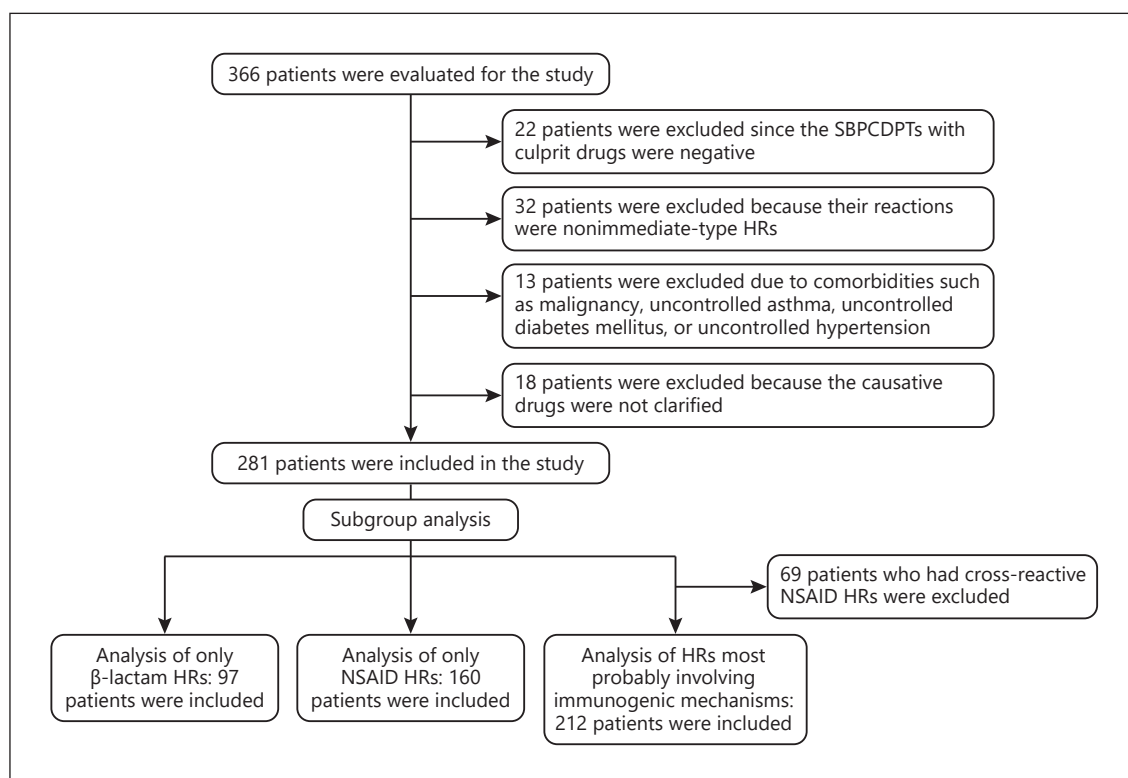


Fig. 1. Number of excluded patients, reasons for exclusion, and subgroup analysis. SBPCDPTs, single-blind placebo-controlled drug provocation tests; HRs, hypersensitivity reactions.

mean $\pm$ standard deviation (SD) or median, and categorical data were compared by χ^2 tests or the Mann-Whitney U test according to data distribution. For the associated factor which was obtained from univariate analysis, multivariate analysis was performed by binary logistic regression analysis. $p < 0.05$ was considered statistically significant. All data analyses were performed with SPSS v21.0.

Results

The study included 281 patients (Fig. 1). Median age was 40 years (range 16–90 years) and 76.5% were female. The median interval between the last reaction in a patient's history and the evaluation was 7 months (range 1–120 months). In 52.3% of the patients, reactions were defined as anaphylaxis. The most common culprit drugs described by patients were NSAIDs (56.9%) and β -lactams (34.7%) (Fig. 2). However, in the anaphylaxis group, β -lactams comprising penicillin ($n = 30$) and cephalosporin ($n = 37$) replaced NSAIDs for the first rank ($n = 70$, 47.6% and $n = 58$, 39.5%, respectively). The culprit drugs were used parenterally in 13.2% of the patients. 34.9% of

the patients had comorbid diseases and 24.6% were using additional drugs, the most common being antihypertensives (10%). Atopy was determined in 28.8% of patients. Median serum level of baseline tryptase and total IgE was 3.5 $\mu\text{g/L}$ and 77 kU/L, respectively. Demographic and clinical features are detailed in Table 1. HR types are illustrated in Figure 3.

Anaphylaxis developed very rapidly in most patients after the ingestion or injection of the drug: within 10 min in 90 patients, 10–30 min in 50 patients, and 30–60 min in 7 patients. Immediate-type HRs other than anaphylaxis developed within 10–30 min in 60 patients, 30–60 min in 51 patients, 1–6 h in 21 patients, and within 10 min in 2 patients.

In 147 patients (52.3%), skin testing with culprit drugs were performed. The remaining patients did not undergo skin testing since they had non-IgE-mediated HRs, their suspected culprit drugs did not have a parenteral form, or they did not want to be tested. In 46.3% ($n = 68$) of the patients, skin tests with culprit drugs were positive. The skin test positivity ratio was higher in the anaphylaxis group ($p = 0.002$). SBPCDPT with culprit drugs was pos-

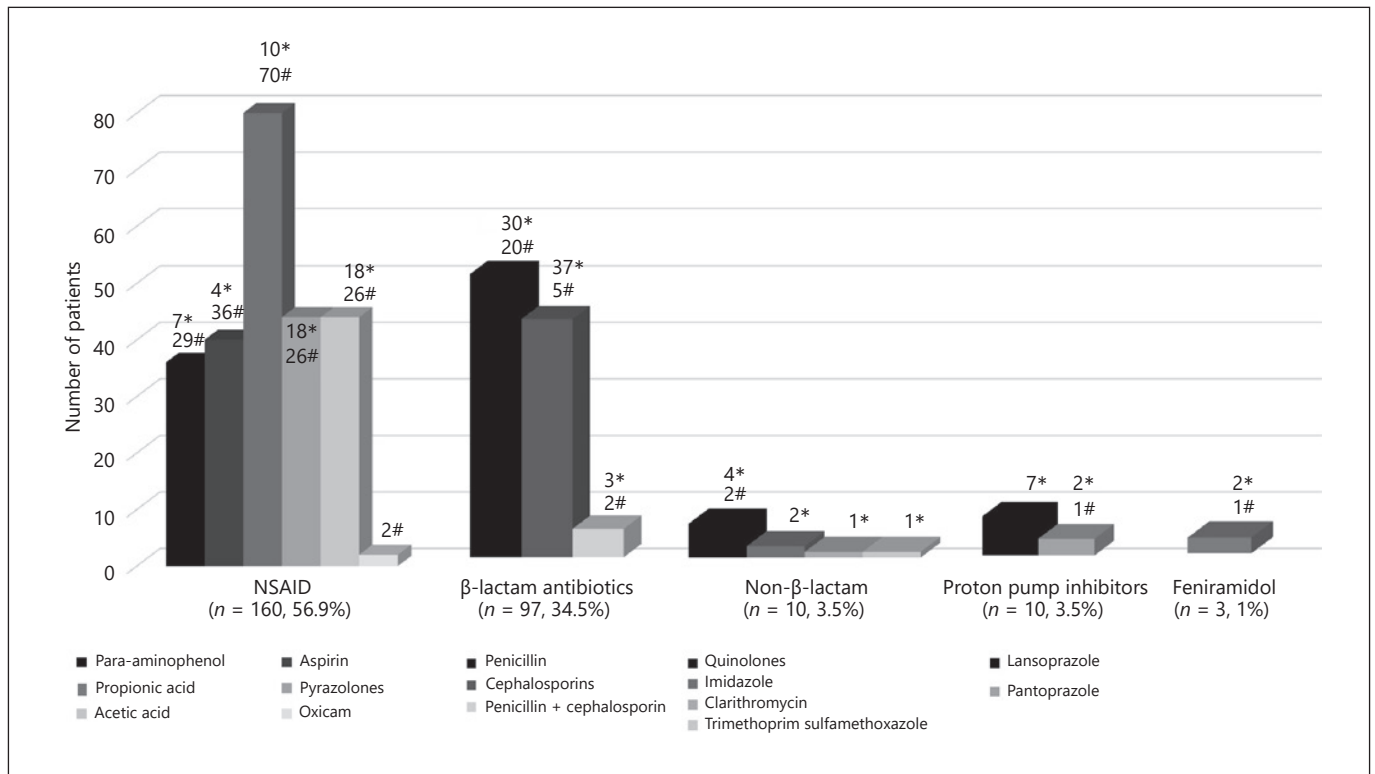


Fig. 2. Culprit drugs in the history. * Number of patients in the anaphylaxis group. # Number of patients in the nonanaphylaxis group.

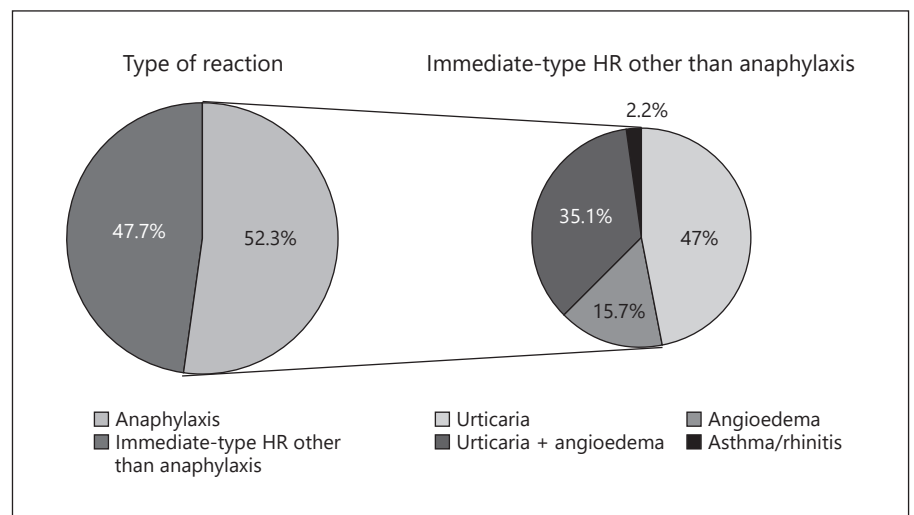


Fig. 3. Reaction types in the history.

itive in 66 patients. The results of skin and SBPCDPTs are illustrated in Table 2.

In 4 patients, anaphylaxis developed during the SPT with the culprit drug cefuroxime. In 3 of these patients, the reaction in the history was anaphylaxis; in the remaining patients, it was urticaria. Among 281 patients, 33 ex-

perienced HRs with cefuroxime in the history, 30 of whom underwent skin testing. The rate of anaphylaxis during skin testing with cefuroxime was 13%. In 118 NSAID-hypersensitive patients, 47 of whom were in the anaphylaxis group, SBPCDPT with aspirin was performed to distinguish cross-reactive patients from selec-

Table 1. Demographic and clinical features of patients and comparison of these features in the anaphylaxis and nonanaphylaxis groups by univariate analysis

	All patients	Anaphylaxis group	Nonanaphylaxis group	<i>p</i> value	OR (95% CI)
Female gender	215 (76.5)	120 (55.8)	95 (44.2)	0.034	0.54 (0.31–0.95)
Current smoker	79 (28.1)	42 (48.6)	37 (27.6)	ns	–
Comorbid diseases	98 (34.9)	48 (32.7)	50 (37.3)	ns	–
Asthma	8 (8.2)	4 (2.2)	4 (2.2)	ns	–
Allergic or nonallergic rhinitis/rhinosinusitis	43 (43.8)	15 (10.2)	28 (20.9)	ns	–
Chronic urticaria	10 (10.2)	2 (1.4)	8 (6.0)	ns	–
Hypertension	27 (27.5)	19 (70.4)	8 (29.6)	0.048	2.3 (0.98–5.5)
Diabetes mellitus	5 (5.1)	3 (2.0)	2 (1.5)	ns	–
Atherosclerotic cardiac diseases	4 (4.1)	4 (2.7)	0	ns	–
Reflux/dyspepsia	9 (9.2)	5 (3.4)	4 (2.7)	ns	–
Thyroid disorders	13 (13.3)	8 (5.4)	5 (3.7)	ns	–
Rheumatologic diseases	6 (6.1)	2 (1.4)	4 (2.7)	ns	–
Psychiatric disorders	6 (6.1)	3 (2.2)	3 (2.2)	ns	–
Presence of atopy	81 (28.8)	48 (59.3)	33 (40.7)	0.013	0.51 (0.3–0.87)
Mites	66 (23.5)	24 (36.4)	42 (63.6)	ns	–
Pollen	22 (10)	9 (32.1)	16 (67.9)	ns	–
Mold	5 (1.8)	2 (1.4)	3 (2.2)	ns	–
Venom	6 (2.1)	5 (3.4)	1 (0.7)	ns	–
Food	2 (0.7)	1 (0.7)	1 (0.7)	ns	–
Latex	2 (0.7)	1 (0.7)	1 (0.7)	ns	–
Concomitant drug usage	69 (24.5)	41 (59.4)	28 (40.6)	ns	–
Antihypertensives	28 (40.5)	20 (71.4)	8 (28.6)	0.033	2.4 (1.05–5.8)
ACEIs/ARBs	20 (29)	15 (75)	5 (25)	0.035	2.93 (1.03–8.3)
Other antihypertensives	14 (20.3)	10 (6.8)	4 (3.0)	ns	–
Oral antidiabetics	5 (7.4)	3 (2.0)	2 (1.5)	ns	–
Antidepressants	5 (7.4)	2 (1.4)	3 (2.2)	ns	–
Aspirin	5 (7.4)	5 (3.4)	0	ns	–
Proton pump inhibitors	21 (30.4)	15 (10.2)	6 (4.5)	ns	–
L-tyroxine	13 (18.8)	8 (5.4)	5 (3.7)	ns	–
Inhaler corticosteroids	8 (11.6)	3 (2.0)	5 (3.7)	ns	–
Antihistamines/montelukast	8 (11.6)	2 (1.4)	6 (4.5)	ns	–
Family history					
Allergic diseases	34 (12.1)	18 (12.2)	16 (11.9)	ns	–
Drug hypersensitivity	15 (5.3)	10 (6.8)	5 (3.7)	ns	–
Culprit drug					
β-Lactams	97 (34.7)	70 (72.2)	27 (27.8)	<0.001	3.6 (2.12–6.13)
Cephalosporins	48 (17.1)	41 (85.4)	7 (14.6)	<0.001	7.01 (3.02–16.29)
Non-β-lactam antibiotics	10 (3.6)	7 (4.8)	3 (2.2)	ns	–
NSAIDs	160 (56.9)	9 (90)	1 (10)	0.021	8.6 (1.08–69.4)
Proton pump inhibitors	10 (3.6)	58 (36.3)	102 (63.7)	<0.001	0.2 (0.12–0.34)
Application route of culprit drug					
Parenteral	37 (13.2)	35 (94.6)	2 (5.4)	<0.001	20.6 (4.8–87.6)
Oral	244 (86.8)	112 (55.9)	132 (54.1)		
Skin test positivity with the culprit drug	68 (24.2)	55 (80.9)	13 (19.1)	0.002	0.3 (0.14–0.66)
Interval between the last reaction in the patient's history and the evaluation, months	7 (1–120)	8 (1–120)	6.5 (1–120)	ns	–
Number of reactions in the history	1 (1–5)	1 (1–3)	2 (1–5)	ns	–
Basal tryptase level, µg/L	3.5 (0.1–17.20)	3.5 (1.1–17.2)	3.5 (1.1–9.39)	ns	–
Total IgE, IU/L	77 (1.71–1,960)	77.5 (3.8–924)	74.2 (1.7–1,960)	ns	–

Values express n (%) or median (range). ACEIs, angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blocker; NSAIDs, nonsteroidal anti-inflammatory drugs; ns, not significant.

Table 2. Results of skin tests and drug provocation tests with the culprit drugs

Culprit drug	Skin tests, <i>n</i>			SBPCDPTs, <i>n</i>		Total
	not performed	positive	negative	not performed	positive	
NSAIDs	85	12	63	106	54	160
Para-aminophenol	15	3	18	19	17	36
Aspirin	37	0	3	15	25	40
Propionic acid	68	0	12	40	40	80
Acetic acid	18	3	23	32	12	44
Pyrazolones	21	5	18	35	9	44
Oxicam	1	1	0	1	1	2
β-Lactam antibiotics	37	52	8	89	8	97
Penicillin	28	20	7	48	7	55
Cephalosporins	9	32	1	41	1	42
Non-β-lactam antibiotics						
Quinolones	2	1	3	4	2	6
Imidazole	0	1	1	2	0	2
Clarithromycin	0	0	1	1	0	1
Trimethoprim sulfamethoxazole	0	1	0	1	0	1
Proton pump inhibitors	7	0	3	9	1	10
Feniramidol	2	0	1	3	0	3

NSAID, nonsteroidal anti-inflammatory drug; SBPCDPTs, single-blind, placebo-controlled drug provocation tests.

tive responders; it was positive in 44 patients, none of whom were in the anaphylaxis group. As a result, 43.75% ($n = 70$) of the NSAID-hypersensitive patients were cross-reactive, and their HR involved multiple NSAID-induced urticaria/angioedema (NIUA, $n = 55$), NSAID-exacerbated cutaneous diseases (NECD, $n = 11$), and NSAID-exacerbated respiratory disease (NERD, $n = 4$). The remaining 56.25% ($n = 90$) were cases of single NSAID-induced urticaria/angioedema/anaphylaxis (SNIUAA).

Anaphylaxis was more common in the patients who were hypertensive, atopic, using angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs), and in those who used the culprit drug parenterally ($p = 0.034$, $p = 0.04$, $p = 0.03$, $p = 0.035$, $p = 0.013$, and $p < 0.001$, respectively).

While β-lactam antibiotics, especially cephalosporin and proton pump inhibitors (PPIs), caused anaphylaxis more commonly than other causative agents ($p < 0.001$, $p < 0.001$, and $p = 0.021$), NSAIDs led to nonanaphylactic immediate-type HRs more frequently ($p < 0.001$) (Table 1). Age, smoking, family history, serum level of baseline tryptase and total IgE level did not differ between groups. In the multivariate analysis, it was observed that parenteral use of the drug and the presence of atopy were significantly higher in the anaphylaxis group than in the nonanaphylaxis group ($p < 0.001$, odds ratio [OR] =

20.05, confidence interval [CI] 4.75–88.64; $p = 0.012$, OR = 2.1, CI 1.17–3.74) (Table 3). Since these results varied according to the type of drug, we performed an additional analysis. Further comparative analysis between groups with these parameters was performed in β-lactam- and NSAID-hypersensitive patients. In β-lactam-hypersensitive patients, parenteral application of the drug and concomitant drug use were higher in the anaphylaxis group than in the nonanaphylaxis group ($p = 0.01$, OR = 6.117, CI 1.33–28.08; $p = 0.010$, OR = 6.117, CI 1.33–28.1), but there were no relations regarding specific drug subgroups such as antihypertensives, antidepressants, PPIs, etc. In both β-lactam- and NSAID-hypersensitive patients, parenteral drug administration was associated with more severe anaphylaxis ($p = 0.010$, OR = 6.12, CI 1.33–28.1; $p < 0.001$, OR = 1.23, CI 1.09–1.39). Other parameters involving atopy and the level of serum total IgE and basal tryptase were not associated with anaphylaxis in either β-lactam- or NSAID-hypersensitive patients.

A subgroup of the study population that excluded 69 patients who had cross-reactive NSAID HRs (presumably mediated by a non-IgE mechanism involving NERD, NIUA, and NECD) was reanalyzed. Of 212 patients, 168 were female, mean age was 40.7 ± 17.7 years, and the median interval between the HR and the evaluation was 6.5

Table 3. Multiple regression analysis of the factors associated with anaphylaxis

Factor	Anaphylaxis	
	OR (95% CI)	<i>p</i> value
Female	0.6 (0.34–1.15)	>0.05
Hypertension	0.7 (0.4–2.3)	>0.05
Use of an antihypertensive	0.5 (0.1–2.6)	>0.05
Use of an ACEI/ARB	0.4 (0.05–3.1)	>0.05
Parenteral route	20.05 (4.75–88.64)	<0.001
Atopy	2.1 (1.17–3.74)	0.012

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

months. In 145 patients, the reactions were anaphylaxis and the culprit drugs were NSAIDs, β -lactams, non- β -lactam antibiotics, PPIs, and feniramidol in 91, 97, 10, 10, and 3 patients, respectively. In 17% of the patients, the culprit drugs were administered parenterally. In 34.4% of the patients, the skin tests with culprit drugs were positive, 31.6% of the patients had comorbid diseases, 24.1% were using other drugs concomitantly, and atopy was detected in 22.2%. In the comparative analysis between groups with the same parameters above, parenteral administration of the culprit drug, concomitant drug usage, and skin test positivity were higher in the anaphylaxis group, and cephalosporins caused anaphylaxis more commonly than the other symptoms ($p < 0.001$, OR = 9.9, CI 2.31–42.8; $p = 0.034$, OR = 2.24, CI 1.04–4.82; $p = 0.005$, OR = 2.7, CI 1.33–5.52; $p = 0.004$, OR = 3.37, CI 1.42–8.01). Although the use of antihypertensives was higher in the anaphylaxis group than in the nonanaphylaxis group, this had a marginal level of significance statistically ($p = 0.043$, OR = 3.42, CI 0.9–11.98). Serum basal tryptase and total IgE level and the other parameters were similar between groups.

Discussion

This study evaluated the risk factors for drug-induced anaphylaxis by comparing anaphylaxis with nonanaphylactic immediate-type drug reactions. Most studies indicate that the most common cause of anaphylaxis in adult patients is medications and can lead to more severe reactions and fatalities [7–10, 20]. Accordingly, studying drug-induced anaphylaxis to determine specific risk factors is of great importance. Previous studies have focused

on the general risk factors for severe anaphylaxis or compared anaphylaxis according to the causative agents such as foods or drugs [38–41]. Up to now, no study has compared drug-induced anaphylaxis with nonanaphylactic immediate-type drug reactions in terms of risk factors for adult patients.

The main findings of our study were that the parenteral route of drug administration increased the risk of anaphylaxis 20-fold and atopy increased this risk 2-fold. In a separate analysis of β -lactam- and NSAID-hypersensitive groups, parenteral drug usage was still a risk for anaphylaxis, but atopy was not.

Parenteral administration, particularly via the intravenous route, has already been defined as a risk factor for drug-induced anaphylaxis [11, 42]. Another study analyzing cephalosporin-related adverse reactions retrospectively found that physician-documented anaphylaxis ratios due to oral or parenteral administration of cephalosporins were similar; our study once more points out the importance of the route of drug administration for the development of anaphylaxis, independent of the type of causative drug [43]. This matter should be taken carefully into account when treating patients with a history of any drug hypersensitivity.

Regarding the association between atopy and DHRs, whether atopy predisposes to a new allergen sensitization or is a risk factor for severe reactions is not known. Although there are some studies about this association, to draw a conclusion from their results would not be accurate due to the differences in methodology, selection of patients, and reaction types as well as insufficient assessments of atopy. In the late 1960s, atopy was reported for the first time as a risk factor for penicillin allergy [23]. More recently, authors from southern Spain and the USA observed that atopy was related to β -lactam allergy in their patients [44, 45]. In France, another study group reported that atopy is a personal risk factor for NSAID hypersensitivity [46]. However, Aun et al. [13] and Faria et al. [14] reported that anaphylaxis did not differ among different causative types of drugs such as NSAIDs, β -lactams, non- β -lactam antibiotics, or general anesthetics but they did not compare an anaphylaxis group with nonanaphylaxis patients. In another study performed in Latin America, the authors observed that drug-induced anaphylaxis was less severe in atopic patients, but they also did not compare anaphylaxis with nonanaphylaxis [15]. Their study bears a resemblance to ours by comparing anaphylaxis to nonanaphylactic immediate-type HRs (less severe than anaphylaxis) in terms of severity [15]. We observed that atopy increased the anaphylaxis risk

2-fold but was not associated with specific groups of drugs such as β -lactams or NSAIDs; there was a different association when we excluded non-IgE-mediated NSAID HRs. Such variations can be caused by different study methodologies as well as the geographical and racial differences which affect atopy development. Therefore, to identify the exact effect of atopy on DHRs, more comprehensive studies are needed.

While the most common causative drugs in our study patients were NSAIDs, β -lactam antibiotics were found to be the leading drugs in the anaphylaxis group, a finding which concurs with those of other studies [34, 38, 47].

An important finding of our study was the high ratio of anaphylaxis among cephalosporin-hypersensitive patients. In the early 2000s, Kelkar and Li [48] reported that cephalosporins rarely caused anaphylaxis. A few years later, other authors observed that cephalosporin-induced anaphylaxis has increased over the years [49].

Anaphylaxis occurred during the SPT with cefuroxime in 13% of our patients. Mota et al. [50] from Portugal recently published the results of their 3-year follow-up study which evaluated HRs to β -lactam antibiotics. They did not observe any systemic reactions during skin testing. Somech et al. [51] from Canada also did not observe any systemic reactions during skin testing in their study assessing immediate-type HRs (mostly nonanaphylaxis) to cephalosporins. On the other hand, Riezzo et al. [52] from Italy reported that fatal anaphylactic shock developed during intradermal testing with ceftriaxone in a patient. Variations in race and reaction types could be the reason for this discrepancy.

Regarding our finding that cephalosporins are a common cause of anaphylaxis, especially when given parenterally (also with skin testing), we suggest that physicians should be more careful when prescribing cephalosporins for common infections such as upper and lower respiratory tract infections and cellulitis [50]. They should avoid the parenteral route unless it is absolutely necessary, and allergists should be cautious while skin testing the patient with cefuroxime.

Previously, our group reported that the total IgE level was higher in quinolone-induced anaphylaxis [30] and Pastorello et al. [53] reported that higher total IgE level was associated with severity in amoxicillin-induced anaphylaxis. However, in this study, serum total IgE levels were not associated with anaphylaxis in the general study population, and also not in β -lactam- or NSAID-hypersensitive patients. Similarly, Kim et al. [40] reported that total IgE level was not associated with drug-induced anaphylaxis.

Anaphylaxis is seen in 22–49% of adult patients with systemic mastocytosis [54]. It can thus be assumed that a high serum tryptase level, with no clonal disorder but reflecting a mast-cell burden, can be associated with anaphylaxis. Regarding this hypothesis, many authors have investigated the role of basal serum tryptase levels in anaphylaxis. A high basal serum tryptase level has been reported as a risk factor for food-induced anaphylaxis and overall anaphylaxis by some authors [25, 26]. However, the role of basal serum tryptase in drug-induced anaphylaxis is controversial. While some authors report that a high level is related to both drug-induced anaphylaxis and severe reactions, it is not associated with drug-induced anaphylaxis in children or NSAID-induced HRs in other studies and also indicated by our findings [27–29].

The role of comorbidities and concomitant drug usage in drug-induced anaphylaxis has been somewhat debated. Some studies which evaluated the risk factors for severe reactions in drug-induced anaphylaxis reported that comorbidities involving chronic lung diseases or cardiac diseases and drugs used simultaneously such as β -blockers, ACEI/ARBs, or PPIs increased the risk of severe anaphylaxis, but others did not observe such a relationship [39, 55, 56]. We observed that anaphylaxis was more common in hypersensitive patients and the patients who used ACEI/ARBs in the univariate analysis. However, based on the multivariate analysis, we could not define these as risk factors.

Another finding was that immediate-type HRs due to PPIs were mostly anaphylaxis. PPIs are widely used drugs which are generally well-tolerated, causing side effects in only 1–3% of patients and anaphylaxis in around 0.2–0.7% [57, 58]. Özdemir et al. [59] from Turkey reported that anaphylaxis was the most common HR type among 60 PPI hypersensitive patients (66.7%) and the most common culprit PPI was lansoprazole (68.3%), followed by pantoprazole (20.0%). These findings are in agreement with our results. The most common culprit PPI changes from country to country depending on prescription habits. In countries other than Turkey, the most frequent culprit drugs are esomeprazol, omeprazol, and pantoprazol [60, 61]. Although PPI-induced anaphylaxis seems to be rare, physicians must be aware of the possibility, in order to avoid severe reactions and recurrence.

To avoid recurrence of anaphylaxis and anaphylactic shock, an accurate diagnosis involving determination of the culprit drug is very crucial. Drug skin testing is not helpful for non-IgE mechanisms and not reliable for most drugs. The drug provocation test, which is the gold standard for the diagnosis of drug allergy, can be frightening because of the possibility of a severe reaction [2, 62]. In

this study, skin test positivity was higher in the anaphylaxis group than in the group that had nonanaphylactic immediate-type HRs, an observation reflecting the higher IgE-related mechanism involved in anaphylaxis. Therefore, we can recommend skin testing in drug-induced anaphylaxis to identify the culprit drug.

In conclusion, this was a unique study which evaluated the potential risk factors for drug-induced anaphylaxis by comparing it with nonanaphylactic, immediate-type HRs in a relatively homogenous group. The findings emphasize that the parenteral route increases anaphylaxis risk independent of the type of causative drug, while atopy has a lesser, but nonetheless apparent, effect on this risk. It was found that skin test positivity with culprit drugs, the most common being β -lactam antibiotics, was higher in patients who experienced anaphylaxis, suggesting that those who have IgE-mediated sensitivity are indeed more prone to anaphylaxis.

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Statement of Ethics

The study was approved by the ethics committee of the Istanbul Training and Research Hospital and informed consent was obtained for all patients.

Disclosure Statement

We declare that we have no conflicts of interest.

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Author Contributions

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