

Characteristics of drug-induced anaphylaxis in children and adolescents

Ozlem Cavkaytar, M.D., Betül Karaatmaca, M.D., Pinar Gur Cetinkaya, M.D., Saliha Esenboga, M.D., Ebru Arik Yilmaz, M.D., Umit M. Sahiner, M.D., Bulent E. Sekerel, M.D., and Ozge Soyer, M.D.

ABSTRACT

Background: Although data on anaphylaxis in the general population exist for different allergens, there is still lack of detailed etiologic data on drug-induced anaphylaxis (DIA), particularly in children.

Objective: To define the etiology of DIA, to determine the accuracy of drug-related anaphylaxis histories, along with the severity and culprit drug associations among individuals <18 years old.

Methods: Patients with a history of drug hypersensitivity reaction (DHR) referred to our center between January 2012 and February 2016 were included. After the collection of European Network for Drug Allergy questionnaire results, initial skin tests and/or provocation tests were performed for the offending drug.

Results: Among 561 children and adolescents referred due to a suspected DHR, 113 (19%) (median age [interquartile range], 9.6 years [5.4–13.8 years]; 55% boys) had anaphylaxis in their history. At the end of diagnostic evaluation of the patients, 84 (74% of the patients with a history of DIA) were actually hypersensitive to the offending drug. Major drugs that resulted in DIA were antibiotics (33%), nonsteroidal anti-inflammatory drugs (25%), and chemotherapeutics (19%). The majority of patients reported grade 2 (moderate) (45%) and grade 3 (severe) (33%) anaphylactic reactions. A history of systemic illness (41.7 versus 7.1%; $p = 0.001$), concomitant intake of other drugs regularly (36.9 versus 10.3%; $p = 0.007$), and the use of chemotherapeutics as the culprit drug (19 versus 0%; $p = 0.011$) were more frequent, whereas the use of antibiotics was less frequent (34.5 versus 75.9%; $p < 0.001$) among patients with actual DIA compared to drug tolerant patients.

Conclusion: Three-fourths of the children and adolescents referred due to a suspected history of DIA were found to actually be drug hypersensitive. Prediagnosed systemic illness and different types of drugs would have an impact on the risk of DIA; however, atopic disease or a family history of drug hypersensitivity did not have an impact on actual DIA.

(Allergy Asthma Proc 38:e56–e63, 2017; doi: 10.2500/aap.2017.38.4064)

Drug hypersensitivity reactions (DHR) occur as a consequence of an unpredictable and unexpected response to a drug, and DHRs constitute 15% of all adverse drug reactions.¹ An accurate diagnosis of DHRs is required to prevent suboptimal treatment of the individual.² During the past few years, analysis of the cumulative epidemiologic data on the definitive diagnosis of drug hypersensitivity for children and adolescents indicates that children display similar rates of actual drug hypersensitivity compared with adults when suspected hypersensitivity reactions were evaluated through objective diagnostic tests.^{3,4} As an example, in a study by Rubio *et al.*,⁵ 15.7% of adults with a history of nonsteroidal anti-inflammatory drug (NSAID) induced hypersensitivity

reactions were diagnosed as actually hypersensitive, whereas 18.5% of children with a history of NSAID-induced hypersensitivity reactions were diagnosed as actually hypersensitive.⁵

Anaphylaxis is a series of life-threatening systemic hypersensitivity reactions on exposure to various types of allergens as well as drugs.⁶ The European Anaphylaxis Registry reported that the rate of drug-induced anaphylaxis (DIA) increased during the first 10 years of life and remained stable after the age of 10 years. Drugs were the third most frequent elicitors of anaphylaxis after foods and insect venoms in the pediatric age group.⁴ Despite the availability of some etiologic data on anaphylaxis in the general population,^{4,7,8} etiologic studies that focused on DIA in the pediatric age range are still insufficient. As an example, the study by the Allergy Vigilance Network evaluated a large group of patients with severe anaphylaxis through predominantly diagnostic tests; however, children and adolescents constituted only a minor fraction as 10% of the study participants.⁹ There also was a lack of specific information on the incidence of anaphylaxis with the culprit drug associations. Therefore, in this study, we aimed to define the etiology of DIA, the accuracy of drug-related anaphylaxis histories, and the severity of

From the Department of Pediatric Allergy, Hacettepe University Faculty of Medicine, Ankara, Turkey

No external funding sources reported

The authors have no conflicts of interest to declare pertaining to this article

Supplemental data available at www.IngentaConnect.com

Address correspondence to Ozge Soyer, M.D., Department of Pediatric Allergy, Hacettepe University Ihsan Dogramaci Childrens' Hospital, 06100 Sıhhiye Ankara, Turkey

E-mail address: ozgeusoyer@gmail.com

Copyright © 2017, OceanSide Publications, Inc., U.S.A.

DIA, along with the culprit drug associations among individuals <18 years old.

METHODS

Patients

Between January 2012 and February 2016, all children and adolescents who were referred to the Department of Pediatric Allergy, Hacettepe University Ihsan Dogramaci Childrens' Hospital, due to a suspected DIA history were included in this study. Demographic features and a medical history of the patients were recorded, and a European Network for Drug Allergy questionnaire, including details of DHR was filled out for each participant.¹⁰ Suspected DIA, determined according to the guidelines of the World Allergy Organization,¹¹ was defined as the occurrence of at least two of the following clinical conditions immediately after exposure to a drug: (1) skin or mucosal signs and symptoms (urticaria, angioedema, itch and/or flush), (2) respiratory signs and symptoms (cough, hoarseness, dyspnea, wheezing, rhinitis, stridor, hypoxemia), (3) reduced blood pressure or symptoms of end-organ dysfunction (hypotonia, loss of consciousness, collapse, hypoxemia), or (4) gastrointestinal signs and symptoms (nausea and/or vomiting, cramping abdominal pain).

The severity of DIA was ascertained according to the European Academy of Allergy and Clinical Immunology guidelines¹² on management of anaphylaxis in childhood as grade 1 (mild), grade 2 (moderate), and grade 3 (severe) anaphylactic reactions. None of the patients had a previously described trigger of anaphylaxis in their medical history. The patients were subjected to further diagnostic testing (skin tests [ST] and/or provocation tests) to prove actual DIA. The patients who had been using more than one drug at the time of anaphylactic reaction had been assessed thoroughly for the possible association between the drug intake and the reaction onset for each drug. Because anaphylaxis is an immediate reaction, the diagnostic tests were performed for the most relevant drug that was taken at most 2 hours before the reaction. Some of these patients had already been using the drugs other than the culprit drug for a long period of time for their systemic illness. They neither reported any DHRs before the anaphylactic episode or after with these drugs.

Furthermore, patients with and without actual diagnosis of DIA who were determined according to the results of diagnostic tests were compared according to their demographic and clinical features, timing of the reaction, and route of the culprit drug administration. In addition, the patients with actual diagnoses of DIA were classified according to the culprit drugs (*e.g.*, antibiotics, NSAIDs, and chemotherapeutics) and age groups (0–6 years, 6–12 years, and >12 years). These

groups were compared according to the above-mentioned criteria. The patients were grouped according to concurrent atopic diseases that included the ones previously diagnosed with allergic rhinoconjunctivitis and/or asthma. Allergic rhinoconjunctivitis and asthma were diagnosed according to the ARIA (Allergic Rhinitis and its Impact on Asthma) and GINA- (Global Initiative for Asthma) guidelines.^{13,14} This study was approved by the ethics committee of Hacettepe University Medical Faculty, which is concordant with the Helsinki Declaration, and written informed consents were obtained from the patients and their parents.

Measurements of the Study: Diagnostic Tests on Actual DIA

Study participants underwent skin-prick tests (SPT) and intradermal tests (IDT) (in case of a negative SPT result) with the culprit drug by using a validated and previously published ST protocol that was available for the respective drug.^{15–23} In all cases of anaphylaxis, the minimum ST concentration was 1/100th or 1/1000th of validated concentrations in accordance with the current guidelines.¹⁵ Serial dilutions, of 0.02 mL, of the commercial injectable solution of the respective culprit drug were used for IDT. Details of the nonirritating concentrations used during SPT and IDT are given in Supplemental Table 1. Results of the SPT or IDT were considered positive if the mean wheal diameter was at >3 mm than that of negative control (0.9% saline solution) 15 and 20 minutes after the application, respectively, in the presence of a positive response with histamine (10 mg/mL; Stallergenes; Anthony, France).

Patients with mild (grade 1) or moderate (grade 2) anaphylaxis in their histories further underwent provocation tests if the initial SPT and IDT results were negative or they were directly probed with the culprit drug when there was no injectable form of the culprit drug appropriate for ST, as in the case of NSAIDs (*e.g.*, ibuprofen, aspirin, naproxen, dextro-ketoprofen, propyphenazone) and of antibiotics (*e.g.*, cefixime and cefaclor). Provocation tests were done with the previously used form of the drug, and the doses were determined according to the validated and previously published protocols.^{24–27} The total dose used during a DPT corresponded to a maximum single dose that was suitable for patient use according to the prescription and was determined according to the weight of each participant. The DPTs started with a low dose (1/10000 to 1/100 of the total dose) and continued in an incremental order divided into four or five doses.^{24–26} All the diagnostic tests were performed under strict medical surveillance, and the patients were observed for an additional 4 hour at the hospital in case of a negative drug provocation result. A positive DPT

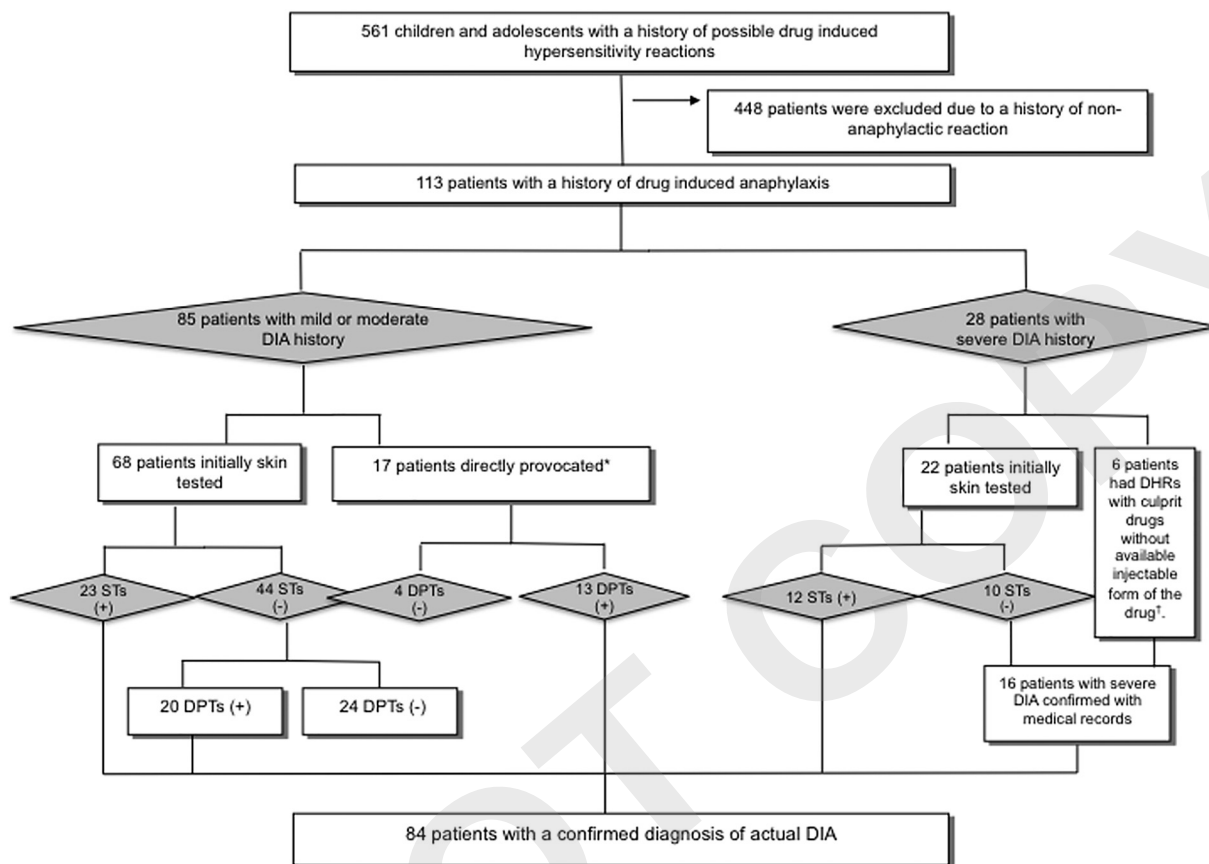


Figure 1. Flowchart of the study and the diagnostic approach of patients with actual DIA. DIA = Drug-induced anaphylaxis; DPT = drug provocation test; ST = skin test (skin-prick test and/or intradermal test with the culprit drug). *These patients were directly probed with the culprit drug (aspirin, ibuprofen, naproxen, dextroketoprofen, cefixime, cefaclor) due to the lack of an injectable form of the drug appropriate for skin testing. †These patients had severe DIA with ibuprofen, aspirin, and factor 9.

result was defined as the occurrence of any objective physical finding in relation to a hypersensitivity reaction, including cutaneous, respiratory, gastrointestinal, and cardiovascular system symptoms.²⁵

The patients with grade 3, severe anaphylaxis, who had either negative ST results or those who could not have an ST due to the lack of an injectable form of the drug appropriate for ST did not undergo provocation due to the severity of the reactions, which were confirmed with medical records, and this approach was in accordance with the guidelines and previous publications.^{2,25,28} These patients and the ones with a positive ST or provocation test result with the culprit drug were defined as having actual DIA. It is important to note that all of the patients with concurrent asthma were under control at the time of diagnostic tests. The patients with a history of DHR due to drugs used during anesthesia were also evaluated for latex sensitization by their history, specific IgE levels, and/or provocation when needed to rule out latex-induced anaphylaxis. Additional data about other measurements, including aeroallergen sensitization, total IgE and eosinophil levels are given in the Supplemental Material.

Statistical Analysis

Statistical analyses were performed by using the SPSS 21 software program (SPSS, Inc., Chicago, IL). Quantitative variables were non-normally distributed and are expressed as median (interquartile range [IQR]). Comparisons of quantitative variables were performed by using the Kruskal-Wallis test. As a *post hoc* analysis, pairwise comparisons were performed to find out the adjusted significance in between each paired variable by using the independent samples test when triple comparisons were found to be significant. Comparisons of qualitative variables were done by means of the χ^2 test. A *p* value of <0.05 was considered statistically significant.

RESULTS

Five hundred and sixty-one children and adolescents were referred to our center due to DHRs (Fig. 1). One-hundred and thirteen (19%) (55% boys; median [IQR] age, 9.6 years [5.4–13.8 years]) had anaphylaxis in their history. In total, 90 patients (79.6%) initially had an ST with the culprit drugs, and 17 patients (15%) had a

DPT as an initial diagnostic evaluation (Fig. 1). Additional 44 DPTs were performed in patients who had an initial negative ST result. At the end of the diagnostic evaluation of the participants, 84 (74%) with a history of suspected DIA were defined as actually hypersensitive to the offending drug (15% of all the patients) (Fig. 1). The culprit drugs responsible for an actual DIA were β -lactam antibiotics (penicillin, amoxicillin-clavulanic acid, ceftriaxone, cefixime, cefaclor, piperacillin-tazobactam) ($n = 28$ [33%]), NSAIDs ($n = 21$ [25%]), chemotherapeutics (asparaginase, oxaliplatin, etoposide, docetaxel) ($n = 16$ [19%]), biologic agents and enzymes ($n = 10$ [12%]) ([rituximab, eculizumab], enzymes [$n = 6$], [galsulfase, idursulfase] [$n = 4$]), anesthetic and neuromuscular blocking agents (propofol, midazolam, rocuronium) ($n = 4$ [5%]), and others ($n = 5$ [6.0%]), (ranitidine, triptorelin, cyclopentolate, iopromide, factor 9). The distribution of the culprit drugs according to the severity of anaphylaxis is given in Table 1. None of the patients with a history of DHR due to drugs used during anesthesia were found to be hypersensitive to latex.

Thirty-seven participants had previous systemic illness and were diagnosed with malignancy ($n = 16$), storage disease ($n = 4$), cardiovascular disease ($n = 3$), seizure disorder ($n = 3$), renal disease ($n = 3$), coagulation abnormality ($n = 3$), rheumatologic disease ($n = 2$), respiratory disease ($n = 1$), primary immune deficiency ($n = 1$), and endocrinologic disease ($n = 1$). None of the patients used β -blockers or angiotensin receptor blockers as part of their treatment of their systemic illnesses. A history of systemic illness (41.7 versus 7.1%; $p = 0.001$), and concomitant regular intake of drugs other than the culprit drug (36.9 versus 10.3%; $p = 0.007$) were more frequent in patients with actual DIA versus participants who were drug tolerant (Table 2). Atopic disease, aeroallergen sensitization, family history of atopic disease, or drug hypersensitivity did not have an impact on actual DIA. Regarding the type of culprit drug, the use of chemotherapeutics (19 versus 0%; $p = 0.011$) were more frequent, whereas the use of antibiotics was less frequent (34.5 versus 75.9%; $p < 0.001$) (Table 2) in patients with an actual DIA compared with patients in the drug tolerant group. It is important to note that there was a longer delay in the evaluation of the patients in the drug tolerant group versus the patients who were hypersensitive (median [IQR], 6 months [3–7 months] versus 3 months [1.5–5 months]; $p = 0.003$).

Eighteen of the patients with an actual DIA (22%) reported grade 1 (mild anaphylaxis), whereas the majority reported grade 2 (moderate) (45%) and grade 3 (severe) (33%) anaphylactic reactions (Table 1). However, the degree of severity of anaphylaxis did not differ among the patients who used these major groups of culprit drugs (Table 3). It is important to note that

Table 1 Drugs responsible from actual drug-induced anaphylactic reactions according to severity of the reactions

Severity of Reactions	Drug Groups*									
	Antibiotics			NSAIDs			Chemotherapeutics			Others
	ST (+)	DPT (+)	ST (+)	ST (+)	DPT (+)	ST (+)	DPT (+)	ST (+)	DPT (+)	
Mild (grade 1) ($n = 18$)	Ceftriaxone (1) Penicillin (1)	Ceftriaxone (1) Amoxicillin-clavulanate (2)	—	—	Aspirin (1) Ibuprofen (1) Metamizole (1)	Asparaginase (5) Docetaxel (1)	Asparaginase (1) Docetaxel (1)	—	Rituximab (2) Eculizumab (1)	
Moderate (grade 2) ($n = 38$)	Ceftriaxone (6) Penicillin (2) Amoxicillin-clavulanate (2)	Ceftriaxone (1) Cefixime (1) Cefaclor (1)	Metamizole(1)		Aspirin (1) Ibuprofen (5) Paracetamol (2) Propyphenazone (1) Dextroketoifen (1) Naproxen (1)	Asparaginase (3)	Asparaginase (3)	Rocuronium (1) Ranitidine (1)	Galsulfase (2) Idursulfase (1) Rituximab (2)	
Severe (grade 3) ($n = 28$)#	Ceftriaxone (5) Amoxicillin-clavulanate (2) Penicillin (1) Piperacillin-tazobactam (1)							Rocuronium (1) Midazolam (1) Iopramide (1)		

NSAID = Nonsteroidal anti-inflammatory drug; ST = skin test (including both skin-prick and intradermal test results); (+) = positive; DPT = drug provocation test.
*Data within parentheses indicate the number of patients.
#The other culprit drugs that resulted in severe anaphylactic reactions and confirmed with medical records with negative skin test results were asparaginase ($n=1$), oxaliplatin ($n=1$), etoposide ($n=1$), penicillin ($n=1$), metamizole ($n=1$), rituximab ($n=1$), propofol ($n=1$), triptorelin ($n=1$), cyclopentolate ($n=1$), idursulfase ($n=1$), aspirin ($n=2$), ibuprofen ($n=3$).

Table 2 Demographic and clinical characteristics of the patients with a history of drug-induced anaphylaxis

	Drug Hypersensitivity (n = 84)	Drug Tolerant (n = 29)	p
Boys, no. (%)	47 (56.0)	15 (51.7)	NS
Age at drug-induced anaphylaxis, median (IQR), y	8.8 (4.6–13)	10.6 (6.5–14.4)	NS
Previously known systemic illness, no. (%)	35 (41.7)	2 (7.1)	0.001
Chronic use of drugs, no. (%)	31 (36.9)	3 (10.3)	0.007
Asthma, no. (%)	12 (14.6)	3 (10.3)	NS
Allergic rhinoconjunctivitis, no. (%)	7 (9.6)	5 (20.0)	NS
Aeroallergen sensitization, no. (%)	11 (14.7)	7 (25.0)	NS
Family history of allergic disease, no. (%)	17 (20.7)	5 (20.0)	NS
Family history of drug hypersensitivity, no. (%)	14 (17.1)	7 (24.1)	NS
Culprit drugs, no. (%)			
Antibiotics	29 (34.5)	22 (75.9)	<0.001
NSAIDs	20 (23.8)	4 (13.8)	NS
Chemotherapeutics	16 (19.0)	—	0.011
Anesthetic agents	4 (4.8)	2 (6.9)	NS
Biologic agents and enzyme therapy	10 (11.9)	—	NS
Route of drug administration, no. (%)			NS
Oral	32 (14.6)	10 (34.5)	
Parenteral	52 (85.4)	19 (65.5)	
Period between the reaction and diagnostic workup, median (IQR), mo	3 (1.5–5)	6 (3–7)	0.003
Total IgE level, median (IQR)	56.1 (23.2–143.5)	115 (23.4–218.5)	NS
Eosinophils, median (IQR), %	1.9 (0.8–3.1)	1.4 (0.7–4.1)	NS

NS = Nonsignificant; IQR = interquartile range; NSAID = nonsteroidal anti-inflammatory drug; IgE = immunoglobulin E.

the majority of patients who used antibiotics and chemotherapeutics had anaphylaxis while they were using the parenteral form of the drug. However, all of the patients who used NSAIDs had anaphylaxis with the oral form of the drug (67.9% and 93.8% versus 0 for the frequency of the parenteral form use, for the patients using antibiotics, chemotherapeutics and NSAIDs respectively; $p < 0.001$) (Table 3). As a result of pairwise comparisons, in relation to the route of drug administration, the patients who used NSAIDs were found to be significantly different from patients who used either chemotherapeutics or antibiotics ($p < 0.001$ for both comparisons).

Among the patients with an actual DIA when the three major group of drugs were used, the patients with chemotherapeutics as the culprit drug were younger (median [IQR], 6 years [3–12.5 years]) at the time of the actual DIA compared with the patients who used NSAIDs and antibiotics (Supplemental Fig. 1) (median [IQR], 12.2 years [9–14.5 years] and 7.5 years [5–13.4 years], respectively; $p = 0.045$) (Table 3). Pairwise comparisons as a *post hoc* analysis revealed that the difference between the patients who used chemotherapeutics and NSAIDs was significant ($p = 0.044$, adjusted significance). The frequencies of cutaneous,

respiratory, gastrointestinal, or cardiovascular system involvement during the DIA according to the history in these three groups of patients were similar. The median (IQR) time of onset of the symptoms was the earliest for the patients with antibiotics as the culprit drug (5 minutes [1.25–30 minutes]) compared with patients who took chemotherapeutics and NSAIDs (10 minutes [2.75–60 minutes] and 30 minutes [10–120 minutes], respectively; $p = 0.022$) (Supplemental Fig. 2). Pairwise comparisons showed that the difference between the patients who used antibiotics and NSAIDs was significant ($p = 0.019$, adjusted significance).

The patients were classified according to their ages when the actual DIA appeared, and, when they were compared in relation to the demographic and clinical features, it was realized that boys in the >12 years age group (33.3%) were less frequent than the 0–6 and 6–12 years age groups (67.7 versus 65.4%) ($p = 0.016$) (data not shown). There was a significant difference between 0–6 years age group and the >12 years age group (adjusted $p = 0.009$). During DIA, use of oral form of the culprit drug was significantly more frequent in the >12 years age group compared with the 0–6 years age group, $p = 0.009$ and $p = 0.01$, respectively. However, atopy, atopic diseases, or a family

Table 3 Comparison of patients who experienced an actual DIA according to the culprit drugs

	Antibiotics (n = 28)	NSAIDs (n = 21)	Chemotherapeutics (n = 16)	p
Boys, no. (%)	15 (53.6)	12 (57.1)	7 (43.8)	NS
Age at DIA, median (IQR), y	7.5 (5–13.4)	12.2 (9–14.5)	6 (3–12.5)	0.045
Previously known systemic illness, no. (%) [*]	3 (10.7)	2 (9.5)	16 (100)	<0.001
Chronic use of drugs other than the culprit drug, no. (%) [*]	3 (10.7)	1 (4.8)	16 (100)	<0.001
Concurrent atopic disease, no. (%) [#]	13 (44.8)	5 (25)	1 (6.3)	0.015
Family history of atopic disease, no. (%)	5 (17.9)	5 (23.8)	3 (20)	NS
Family history of drug hypersensitivity, no. (%)	4 (14.3)	1 (4.8)	—	NS
Anaphylaxis severity, no. (%)				
Mild (grade 1)	5 (17.9)	3 (14.3)	7 (43.8)	NS
Moderate (grade 2)	13 (46.4)	12 (57.1)	6 (37.5)	
Severe (grade 3)	10 (35.7)	6 (28.6)	3 (18.8)	
Delay between the reaction and the drug intake, median (IQR), min	5 (1.25–30)	30 (10–120)	10 (2.75–60)	0.022
Route of drug administration, no. (%)				
Oral	9 (32.1)	21 (100)	1 (6.3)	<0.001
Parenteral	19 (67.9)	—	15 (93.8)	
Period between the reaction and diagnostic workup, median (IQR), mo [§]	5 (3–6)	4 (3–6.5)	1 (1–2.75)	<0.001

DIA = Drug-induced anaphylaxis; NSAID = nonsteroidal anti-inflammatory drug; NS = nonsignificant; IQR = interquartile range.

^{*}Pairwise comparisons revealed that the difference was significant between both chemotherapeutics and NSAIDs groups, and the chemotherapeutics and antibiotics groups (adjusted $p < 0.001$).

[#]Pairwise comparisons showed that the difference between the chemotherapeutics and antibiotics groups was significant (adjusted $p = 0.018$).

[§]Pairwise comparisons showed that the period between the reaction and diagnostic workup was significantly lower for the patients who used NSAIDs compared with the patients who used either antibiotics or chemotherapeutics ($p = 0.001$ for both).

history of atopic disease, and the types of reactions in relation to system involvements that could be seen during DIA did not differ between the different age groups.

DISCUSSION

In this study, the patients referred due to a presumed history of DIA were thoroughly evaluated with diagnostic tests, and nearly three-fourths of them actually showed drug hypersensitivity. In addition, the features of the patients with an actual DIA, the reaction types, and the features of drug administration during actual anaphylactic DHRs in relation to different types of culprit drugs were thoroughly investigated. In this study, the culprit drug types had a broad range and were different from the ones reported in other studies. In the study by Aun *et al.*,²⁹ all of the participants were <18 years old, and none of them experienced a DIA when on chemotherapeutics. Faria *et al.*³⁰ reported that there was only one child who had a DIA induced by a cytostatic drug, whereas this group of drugs was found to be the third most frequently administered drug after

antibiotics and NSAIDs. In our study, besides these drugs, biologic agents and enzyme therapies were also included. The hospital where this study was performed was a tertiary care referral center for the country, with numerous subspecialist departments that deal with complex illnesses.

Our study showed that antibiotics were the most frequently encountered group of drugs that caused anaphylaxis, but, interestingly, the use of antibiotics was less frequent in the patients with an actual DIA compared with the drug-tolerant group. This was because antibiotics are frequently used and labeled as “allergic,” but the actual antibiotic hypersensitivity is far less frequently confirmed in the pediatric age.^{5,31,32} However, all of the patients who used chemotherapeutics were noted as actually having had drug hypersensitivity according to the results of the present study, which further indicated that there may be differences in the capability of certain groups of drugs to elicit anaphylaxis.

One of the interesting findings of this study was the variation in the period of onset of the symptoms after

the culprit drug intake among different drug groups, which revealed that the major difference was between NSAIDs and antibiotics. All the patients with actual NSAID hypersensitivity had taken the drug orally, and there were participants who were NSAID hypersensitive who experienced the DIA 2 hours after the drug administration. However, there might be other factors that influenced the time of onset of the symptoms other than the route of administration of the drug because, although the majority of the patients who underwent chemotherapeutics received the drug parenterally, the time of onset of symptoms was later than that of the patients who took antibiotics orally. The predominant reason for this difference was the slower administration of chemotherapeutic infusions compared with antibiotic infusions. There seemed to be a threshold dose of the culprit drug for the onset of symptoms in anaphylactic reactions, therefore, for slower infusions, more time is needed until the cumulative threshold dose is reached.³³

The influence of atopy and allergic diseases, including asthma, on DHRs has frequently been studied, and even severe reactions were not reported to be associated with these conditions.^{34,35} In the present study, asthma and other allergic conditions were also not shown to have an impact on the patients with an actual DIA when compared with the patients without an actual DIA. Indeed, the prevalence of asthma was similar between the drug-tolerant and drug-hypersensitive groups, which resembled the actual rate established in an International Study of Asthma and Allergies in Childhood study conducted in Turkey.³⁶ In addition, in another study in which all the children and adolescents referred due to anaphylaxis were investigated, it was shown that atopic diseases were common in patients with food-induced anaphylaxis but not in patients with hymenoptera sting anaphylaxis.⁷ Therefore, the ethnicity and different triggers of anaphylaxis seemed to have an effect on this issue, and more studies are needed to compare various types of allergens.

One of the strengths of this study was the thorough evaluation of the participants with further diagnostic tests, which may not be the primary issue of concern in other studies. In the study by Faria *et al.*,³⁰ a diagnosis of DIA was based on the medical history of the participants. Although some of the patients had recurrence of anaphylaxis to the same drug, which strengthened the diagnosis of DHR based on the history, this situation was valid only for a minority of the patients. It is important to note that all of the participants would not have had actual drug hypersensitivity if further diagnostic tests were performed.³⁰ In other studies that reported provocation tests, although STs were performed with the culprit drug, provocation tests were often conducted to find a safe alternative.^{9,34}

In our study, the majority of the patients were tested with STs and/or provocation tests with the culprit drug, only participants with a history of severe anaphylaxis were not tested further. At the end of the diagnostic evaluation of all the patients, 29 (25.7%) were found to be drug tolerant. Therefore, we believed that our method increased the accuracy of our findings on anaphylactic drug reactions. However, when a severe anaphylactic reaction, such as anaphylactic shock, suffocating laryngeal angioedema, or severe bronchospasm, is induced by a certain drug in the history of the patients, the benefit-to-risk ratio of diagnostic testing should be carefully appraised for each individual. Such patients would not need to be challenged with the culprit drug as in the case of another study,⁹ and severe anaphylaxis is labeled as a contraindication according to the guidelines.¹⁹ One may think that there would be referral bias that might influence the results of our study, which may be considered as a limitation; however, Hacettepe University is a tertiary referral center located in central Anatolia and receives patients not only from the local environment but also from various parts of Turkey. Therefore we believe that the results of our study reflected the situation in Turkey.

CONCLUSION

Three-fourths of the children and adolescents with a history of presumed DIA referred to our medical center were found to actually be drug hypersensitive. Prediagnosed known systemic illness and different types of drugs would have an impact on the risk of DIA; however, atopic disease or a family history of drug hypersensitivity did not have an impact on actual DIA. In addition, there may be age- and time-related differences for the onset of anaphylactic reactions in comparison with various groups of culprit drugs. As survival and continual use of drugs increase in chronic diseases during childhood, pediatricians will frequently face severe DHRs; therefore, pediatricians should improve their knowledge about DIA, concerning risk factors, and different presentations.

REFERENCES

1. Gomes ER, and Demoly P. Epidemiology of hypersensitivity drug reactions. *Curr Opin Allergy Clin Immunol* 5:309–316, 2005.
2. Demoly P, Adkinson NF, Brockow K, et al. International consensus on drug allergy. *Allergy* 69:420–437, 2014.
3. Cavkaytar O, Arik Yilmaz E, Karaatmaca B, et al. Different phenotypes of non-steroidal anti-inflammatory drug hypersensitivity during childhood. *Int Arch Allergy Immunol* 167:211–221, 2015.
4. Grabenhenrich LB, Dolle S, Moneret-Vautrin A, et al. Anaphylaxis in children and adolescents: The European Anaphylaxis Registry. *J Allergy Clin Immunol* 137:1128–1137.e1, 2016.
5. Rubio M, Bousquet PJ, Gomes E, et al. Results of drug hypersensitivity evaluations in a large group of children and adults. *Clin Exp Allergy* 42:123–130, 2012.

6. Muraro A, Roberts G, Worm M, et al. Anaphylaxis: Guidelines from the European Academy of Allergy and Clinical Immunology. *Allergy* 69:1026–1045, 2014.
7. Hoffer V, Scheuerman O, Marcus N, et al. Anaphylaxis in Israel: Experience with 92 hospitalized children. *Pediatr Allergy Immunol* 22:172–177, 2011.
8. de Silva IL, Mehr SS, Tey D, and Tang ML. Paediatric anaphylaxis: A 5 year retrospective review. *Allergy* 63:1071–1076, 2008.
9. Renaudin JM, Beaudouin E, Ponvert C, et al. Severe drug-induced anaphylaxis: Analysis of 333 cases recorded by the Allergy Vigilance Network from 2002 to 2010. *Allergy* 68:929–937, 2013.
10. Demoly P, Kropf R, Bircher A, and Pichler WJ. Drug hypersensitivity: Questionnaire. EAACI interest group on drug hypersensitivity. *Allergy* 54:999–1003, 1999.
11. Simons FE, Arduoso LR, Bilo MB, et al. World Allergy Organization anaphylaxis guidelines: Summary. *J Allergy Clin Immunol* 127: 587–593.e1–22, 2011.
12. Muraro A, Roberts G, Clark A, et al. The management of anaphylaxis in childhood: Position paper of the European Academy of Allergology and Clinical Immunology. *Allergy* 62:857–871, 2007.
13. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 63(suppl. 86):8–160, 2008.
14. Global Strategy for Asthma Management and Prevention. (updated 2015). Available online at <http://www.ginasthma.org/>; accessed May 12, 2015.
15. Brockow K, Garvey LH, Aberer W, et al. Skin test concentrations for systemically administered drugs—An ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy* 68:702–712, 2013.
16. Soyer OU, Aytac S, Tuncer A, et al. Alternative algorithm for L-asparaginase allergy in children with acute lymphoblastic leukemia. *J Allergy Clin Immunol* 123:895–899, 2009.
17. Song WJ, Kim MH, Lee SM, et al. Two cases of h(2)-receptor antagonist hypersensitivity and cross-reactivity. *Allergy Asthma Immunol Res* 3:128–131, 2011.
18. Gomez E, Blanca-Lopez N, Torres MJ, et al. Immunoglobulin E mediated immediate allergic reactions to dipyrone: Value of basophil activation test in the identification of patients. *Clin Exp Allergy* 39:1217–1224, 2009.
19. Brennan PJ, Rodriguez Bouza T, Hsu FI, et al. Hypersensitivity reactions to mAbs: 105 desensitizations in 23 patients, from evaluation to treatment. *J Allergy Clin Immunol* 124:1259–1266, 2009.
20. Kim J, Park MR, Kim DS, et al. IgE-mediated anaphylaxis and allergic reactions to idursulfase in patients with Hunter syndrome. *Allergy* 68:796–802, 2013.
21. Madrigal-Burgaleta R, Berges-Gimeno MP, Angel-Pereira D, et al. Hypersensitivity and desensitization to antineoplastic agents: Outcomes of 189 procedures with a new short protocol and novel diagnostic tools assessment. *Allergy* 68:853–861, 2013.
22. Tayman C, Mete E, Catal F, and Akca H. Anaphylactic reaction due to cyclopentolate in a 4-year-old child. *J Investig Allergol Clin Immunol* 20:347–348, 2010.
23. Bégin P, Chapdelaine H, Lemyre E, et al. Successful desensitization in a type VI mucopolysaccharidosis patient with probable IgE-mediated allergy to galsulfase [Naglazyme]. *Ann Allergy Asthma Immunol* 110:55–56, 2013.
24. Messaad D, Sahla H, Benahmed S, et al. Drug provocation tests in patients with a history suggesting an immediate drug hypersensitivity reaction. *Ann Intern Med* 140:1001–1006, 2004.
25. Aberer W, Bircher A, Romano A, et al. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: General considerations. *Allergy* 58:854–863, 2003.
26. Nizankowska-Mogilnicka E, Bochenek G, Mastalerz L, et al. EAACI/GA2LEN guideline: Aspirin provocation tests for diagnosis of aspirin hypersensitivity. *Allergy* 62:1111–1118, 2007.
27. Topal E, Celiksoy MH, Catal F, et al. The value of the clinical history for the diagnosis of immediate nonsteroidal anti-inflammatory drug hypersensitivity and safe alternative drugs in children. *Allergy Asthma Proc* 37:57–63, 2016.
28. Guvenir H, Dibek Misirlioglu E, Vezir E, et al. Nonsteroidal anti-inflammatory drug hypersensitivity among children. *Allergy Asthma Proc* 36:386–393, 2015.
29. Aun MV, Blanca M, Garro LS, et al. Nonsteroidal anti-inflammatory drugs are major causes of drug-induced anaphylaxis. *J Allergy Clin Immunol Pract* 2:414–420, 2014.
30. Faria E, Rodrigues-Cernadas J, Gaspar A, et al. Drug-induced anaphylaxis survey in Portuguese Allergy Departments. *J Investig Allergol Clin Immunol* 24:40–48, 2014.
31. Gomes ER, Brockow K, Kuyucu S, et al. Drug hypersensitivity in children: Report from the pediatric task force of the EAACI Drug Allergy Interest Group. *Allergy* 71:149–161, 2016.
32. Seitz CS, Brocker EB, and Trautmann A. Diagnosis of drug hypersensitivity in children and adolescents: Discrepancy between physician-based assessment and results of testing. *Pediatr Allergy Immunol* 22:405–410, 2011.
33. Yun J, Mattsson J, Schnyder K, et al. Allopurinol hypersensitivity is primarily mediated by dose-dependent oxypurinol-specific T cell response. *Clin Exp Allergy* 43:1246–1255, 2013.
34. Jares EJ, Baena-Cagnani CE, Sanchez-Borges M, et al. Drug-induced anaphylaxis in Latin American countries. *J Allergy Clin Immunol Pract* 3:780–788, 2015.
35. Banerji A, Rudders S, Clark S, et al. Retrospective study of drug-induced anaphylaxis treated in the emergency department or hospital: Patient characteristics, management, and 1-year follow-up. *J Allergy Clin Immunol Pract* 2:46–51, 2014.
36. Saraclar Y, Sekerel BE, Kalayci O, et al. Prevalence of asthma symptoms in school children in Ankara, Turkey. *Respir Med* 92:203–207, 1998. □

Copyright of Allergy & Asthma Proceedings is the property of OceanSide Publications Inc. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.