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Evaluation of Re-Exposure to Culprit Drug and Occurrence of Reactions in Children with Drug Allergy

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ABSTRACT

Objective: Patients diagnosed with drug allergy should be carefully instructed to avoid using the culprit drug and provided with drug allergy passports to alert healthcare providers. However, accidental re-exposure to the offending drug may occur.

To determine the rate of re-exposure to culprit drugs in patients diagnosed with drug allergy and the characteristics of reactions they experienced.

Materials and Methods: Patients who were diagnosed with drug allergy confirmed with diagnostic tests in the Pediatric Allergy Clinic between 2010 and 2020 were contacted by phone to obtain information on re-exposure to the offending drug after diagnosis and to determine whether the drug reuse was associated with any reaction.

Results: A total of 92 patients with confirmed drug allergy who were contacted by phone were included in the study. The mean age of the study patients was 152 months (range, 108-204) and 54.3% (n=50) of the patients were female. Culprit drugs were antibiotics in 68.5% (n=63), NSAIDs in 23.9% (n=22), antiepileptics in 4.3% (n=4), and other drugs in 3.3% (n=3) of the patients. All of the patients reported that they carry a drug allergy passport at all times and informed the physician about their drug allergy during an examination. Three of the study patients were re-exposed to the culprit drug and two of them had developed a reaction. One had urticaria and the other experienced anaphylaxis after re-exposure.

Conclusion: Patients with confirmed drug allergy should be advised to avoid re-exposure to the culprit drug and to carry their drug allergy passports at all times to alert physicians when they are prescribing a drug treatment.

Keywords: Confirmed drug allergy, re-exposure, child, NSAID, drug allergy passport

AEDs: Antiepileptic drugs, **AGEP:** Acute generalized exanthematous pustulosis, **COX:** Cyclooxygenase, **DAIG:** Drug Allergy Interest Group, **DPTs:** Drug provocation tests, **DRESS:** Drug reaction with eosinophilia and systemic symptoms, **EAACI:** European Academy of Allergy and Clinical Immunology, **ENDA:** European Network of Drug Allergy, **MDM:** Minor determinant mixture, **MPEs:** Maculopapular eruptions, **NECD:** Nonsteroid exacerbated cutaneous disease, **NERD:** Nonsteroid exacerbated respiratory disease, **NIUA:** Nonsteroid induced urticaria/angioedema, **NSAIDs:** Nonsteroidal anti-inflammatory drugs, **PPL:** Penicilloyl-polylysine, **SJS:** Stevens-Johnson syndrome, **SPT:** Skin prick test, **TEN:** Toxic epidermal necrolysis

INTRODUCTION

It has been estimated that adverse drug reactions account for 3-6% of all hospitalizations and occur in 10-15% of hospitalized patients (1,2). The prevalence of drug allergies among children reported by cross-sectional, survey-based screening studies from different countries ranges from 2.8 to 7.8% (3,4). However, when evaluated further using detailed tests, drug allergy could be confirmed in only 1-5% of these patients (3-5). Common culprit drugs causing drug allergies in children

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include antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), antiepileptic drugs (AEDs), and vaccines (6,7). Immediate hypersensitivity reactions to penicillin are the leading cause of allergic reactions to drugs, which are IgE-mediated drug reactions (8). In children, cutaneous symptoms, particularly maculopapular eruptions (MPEs), are the most commonly reported reactions (4,9,10). Although drug-related MPEs are usually non-serious reactions, they are occasionally followed by the development of more severe reactions such as Stevens-Johnson syndrome (SJS)/Toxic epidermal necrolysis (TEN) or drug reaction with eosinophilia and systemic symptoms (DRESS). Drug provocation tests (DPT) remain the "gold standard" method for definitive diagnosis of drug allergies (2,11). While a positive DPT result is diagnostic for drug allergy, a negative result largely rules it out.

The primary approach for the management of drug allergies is avoidance of the offending drug. Patients diagnosed with drug allergy should be carefully instructed to avoid using the culprit drug and provided with drug allergy passports to alert healthcare providers. However, accidental re-exposure to the offending drug may occur. In drug allergies, tolerance may develop over time, especially in those involving IgE-mediated reactions. It is well known that tolerance development naturally occurs in children with food allergy, particularly in children with milk and egg allergies, and the majority of children become tolerant by the age of 5 years (12). Data on the natural history of drug allergy are scarce. Loss of sensitivity over time has been demonstrated for *in vitro* tests (specific IgE or basophil activation test) as well as skin tests in IgE-mediated immediate reactions to beta-lactams (13). However, it is still uncertain whether diminished sensitivity is associated with the development of tolerance.

The current study aimed to determine the rate of re-exposure to offending drugs in patients with drug allergy confirmed by allergologic work-up and the type of reactions they experienced.

MATERIALS and METHODS

A total of 176 pediatric patients who presented to our clinic between 2010 and 2020 with suspected drug allergy and whose diagnosis was confirmed by allergologic work-up were identified. Among them, 92 patients who could be contacted by phone were included in the study. Patient data were reviewed retrospectively. The questions included in the standardized drug hypersensitivity questionnaire developed by the European Academy of Allergy and Clinical Immunology (EAACI)/European Network of Drug Allergy (ENDA) were checked against the patient files (14). Demographic characteristics (age, sex), the drug responsible for the allergy, features of the allergic reaction (time and type), the diagnostic tests used, and reactions occurring at the time of the diagnostic tests were recorded.

The study patients were contacted by phone and questioned whether they used the culprit drug(s) again after the diagnostic tests, and if yes, when they used them and whether re-exposure to the drug was associated with any reactions, and if yes, the nature and type of reaction(s). The study protocol was approved by the local ethics committee of the local institute (approval number: E2- 21 -339) and written informed consent was obtained from the parents.

Diagnostic Tests

Skin Tests

Skin Prick and Intradermal Tests

Skin prick and intradermal tests with the drug were conducted for patients with a suspected IgE-mediated reaction. The drugs were tested on the forearm skin using the prick method. A wheal size ≥3 mm larger than the negative control at 20 minutes post-injection was considered positive. Intradermal tests were performed if the skin prick test (SPT) was negative. Injectable formulations of the drugs were administered at the maximal non-irritant dose intradermally and readings were taken at 20 minutes post-injection. Histamine 10 mg/mL was used as positive control and 0.9% NaCl as negative control. The penicillin test kit; penicilloyl-polylysine (PPL), minor determinant mixture (MDM), penicillin G (10.000 IU/mL), and injectable forms of other suspected drugs were used in the SPT for penicillins.

Patch tests

Patch tests were performed for delayed mild cutaneous adverse drug reactions (maculopapular exanthema, contact dermatitis, fixed drug eruption and severe cutaneous drug reactions (AGEP (acute generalized exanthematous pustulosis), DRESS, TEN, SJS). Patients presenting with DRESS and SJS/TEN at least 6 weeks following the drug reaction underwent patch tests at least 6 months later. Powder vial forms or tablet forms of the suspected drugs were chosen and mixed with white petroleum jelly to obtain concentrations of 5%, 10%, and 30%. Patches were

applied on the upper back, over the upper middle of the scapula, and taped in place. The patches were examined at 48 and 72 hours. The presence of erythema, indurations and vesicles was considered as a positive test result.

Drug Provocation Tests

In patients with negative SPT and intradermal test results, Drug Provocation Tests (DPTs) were performed at least 4-6 weeks following the reaction. Drug provocation tests were not conducted for patients with a history of severe cutaneous drug reactions. In recent years, direct drug provocation testing has been performed for patients with mild cutaneous reactions (maculopapular rash, delayed urticaria) in line with latest approaches and guidelines (15). DPTs were conducted with emergency resuscitation equipment available and under the supervision of a pediatric allergist as recommended by the ENDA guidelines. The age- and weight-adjusted daily dose of the suspected drug was administered orally in 4 -5 divided doses, with dose increases at 30-minute intervals (16).

DPT was discontinued and considered positive in the case of any objective clinical signs including urticaria, rash, angioedema, hypotension, protracted vomiting, cough, and wheezing. All patients were monitored in the clinic for at least 2 hours following administration of the last dose. If no reaction was observed in the clinic, the patients continued to receive the calculated daily doses of the drug for 4 more days at home and the parents were advised to return to the clinic upon the development of any reaction at home.

Statistical Analyses

The SPSS for Windows software package, version 22 (IBM, Chicago, IL, USA) was used for statistical analyses. Discrete variables were reported as numbers and percentages. Continuous variables were expressed as mean and standard deviation for normally distributed data, and median and interquartile range (IQR) for non-normally distributed data.

RESULTS

A total of 176 patients with drug allergy confirmed by allergologic work-up were identified through a review of 10-year data, and 92 patients who could be contacted by phone were included in the study (Figure 1). The mean age of the study patients was 12.6 years (range, 9-17), and 54.3% (n=50) of the patients were female. The mean age at the time of initial drug reaction was 8 years (range 0.25-17 years; IQR, 4.5-11) and the median age at diagnosis was 8.5 years (IQR, 5.9-13). The median time from diagnosis to telephone contact was 2.8 years (IQR:1.8-6.8).

Culprit drugs were antibiotics in 68.5% (n=63), NSAIDs in 23.9% (n=22), antiepileptics in 4.3% (n=4), and other drugs in 3.3% (n=3) of the patients (Table I). Among the drug reactions, 73 (79.3%) were immediate-type and 19 (20.7%) were delayed-type reactions. Of patients with delayed reactions, 6 had severe a drug hypersensitivity reaction that was confirmed by a patch test (DRESS (n=2), SJS (n=3), AGEP (n=1)). In the 92 patients, the diagnosis of drug allergy was confirmed by the oral provocation test (OPT) in 65.2% (n=60) while 23 of them underwent OPT without prior skin testing and 37 of them had positive OPT despite negative skin test results. The diagnosis of drug allergy was confirmed by an intradermal test in 19.6% (n=18), skin prick test in 6.5% (n=6), and patch test in 8.7% (n=8). All of the patients reported that they carry a drug allergy passport at all times and informed the physician about their drug allergy during an examination.

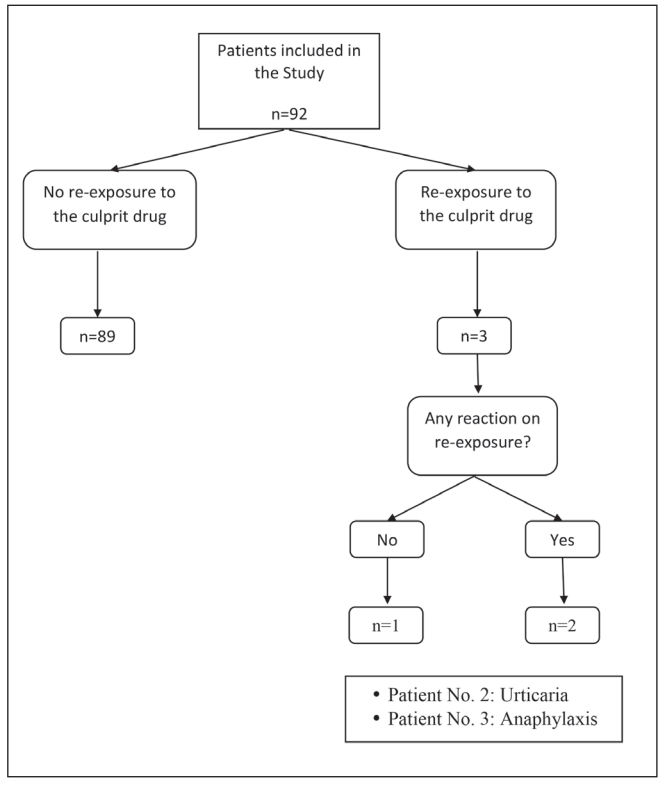

Figure 1. Study flow diagram.

Three of the study patients were re-exposed to offending drugs and 2 of them developed hypersensitivity reactions. Drug allergy was diagnosed using a provocation test in all 3 patients (Table II).

The patient (a 13-year-old boy) who did not experience further reaction on re-exposure to the culprit drug had a diagnosis of asthma and recurrent urticaria. The patient had a history of angioedema with ibuprofen (within one hour) at 6 years of age. He underwent a provocation test with ibuprofen at 8 years of age and showed decreased FEV_1 on pulmonary function test and developed angioedema. The angioedema regressed after giving antihistamine to the patient, and FEV1 resolved spontaneously without the need for a bronchodilator. A provocation test with paracetamol was planned for the patient, but it was not performed because he had urticaria at the time and later the patient did not come for the OPT. The patient was exposed to the offending drug 24 months after the diagnosis without developing any reaction.

Of the 2 patients who had a reaction on re-exposure to the culprit drug after the diagnosis, one (a 9-year-old boy) had a history of urticaria and angioedema with oral amoxycillin-clavulanate at 1 year of age. He had these reactions on the first day of medication 30 minutes after first dose. He developed urticaria following a provocation test with amoxycillin-clavulanate at the age of 1.5 years. No reaction was observed in the cefuroxime provocation test that was performed for finding a safe drug. At 90 months after the diagnosis, amoxycillin-clavulanate was prescribed by a physician and he experienced an urticarial reaction as a result of re-exposure to the drug. The other patient (a 17-year-old girl), developed widespread urticarial and hoarse voice following the administration of paracetamol at the age of 8, and this was considered to due to anaphylaxis and adrenaline was administered. Urticaria and itching developed during the provocation test 6 months after the reaction. No reaction was observed in the ibuprofen provocation test that was performed to find a safe drug. Eighteen months after diagnosis, she developed urticaria and dyspnea during the infusion of IV paracetamol.

Table I: Culprit drugs.

Allergy triggers	n	%
Antibiotics	63 /92	68.5
Aminopenicillin	38	
Cephalosporins	23	
Vancomycin	1	
Trimethoprim/sulfamethoxazole	1	
NSAIDs	22 /92	23.9
İbuprofen	13	
Paracetamol	8	
Acetylsalicylic acid	1	
Antiepileptics	4/92	4.3
Midazolam	2	
Carbamazepine	1	
Valproic acid	1	
Other	3/92	3.3
Local anesthetic	1	
Proton-pump inhibitor	1	
Iron preparations	1	

DISCUSSION

In this study, we evaluated 92 patients with a diagnosis of drug allergy confirmed by allergologic work-up for re-exposure after diagnosis. Re-exposure to the suspected drug was found in 3 patients, 2 of whom developed a hypersensitivity reaction: one had urticaria and the other had anaphylaxis during re-exposure.

In drug allergies, clinical manifestations range from maculopapular and urticarial exanthemas to life-threatening reactions such as anaphylaxis and severe cutaneous adverse reactions (SCARs). Maculopapular exanthemas

Table II: Characteristics of the patients with re-exposure to the culprit drug.

No.	Sex	Age (years)	Culprit drug	Age at the initial reaction	Symptom	Age at diagnosis (years)	Diagnostic test	Allergic reaction at the time of diagnosis	Time from diagnosis to re-exposure	Allergic reaction at the time of re-exposure
1	M	13	Ibuprofen	6	Angioedema	8	OPT	Angioedema and FEV1 drop	24 months	None
2	M	9	Amoxycillin-clavulanate	1	Urticaria and Angioedema	4	OPT	Urticaria	90 months	Urticaria
3	F	17	Paracetamol	8	Anaphylaxis	8	OPT	Urticaria	18 months	Anaphylaxis

(MPEs) are most prevalent skin reactions (8,11,12). Immediate cutaneous reactions including urticaria, pruritus, and erythema are also most commonly triggered by beta-lactam antibiotics and NSAIDs (17). Similarly, the most frequent clinical findings of drug allergy in our study were cutaneous symptoms, with urticaria (36.9%, n=34/92) occurring most commonly. Antibiotics are used frequently for treatment during childhood. In accordance with the literature, allergic reactions were most commonly reported with antibiotics (68.5%), followed by NSAIDs (23.9%) in our study. One of our patients experienced urticaria during re-exposure to amoxycilline clavulanate. Finding safe alternatives for antibiotic allergy is important and the unnecessary use of antibiotics for the treatment of infections should be discouraged.

Two of our patients who were re-exposed to the offending drugs had used NSAIDs and one of them had experienced anaphylaxis during re-exposure. Febrile illness is more common in children than adults, and there are also fewer NSAIDs that can be used in children. In Turkey, only paracetamol and ibuprofen preparations are available for children under 12 years of age. Since the alternative drugs are limited, it is very difficult to avoid NSAIDs. It is important to find a safe alternative if possible and the families should be informed about alternative methods. In addition, frequently used cold medicines often contain paracetamol or ibuprofen as active ingredients. The families should be informed and warned about drugs containing active ingredients that can cause allergies.

In our study, one of the two patients who were re-exposed to NSAIDs did not develop any reaction. The patient (a 13-year-old boy) had a diagnosis of asthma and acute recurrent urticaria and he had a history of angioedema with ibuprofen at 6 years of age. He underwent a provocation test with ibuprofen at 8 years of age and showed angioedema and FEV_1 drop on pulmonary function test 2 hours after the last dose. That patient was exposed to the offending drug 24 months after the diagnosis without developing any reaction.

NSAIDs are the most commonly prescribed drugs worldwide (18). The main mechanism of action of NSAIDs is the inhibition of the enzyme cyclooxygenase (COX). Hypersensitivity reactions to NSAIDs have recently been classified by the European Academy of Allergy and Clinical Immunology (EAACI)/European Network of Drug Allergy (ENDA) as follows: 1- Non-immunologically mediated reactions involving cyclooxygenase (COX)-1 inhibition (NSAID-exacerbated respiratory disease (NERD), NSAID-exacerbated cutaneous disease (NECD) and NSAID-induced urticaria/angioedema (NIUA), and existing cross-intolerance to multiple COX-1 inhibitors), 2- immunologically mediated (urticaria, angioedema and/or anaphylaxis and delayed hypersensitivity reactions induced by NSAIDs) (19). Accompanying chronic urticaria and asthma are also considered during the classification. However there is still confusion in categorizing NSAID hypersensitivity, especially for children (19). Our patient had concomitant asthma and chronic urticaria but we could not make a classification as the family did not provide consent for the aspirin provocation test. His underlying asthma may have caused the low FEV1 measurement during OPT. However, he also had angioedema and the test was positive in any case. As far as we could find, there is no data about factors causing false negativity during OPT with NSAIDs. It is also not well known whether NSAID hypersensitivity subsides within time.

Upper respiratory tract infections are common in the pediatric age group, making it is very difficult to avoid drugs. Families may underestimate allergic reactions and be more courageous in re-use especially in the case of drug allergies with mild symptoms such as mild urticaria or maculopapular rash. These patients should be warned more carefully because later reactions can be severe even if the first reaction is a mild reaction.

It has been reported that unawareness of the doctor about the patient's drug allergy accounts for 12% of prescription errors (20). Several studies have shown that drug allergies caused by prescription errors could be avoided (21,22). Before prescribing or administering any medication, patients should be questioned about previous drug reactions and the medical records should be reviewed for any notes on prior drug allergy. Cross-reactivity between drugs should be considered in patients with a history of allergy. To prevent drug allergies, it is crucial to educate patients or parents about the severity of drug allergies, drugs that are responsible for the reaction, and cross-reacting drugs. Providing appropriate information is important to encourage patients to report their allergic status. A written document (e.g., drug allergy passport, allergy certificate) including the names of the drug(s) to avoid, alternative drugs to prescribe, and the contact information of the medical center to consult in the case

of an emergency should be handed to the parents (23). The Position Paper published by the ENDA/EAACI Drug Allergy Interest Group (DAIG) in 2016 has recommended using a standardized drug allergy passport and/or a drug allergy alert card to increase awareness of drug allergy and to minimize prescription errors while emphasizing to the patients the importance of having this information available at all times (23). Children with confirmed drug allergy may be advised to wear a medical alert bracelet (24). At our clinic, drug allergy passports meeting these criteria are issued to patients and the importance of carrying a drug allergy passport is explained. We found that 96.7% (89/92) of our patients were not re-exposed to the culprit drug and did not experience any reactions. The results suggest that these practices prevented re-use of the offending drugs in the majority of our patients. A total of 176 patients with confirmed drug allergy were identified, and only 52.2% of them (n=92) could be contacted by phone; these patients were included. The fact that we could not reach nearly half of the patients is the limitation of this study. However, the diagnosis of all the patients in the study were confirmed by allergologic work-up and follow-up with a median period of 2.8 years, which is a long period for evaluating re-exposure. These are the strong parts of our study and we think that our data sheds light on this subject where there is there is limited data.

CONCLUSION

It would seem reasonable to conclude that patients with severe cutaneous adverse drug reactions should never be re-exposed to the culprit drug and should be advised to avoid re-exposure and also to carry their drug allergy passports at all times to alert physicians when they are prescribing a drug treatment.

For those with IgE-mediated reactions, reevaluation with skin testing and, if negative, oral challenge may be indicated if sufficient time has passed and the drug is required in the future, and for those with a history of mild and late onset rashes, re-exposure can be considered along with monitoring for any recurrence or worsening of the rash.

Conflict of Interest

None.

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Authorship Contributions

Concept: **Kezban Ipek Demir, Emine Dibek Misirlioglu,** Design: **Kezban Ipek Demir, Sule Buyuk Yaytokgil,** Data collection or processing: **Sule Buyuk Yaytokgil, Betul Karaatmaca,** Analysis or Interpretation: **Kezban Ipek Demir, Ersoy Civelek,** Literature search: **Kezban Ipek Demir, Betul Karaatmaca,** Writing: **Kezban Ipek Demir, Muge Toyran,** Approval: **Muge Toyran, Emine Dibek Misirlioglu.**

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