

# Cutaneous drug reactions in children: a multicentric study

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## Abstract

**Introduction:** According to studies conducted in outpatients, it is estimated that 2.5% of children who are treated with a drug will experience a cutaneous adverse drug reaction (CADR).

**Aim:** To analyze the CADR reports involving pediatric patients recorded by three different university hospitals for describing common, serious, and interesting cutaneous drug eruption patterns.

**Material and methods:** For this purpose, the patients' data from three different universities were reviewed retrospectively. Diagnosis was based on history, clinical findings and laboratory test results. The CADRs were classified into seven categories; urticaria, angioedema, maculopapular eruption, fixed drug eruption, erythema multiforme, acute generalized exanthematous pustulosis, drug rash with eosinophilia and systemic symptoms syndrome.

**Results:** A total of 122 patients who had CADRs were enrolled in the study. The most frequently detected cutaneous drug reactions were urticaria + angioedema. Most of patients had no previous experience with the same drug and the most common causative agent of CADRs was antimicrobials.

**Conclusions:** Since CADRs are relatively rare, the current multicentric study can provide meaningful information about the cutaneous eruption patterns of commonly used drugs.

**Key words:** drug, allergy, cutaneous, children.

## Introduction

Adverse drug reaction (ADR) is defined by the World Health Organization (WHO) as a response to a medicine which is noxious and unintended, and which occurs at doses normally used in a man [1]. Cutaneous adverse drug reaction (CADR) may be defined as an undesirable manifestation of the skin resulting from administration of a particular drug and CADRs are a commonly reported type of ADRs [2, 3]. The incidence of ADRs in hospitalized pediatric patients is 9.53% [4]. However drug metabolism differs in young children and information on efficacy and toxic effects of drugs is rarely available [5]. The correlation between drug use in children and incidence of ADRs has been a matter of growing awareness in several recent studies [4]. Another important issue with ADRs is that drug eruptions, which are a frequent diagnostic

problem for the clinician in an outpatient clinic, commonly have to be differentiated from a viral exanthema [2].

## Aim

In this study, we present the analysis of CADR reports involving pediatric patients (16 years or younger) recorded by three different university hospitals for describing common, serious, and interesting cutaneous drug eruption patterns in a practical manner.

## Material and methods

The present study was approved by the Ethics Committee of the Medical Faculty of Recep Tayyip Erdoğan University. The patients' data from three different universities were reviewed retrospectively. Patients in whom

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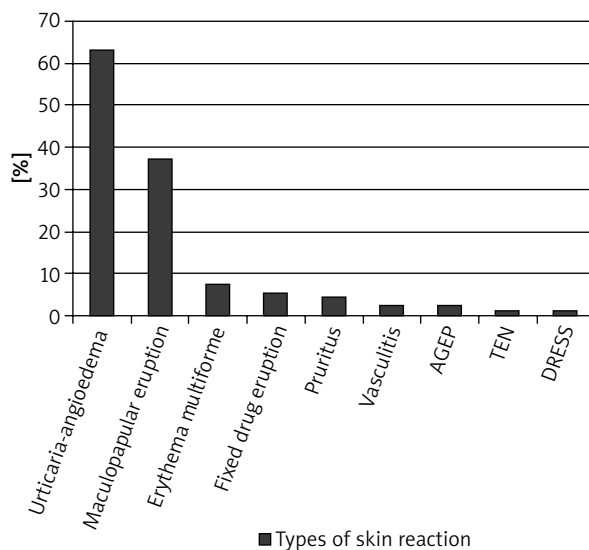
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no medication was given, older than 16 years old and patients with eruption compatible with a viral exanthem were excluded from the study. The data, collected from the subjects were age, sex, implicated drugs, indication of use, time of onset, morphology, type of skin eruption, distribution and duration of the rash, previous experience with the drug, presence of interacting diseases, other drugs or clinical conditions (i.e. infections, cancer, asthma, concomitant drugs, food or drug allergies) and laboratory test results. Diagnosis was based on history, clinical findings and laboratory test results (including complete blood count, serum IgE levels, skin tests and biopsy if needed). In a review of clinical history, the criteria reported by Naranjo *et al.* were taken into account in causality assessments of drugs [3]. The CADRs were classified into 7 categories: urticaria, angioedema, maculopapular eruption, fixed drug eruption, erythema multiforme, acute generalized exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms syndrome (DRESS).

## Results

After applying the exclusion criteria, a total of 122 patients (aged 16 years and under) who had CADRs were enrolled the study. Of the 122 patients, 52 were female and 70 were male. The age of patients ranged between 1 and 16 years (mean age:  $1.99 \pm 0.76$  (standard deviation)). The most frequently detected cutaneous drug reactions were urticaria + angioedema (51.6%), maculopapular drug eruptions (30.3%) and erythema multiforme (5.7%) (Figure 1).

An important finding of our study is that the most of patients had no previous experience and only 21 patients had a family history. Seventeen patients were diagnosed



**Figure 1.** Types of cutaneous drug reactions

by biopsy; most of these patients had DRESS and AGEP. Most of the patients were treated as outpatients (90 patients). Table 1 shows the demographic and clinical data of all patients.

According to our study, urticaria, angioedema, and maculopapular eruption was the most common forms of CADRs and the most common causative agent of CADRs was antimicrobials, analgesic, anti-inflammatory and antipyretic drugs. Table 2 shows forms of cutaneous adverse drug reactions and causative agents.

## Discussion

According to studies conducted in outpatients, it is estimated that 2.5% of children who are treated with a drug, and up to 12% of children treated with an antibiotic will experience a CADR [3]. Considering the age-related problems of children in drug metabolism (relative liver size, liver blood flow, extent of protein binding and the maturation of drug metabolizing enzymes), the above figures are really worrying [6, 7]. Drug allergy not only affects the patient's quality of life, it may also lead to delayed treatment, use of suboptimal alternative medications, unnecessary investigations and even death [8]. The skin is the organ most frequently and prominently affected by drug-induced allergic reactions and various genetic and environmental factors may predispose to these allergic reactions and at least 29 drug-related cutaneous reaction patterns have been reported [3, 8–10]. Drug hypersensitivity reactions can be classified as immediate (occur within 1 h) or non-immediate (more than 1 h) according to the time interval between the last drug administration and onset. Type-I (IgE-mediated) and type-IV (T cell-mediated) pathogenic mechanisms are involved in most immediate and non-immediate reactions, respectively. Usually immediate reactions are manifested clinically by urticaria, angioedema, rhinitis, bronchospasm, and anaphylactic shock, non-immediate reactions manifested by maculopapular rashes. But the later studies have shown that these reactions seem to

**Table 1.** Demographic and clinical data of all patients

Variable	Result
Gender	52 females, 70 males
Age, mean $\pm$ SD	$1.99 \pm 0.76$
Previous adverse drug reaction history with the same drug	4 patients
Previous adverse drug reaction history with different drugs	10 patients
Family history	21
Number of biopsies	17
Place of treatment	90 (outpatients), 32 (hospital)

**Table 2.** Forms of cutaneous adverse drug reactions and causative agents

Drugs	Adverse drug reaction								
	UAO	MPE	Pruritus	FDE	Vasculitis	EM	AGEP	TEN	DRESS
Antibiotics (n = 56):									
Penicillin and its derivatives	23	11				2			
Cephalosporins	3	1		1			1		
Quinolones		2							
Macrolides	2					2			
Teicoplanin	1								
Metronidazole	1	1			1				
Trimethoprim-sulfamethoxazole		1				3	1		
AAA (n = 28):									
Acetaminophen	12	2							
Metamizole	2								
Ibuprofen	3	2		3	1				
Scopolamine butyl bromide	1								
Indomethacin	1								
Naproxen	1								
Vitamins and minerals (n = 9):									
Iron	1								
Iron and zinc		1	1	1					
Zinc	1	1							
Multivitamins		2	1						
Anticonvulsants and antipsychotics (n = 7):									
Valproic acid	1	3							1
Oxcarbazepine		1							
Risperidone	1								
Vaccines (n = 6):									
Influenza vaccine	4		2						
Others (n = 16):									
Radiocontrast agent		1						1	
Antitussive (Dextromethorphan + Pseudoephedrine + Chlorpheniramine)	3	3							
Immune modulator ( $\beta$ -glucan)	2	5							
Laxatives (Lactulose)	1								
Total (n = 122)	63	37	4	5	2	7	2	1	1

UAO – urticaria-angioedema, MPE – maculopapular eruption, FDE – fixed drug eruption, EM – erythema multiforme, AGEP – acute generalized exanthematous pustulosis, TEN – toxic epidermal necrolysis, DRESS – drug rash with eosinophilia and systemic symptoms, AAA – analgesic, anti-inflammatory and antipyretic drugs

be heterogeneous in the pathogenesis of CADR [11]. Five types constitute the vast majority of cutaneous drug eruptions in children. These types are exanthems, fixed drug reactions, urticarial eruptions, serum sickness-like reactions (SSLR), and photosensitive eruptions [12]. Urticaria-angioedema is the most common form of CADR

in our study and mostly caused by antibiotics and analgesic, anti-inflammatory and antipyretic drugs (AAA). Determination of the connection between the drug and cutaneous reactions is very important as infections are associated with the majority of episodes of acute urticaria [3]. This can only be possible with a correct evaluation

of clinical history, clinical and laboratory findings. The decline of lesions after discontinuation of treatment with a suspicious drug may provide an important contribution to efforts in this regard as in our study. While maculopapular eruptions (MPE) are the most frequent pattern of cutaneous drug reactions in other studies, in our study MPEs are the second most common form of CADR and antimicrobials were the most commonly implicated drug [2]. The MPEs are characterized by raised, spotted lesions and originate on the trunk, and eventually spread to the limbs and similar clinical entities may be induced by viruses and immunological mechanisms [8, 13]. In fact, some of our patients (7 patients with maculopapular eruption) had been diagnosed with viral eruption in different centers, therefore discrimination of both entities is very important. In addition to laboratory findings, this information may be useful when making discrimination; viral infections are generally followed by immunological protection, but in drug reactions re-exposure can induce the reaction again [13].

It is reported in the publications that the risk of severe CADR ranges between 1 in 1000 and 1 in 10 000, depending on the kind of reaction and the culprit drug [3]. Severe cutaneous reactions such as AGEP, toxic epidermal necrolysis (TEN) and DRESS were rarely encountered in our study (only 4 cases).

In analysis of drugs which cause CADR, antibiotics were the most common cause of ADRs (45.9%) as in other studies, followed by AAA (22.9%), vitamins and minerals (7.3%), anticonvulsants and antipsychotics (5.7%) [9, 14, 15].

A limitation of our study is that impairment of socio-cultural levels in some patients was hampered by receiving the right clinical history. This situation has created problems especially in learning about previous adverse drug reactions (drug name, type of lesion and so on).

## Conclusions

Since CADR are relatively rare, multicentric studies are required to obtain more data despite some problems in interpretation of data. The current multicentric study is the first comprehensive study on children in our country and provides meaningful information about the cutaneous eruption patterns of commonly used drugs. The authors would like to draw attention that physicians should keep in mind the drug eruption in the differential diagnosis of cutaneous eruption.

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