

Cutaneous drug eruptions in children; a single centre experience

Serap Özmen, Murat Şahin*, Aysel Yöney*, Nilüfer Arda*, Zafer Arslan

Dr. Sami Ulus Obstetrics, Gynecology and Children's Education and Research Hospital, Pediatric Allergy and Asthma Clinic, Ankara, Turkey

*Dr. Sami Ulus Obstetrics, Gynecology and Children's Education and Research Hospital, Ankara, Turkey

Summary

Aim: Cutaneous drug reactions are commonly reported adverse drug reactions. The aim of this study was to describe the clinical pattern of drug eruptions, determine drugs commonly associated with those patterns seen among children and to suggest an approach to this problem.

Material and Method: Patients presenting to Dr. Sami Ulus Obstetrics, Gynecology and Children's Research and Training Hospital, Pediatric Allergy Clinic between May 2006 and May 2007 with suspected drug eruption were prospectively evaluated. One hundred children were enrolled in the study. There were 75 boys and 25 girls with an age range of 6 months to 14 years old (mean 5.6±3.6 years). Statistical analyses were done using SPSS 11.5 package program (SPSS Inc., Chicago, IL). For general information related to variants descriptive statistics and frequency distributions were calculated. While continuously measured variables were shown as mean± SD, categorical variables were expressed as frequency (percentage). The study was approved by the hospital's ethic committee.

Results: The most common indication for using drug therapy was upper respiratory tract infection (64%). The most commonly suspected drugs were amoxicillin/ampicillin in 44% and cephalosporins in 27% of the patients. The types of drug eruption included urticaria (64%), maculopapular eruption (28%), urticaria-purpura (5%), erythema multiforme (1%), fixed drug eruption (1%) and drug hypersensitivity syndrome (1%). While 60% of the patients were diagnosed with probable drug allergy and 16% were diagnosed with possible drug allergy, drug allergy was confirmed only in 18% of the patients who were diagnosed with definite drug allergy.

Conclusions: A detailed drug history, a knowledge of the varied patterns of drug eruptions and appropriate diagnostic tests are essential factors for successful management of a child with drug eruption (*Turk Arch Ped* 2011; 46: 62-6)

Key words: Amoxicillin/ampicillin, children, cutaneous drug eruption, drug hypersensitivity syndrome, erythema multiforme, fixed drug eruption, maculopapular eruption, urticaria

Introduction

Combination of viral eruptions and drug allergy in childhood is a clinical condition which is difficult to follow up and treat. Although the most common reason for cutaneous eruptions in children is viral infection, drugs used during the infection may complicate differential diagnosis, because many infectious agents can cause maculopapular rash and urticaria which are the most commonly seen signs of drug allergy in children (1-3). In addition, early evaluation of cutaneous eruptions is very important for pediatricians in drug reactions which may have a severe

course (4). Very few studies related to drug allergy in children are available in literature written in English and in our country and these are generally published as case reports (5-8). The aim of our study was to investigate the types of drug related cutaneous eruptions in children, drugs most commonly associated with these eruptions and diagnostic methods.

Material and Method

In our prospective study, patients referred to Dr. Sami Ulus Obstetrics, Gynecology and Children's Research

and Training Hospital, Pediatric Allergy Clinic between May 2006 and May 2007 with suspected drug eruption were evaluated. The study was approved by the hospital's ethics committee. Written informed consent was received from the parents and from children whenever appropriate for skin tests for drug related cutaneous reactions and provocation tests. Demographic properties of the subjects including age and gender and drug history were written on a standard form. Type of cutaneous rash, distribution, presence of mucosal and systemic involvement were recorded.

Identification of drug-related eruptions was done as follows:

- Urticaria: presence of transient lesions characterized by itchy, erythematous and edematous papules and plaques with regular borders disappearing in 24 hours.
- Angioedema: swelling of soft tissue with indistinct borders due to subcutaneous invasion of urticaria.
- Maculopapular rash: red unitchy macules or papules which may tend to combine.
- "Fixed" drug eruption: single or multiple, round and red-purple edematous plaques with regular borders.
- Erythema multiforme: red macules showing symmetrical distribution and eruption containing target lesion.

Patients were classified according to diagnostic criteria for drug allergy determined by Sacerdoti et al. (9).

These six criteria are as follows:

1. Presence of a clinical picture compatible with known adverse effects of the suspected drug.
2. Absence of another factor which may cause reaction (if eruption is not caused by exacerbation or recurrence of the underlying disease).
3. Occurrence of suspected drug reaction in the expected time for that drug.
4. Confirming that eruption is not caused by overdose of the drug.
5. Improvement of clinical findings after the drug is stopped.
6. Appearance of eruption when exposed to the suspected drug once again.

Presence of 1-3 criteria was defined as probable drug allergy, presence of 4-5 criteria was defined as possible drug allergy and presence of 6 criteria was defined as "definite drug allergy".

Specific tests were planned for each patient with suspected drug allergy according to the type of cutaneous rash. When Type I hypersensitivity reaction including urticaria/angioedema due to penicillins (phenoxymethyl benzyl penicillin, benzathine penicillin, procaine penicillin) was suspected, specific Immunglobulin E (IgE) was measured. Specific IgE measurements in serum were done by Allerg-O-Liq system of Dr. Focke Laboratorien, GmbH, Germany using "Reversed-Enzyme-Allergo-Sorbent-Test" (REAST) method (Class 0 < 0.35 IU/ml, Class I 0.35-0.7 IU/ml, Class II 0.7-3.5 IU/ml, Class III 3.5-17.5 IU/ml, Class IV 17.5-50 IU/ml, Class V 50-100 IU/ml and Class VI >100 IU/ml).

For type I-mediated reactions prick/intradermal tests were planned for at least 6 weeks after the reaction. Oral provocation was started by giving the commercial dosage form of the drug at a 1/100 dose and the dose was increased gradually with 30-60 minute-intervals to the therapeutic dose which should be taken at one time. For type IV-mediated hypersensitivity reactions including maculopapular and "fixed" drug eruptions patch test was done by using Finn Chamber® with 10% and 30% concentrations.

In addition, complete blood count, peripheral blood smear, liver function tests [including aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP)], renal function tests, acute phase reactants, C-reactive protein (CRP), anti-streptolysin O (ASO) and serologic tests [(Measles, rubella, Epstein-Barr virus, cytomegalovirus, Mycoplasma pneumoniae and hepatitis markers (Hepatitis A-IgM, Hbs Ag, Anti-Hbs, Anti-HCV)] were assessed.

For treatment of drug reactions antihistaminics and/or systemic corticosteroids were given in addition to stopping the suspected drug in all patients.

Statistical Analysis

Statistical analyses were done using SPSS 11.5 package program (SPSS Inc., Chicago, IL). For general information related to variants descriptive statistics and frequency distributions were calculated. While continuously measured variables were shown as mean \pm SD, categorical variables were expressed as frequency (percentage).

Results

Mean age of 100 subjects who were assessed for suspected drug allergy in our division was 5.6 ± 3.6 years (range, 6 months-14 years). 75 of our subjects (75%) were male. 12 of the patients had an additional chronic disease (five acute lymphoblastic leukemia (ALL), six epilepsy and one Wilson disease).

Indications for drug use in the patients are shown in Table 1.

Suspected drugs used by the patients are shown in Table 2. When subjects using multiple drugs were assessed, it was found that 15 subjects used two drugs, six subjects used three drugs and five subjects used four

Table 1. Indications for drug use

Diseases	Number of subjects
Infection	87
URTI*	(64)
Leukemia	5
Rheumatic fever	4
Epilepsy	3
Tuberculosis	3

*URTI; Upper respiratory tract infection

drugs concomitantly (a total of 26 subjects). 75% of the subjects included in the study had used the same drug before. History of similar reaction was present in 33% of the patients who had used the same drug before.

Distribution of suspected drugs by type of eruptions described is shown in Table 3.

When the time of occurrence of eruptions was examined, urticarial rash was seen on the 1-3.rd day in 44 patients, on the 4-7.th day in 14 patients and on the 8-11.th day in 6 patients. None of the twenty subjects who developed urticarial eruption after the 72.nd hour was diagnosed with definitive drug allergy. 14 of these subjects (70%) were diagnosed with probable drug allergy and six (30%) were diagnosed with possible drug allergy.

Time of occurrence of maculopapular eruptions was found to be the first day in 4 subjects, the 2-4.th day in 8 subjects, the 5-7.th day in 8 subjects, the 8-14.th day in 5 subjects and the 15-21.st day in 3 subjects.

In subjects who developed urticaria-purpura, eruptions appeared on the 5-7.th day of drug therapy. Erythema multiforme was seen on the sixth day, "fixed" drug allergy was seen on the first day and drug-related hypersensitivity was seen on the 21.st day.

Forty four of eruptions (44%) were local and 56 were (56%) diffuse. Invasion from the face to the trunk was seen in 65 subjects, invasion from the trunk to the face was seen in seven subjects, invasion from the trunk to the extremities was seen in 6 subjects and invasion from the extremities to the trunk was seen in 22 subjects. Fifteen point three percent of the patients with invasion of eruptions from the face to the trunk were diagnosed with definite drug allergy and 57% of the patients with invasion of eruptions starting from the trunk were diagnosed with definite drug allergy.

Seven of our subjects had high fever and and all had

an underlying infectious disease. Two subjects had symptoms of digestive system and only one subject had respiratory system involvement.

Neutropenia was seen in one subject with infective endocarditis, high transaminase level was seen in two subjects using isoniazid and in one subject followed up with a diagnosis of ALL. Four percent or higher eosinophilia (ranges, 4%-13%) was determined in 18 subjects. Eight of these subjects had maculopapular eruptions and 10 had urticarial eruptions.

Only two subjects had Class II positivity for specific IgE for Penicillin G/V. One patient had positive prick test with penicillin G and positive oral provocation test with penicillin V.

None of the prick tests and intradermal tests performed with amoxycillin, ampicillin and ceftriaxone was positive. Cutaneous patch test was found to be positive in one subject using amoxycillin/clavulanic acid.

Drug provocation test was performed with amoxycillin in 15 patients, with phenoxymethyl penicillin in 5 subjects and with paracetamol in 5 subjects (a total of 25 patients). Provocation with paracetamol was found to be positive in 3 patients.

Cutaneous biopsy was done in 4 subjects with a pre-diagnosis of urticarial vasculitis and in one subject with a prediagnosis of "fixed" drug eruption.

Six of 100 subjects were evaluated as nonspecific

Table 2. Number of patients by suspected drugs

Drugs	Number of subjects
Antibiotics	85
Antituberculosis drugs	3
Antiepileptics	5
L-asparaginase	5
Paracetamol	6
Aspirin	1

Tablo 3. Distribution of drugs by type of eruption

Type of eruption (number of subjects)	Suspected drugs	Number of subjects
Urticaria (angioedema)	(64) Beta-lactam (14) L-Asparaginase Paracetamol	(56) (5) (3)
Maculopapular	(28) Beta-lactam Anticonvulsant Isoniazid	(23) (3) (2)
Urticaria-purpura	(5) Beta-lactam Macrolide	(4) (1)
Erythema multiforme	(1) Beta-lactam	(1)
'Fixed' drug eruption	(1) Paracetamol	(1)
DHS	(1) Isoniazid	(1)

*DHS; Drug hypersensitivity syndrome

Table 4. Number of patients compatible with the definition of drug allergy by cutaneous reaction

Cutaneous eruption	Definite diagnosis	Probable diagnosis	Possible diagnosis	No drug allergy	Total
Urticaria	11	44	8	1	64
Maculopapular	2	13	8	5	28
Urticarial vasculitis	3	2	-	-	5
Erythema multiforme	-	1	-	-	1
Fixed drug eruption	1	-	-	-	1
*DRHS	1	-	-	-	1

*DRHS; Drug related hypersensitivity syndrome

viral eruption. The rest 94 subjects were assessed according to drug allergy diagnostic criteria (9) and 60 subjects were diagnosed with probable drug allergy, 18 subjects were diagnosed with definite drug allergy and 16 subjects were diagnosed with possible drug allergy.

Numbers of subjects defined as definite, probable and possible drug allergy according to the type of eruption are shown in Table 4.

Five percent of the study subjects had a history of atopic disease and 10% of the study subjects had a history of familial drug allergy.

For treatment of skin reactions all subjects were given antihistaminic agents in addition to stopping the suspected drug. Short-term systemic steroids were used in 8 patients.

Desensitization was performed in 9 subjects (with L-asparaginase in 5 subjects, with imipenem in one subject and with isoniazid in 3 subjects).

Discussion

Allergic drug reactions constitute 6-10% of all drug reactions. The most commonly seen adverse drug reactions are in the form of cutaneous reactions (10,11). Allergic drug reactions are observed in approximately 1.5-3% of patients referring to hospitals and in 10-20% of patients hospitalized (12-15).

Mean age of the subjects suspected to have drug allergy was 5.6 ± 3.6 years and 60% were 6 years old or younger. In a study performed by Rebelo Gomes et al. (7) about drug allergy in children, 51% of the subjects were found to be 2 years old or younger. In our study, 75% of the subjects were male. The 3 fold higher ratio of male patients was compatible with the literature (5,16). However, predominance of female gender is seen in studies performed in adults (17). Gender difference was found to be insignificant in a study performed in children (7).

The most prevalent indication for drug use in our subjects was infection with rate of 87%. Among these, upper respiratory infection was the most common cause (74.7%) and the most commonly used drugs were antibiotics (85%). Compatible with the literature, the most commonly used antibiotics were beta lactam group antibiotics (ampicillin/amoxycillin with rate of 44%) (5,18,19).

We were informed that the same drug was used before in 75% of our subjects and similar reaction developed in 33% of these. This shows the importance of questioning detailed history of drug allergy before prescribing any drugs. In addition, intermittent and repeated drug usage is known to cause sensitization with a higher rate (20). In the study performed by Cetinkaya and Cag (21), frequent usage of beta lactam antibiotics was seen to lead to sensitization.

In a study conducted about drug allergy, rates of suspected drugs were as follows in subjects with urticarial eruptions: beta lactams 42%, diclofenac 31%, erythromycin 14% and paracetamol 13% (5). The most com-

monly used beta lactam antibiotic in our subjects with urticaria was from ampicillin/amoxycillin group (41.8%). Only two of our subjects suspected of having beta-lactam allergy had Class II positivity for penicillin G/V specific IgE measurement which constitutes one of the specific in vitro tests. In our study, drug provocation test was done with amoxycillin in 15 patients, with phenoxymethyl penicillin in 5 patients and with paracetamol in 5 patients. The test was found to be positive with paracetamol in only 3 patients (12%).

Maculopapular eruptions were the second most commonly seen type of rash (28%). In our study, 98.5% of patients whose eruptions started from the face were found not to fulfill criteria for definitive drug allergy. This finding is compatible with the fact that viral eruptions tend to start predominantly from the face (22). In maculopapular reactions, patch test and provocation test are recommended for diagnosing drug allergy (23). In our study, patch test was performed in seven subjects and the test was found to be positive only one subject who used amoxycillin/clavulanic acid for upper respiratory tract infection.

Urticaria-purpura was the third commonly seen (5%) cutaneous rash in our subjects. Urticarial vasculitis was considered in the patients with urticaria-purpura. Drugs may be involved in the etiology of vasculitis involving the skin generally caused by type III hypersensitivity reaction (24). For definitive diagnosis biopsy was performed in four subjects and cutaneous biopsy was found to be compatible with urticarial vasculitis in three of them. The antibiotics used by these patients were amoxycillin/clavulanic acid in two subjects and cefaclor in one subject.

In our study, one patient had "fixed" drug eruption and cutaneous biopsy confirmed the diagnosis. "Fixed" drug eruption is considered to be a delayed type reaction mediated by T-cell (Type I) and may be caused by many drugs designated including paracetamol (25).

Erythema multiforme developed in one of our subjects while using amoxycillin. Oral provocation is not recommended in erythema multiforme because of a risk of Stevens-Johnson syndrome/toxic epidermal necrolysis (5). Patch test performed in our subject was found to be negative and a diagnosis of probable drug allergy was made. In one of our subjects, drug-related hypersensitivity had developed on the 21st day of isoniazid treatment.

In literature, hypersensitivity syndrome related to aromatic anticonvulsants (carbamazepine, phenobarbital, phenytoin), sulfonamides and allopurinol has been frequently reported (26).

Forty percent of all drug reactions are observed only as cutaneous eruptions (27). However, drug reactions in children have been reported to have a severe prognosis though rarely (28). Incidence of cutaneous drug reactions (SJS; TEN, anaphylaxis) varies according to the structure of the drug and type of reaction. Incidence of SJS and TEN is 1.5-2 cases per million yearly (11).

According to drug allergy criteria of Sacerdoti et al. (9) 18% of our subjects were diagnosed with definite drug allergy, 60% were diagnosed with probable drug allergy and 16% were diagnosed with possible drug allergy. Six percent of the subjects were considered to be incompatible with the diagnostic criteria. In a study evaluating drug allergies in children younger than 12 years old, 7% of the subjects were diagnosed with definitive drug allergy, 22% were diagnosed with probable drug allergy, 31% were diagnosed with possible drug allergy and 41% were found to be incompatible with drug allergy (5). In a multi-center study performed in Bangkok, 2.8% of the subjects ranging between 2 and 89 years old were considered to have definite drug allergy, 34.4% were considered to have probable drug allergy and 62.7% were considered to have possible drug allergy (29). In contrast to these studies, the higher rate of definite drug allergy in our study may be explained by predominance of urticarial eruption rather than maculopapular eruption.

When patients with a drug allergy mediated by type I hypersensitivity need to receive this specific drug, the drug may be administered via desensitization in the hospital. In our study, a total of 9 subjects were given therapy via desensitization (L-asparaginase for ALL in 5 patients, imipenem for perforated appendicitis in one patient and isoniazid for tuberculosis in 3 patients).

Atopy is not considered to be a risk factor for drug allergy, but it can increase the severity of the reaction (30). In our study, 5% of our subjects had accompanying atopic disease. None of these subjects was diagnosed with definite drug allergy.

Consequently, detailed history should be taken initially from each subject with suspected drug allergy and definitive diagnosis should be made by planning appropriate tests for the type of eruptions. Before completing these investigations, the patients should not be considered to have definite drug allergy. The physician should consider the incidence of drug allergy when prescribing drugs and should prefer drugs with a lower probability of allergy if possible. Considering that viral infections are seen frequently in children and maculopapular eruptions may develop in the course of these infections, avoidance of unnecessary antibiotic prescription should be adopted.

Conflict of interest: None declared

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