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Approach to drug allergies in the childhood

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Abstract

Drug reactions (DR) are adverse or harmful effects of drugs. They constitute 6.5% of all hospital admissions. DR develops with a rate of 15% in patients who are treated by hospitalization. The possibility of DR should be considered in the differential diagnosis when any medical problem occurs in a person who uses medication. Detailed history and physical examination are directive in differentiation, if the reaction is a result of immune mechanisms. Although diagnostic tests are limited, they are beneficial according to the effective immune mechanism and presence of organ-specific or systemic findings. In children, the major difficulty in the diagnosis of DR is differentiation of maculopapular drug eruptions from viral exanthem which is observed very commonly in this age group. In treatment of allergic reactions, the first step is to immediately discontinue the responsible drug. Avoidance of using over-the-counter drugs and use of drugs orally if possible are important in terms of prevention of drug allergies. Cross-reactivity between drugs with similar structure should be considered when choosing an alternative drug. If an alternative drug or a drug which would not lead to cross-reaction can not be found, the drug is administered by desensitization. In this article, the apporach to drug allergies in children will be evaluated in accordance with current guidelines.

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Key words: Child, drug allergy, diagnosis, treatment, approach

Drug reactions (DR) are advers or harmful effects of drugs. They constitute 6.5% of all hospital admissions. DR develops with a rate of 15% in patients who are treated by hospitalization (1). The possibility of DR should be considered in the differential diagnosis when any medical problem occurs in a person who uses medication. It should be investigated if the drug administered had caused to a similar reaction before and if there is reasonable temporal relation with administration of the drug (2).

Classification of drug reactions

Drug reactions are mainly examined in two groups as predictable (type A) and unpredictable (type B) reactions. This classification was proposed by Rawlins and Thompson in 1977; the letter A stands for the word “augmented” and the letter B stands for the word “bizarre” (2-4).

Type A reactions are ordinary reactions which can be observed in healthy individuals and which are related with the pharmacological effect of the drug and the dose administered. This type of reactions constitute more than 80% of drug reactions. This group of reactions include toxicity, side effect, secondary effect and interaction between drugs. Type B reactions are observed in sensitive individuals and are not related with known pharmacological effect of the drug and the dose administered. They constitute a small portion of drug reactions. Type B reactions include drug intolerance, idiosyncrasis, immune (allergy) and pseudo-allergic reactions (Table 1) (5, 6).

DRs which occur as a result of immune mechanisms are divided into three types according to the times of occurence as “immediate”, “accelerated” and “delayed” reactions. Immediate reactions are IgE-mediated reactions which occur in 20 minutes after parenteral administration and in one hour after oral administration. Accelerated reactions are IgE-mediated reactions which occur

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Table 1. Classification of drug reactions (4,6)

Reaction	Example
Type A reactions	
Toxicity-related with high dose	Acetaminophen-hepatic failure
Side effect-at the therapeutic dose	Methylxantines-headache, nausea
Secondary (indirect) effect	Disruption of the intestinal flora by antibiotics
Interaction between drugs	Erythromycine-theophylline and increased digoxin blood level
Type B reaxctions	
Intolerance	Aspirin-tinnitus (at the ordinary dose)
Idiosyncrasia	Antioxidant drug-hemolytic anemia in a patient with G6PD deficiency
Allergy	Beta-lactam antibiotics-anaphylaxis
Pseudo-allergy	Radyokontrast madde-anafilaktoid reaction

in 1-72 hours. Delayed reactions occur after 72 hours and generally occur by non-type 1 immune mechanisms (Table 2) (7, 8).

In aspirin/non-steroid antienflammatory drug (NSAD) hypersensitivity, immediate reaction occurs in the first 24 hours and delayed reaction occurs after 24 hours (9).

Reactions which occur by immune mechanisms can be examined according to Gell and Coombs classification in terms of the immune mechanism which leads to clinical findings. However, all clinical pictures can not be explained by Gell and Coombs classification system. Nevertheless, the new arrangement of the Gell and Coombs classification system is used frequently (5). Gell and Coombs classification in drug allergies is shown in Table 3 and the new classification with subgroups of type 4 reactions is shown in Table 4 (6).

Clinical findings in drug allergies

Drug reactions may be manifested with systemic or organ-specific findings. Classification of the clinical findings occuring in relation with drugs is shown in Table 5 (10).

Diagnosis

History and physical examination

In a patient who presents with suspicious drug reaction, it is important to answer the questions if the clinical picture observed is related with drug reaction and which drug is responsible of drug reaction in the diagnosis.

The most common clinical findings of drug allergies include skin eruptions and anaphylactic reactions (2). Skin findings are mostly observed in the form of maculopapular eruption (MPE). MPE generally starts in 7-14 days after administration of the drug and may continue for 1-2 weeks after discontinuation of the drug. Although MPE related with drugs are usually non-severe reactions, more severe and even fatal reactions including Stevens-Johnson syndrome (SJS)/Toxic epidermal necrolysis (TEN) or drug hypersensitivity syndrome (drug rash eosinophilia and systemic symptoms-DRESS) may sometimes occur following this type of reactions (11, 12). Urticaria and angioedema are the most common findings of IgE-mediated allergies. However, it should be kept in mind that non-IgE-mediated drug allergies may also be manifested as urticaria and angioedema (5).

The major difficulty in the diagnosis of drug allergies in children is differentiation of maculopapular/morbilliform eruptions from

Table 2. Classification of beta-lactam reactions by the time between administration of the drug and the reaction and by its relation with IgE (7,8)

Early (<1 hour) and rapid reaction (1-72 hours) (IgE-mediated):
Urticaria
Laryngeal edema
Bronchospasm
Hypotension
Regional swelling
Delayed (after 72 hours):
Morbilliform rash
Urticaria
Severe delayed reactions (non-IgE-mediated):
SJS
TEN
DRESS
Interstitial nephritis
Pulmonary involvement
Vasculitis
Hemolytic anemia

SJS: Steven-Jonhson syndrome; TEN: toxic epidermal necrolysis; DRESS: drug rash eosinophilia and systemic sypmtoms

Table 3. Gell and Coombs classification of drug allergies (6)

Type	Mechanism	Example
Type 1	IgE antibodies mast cell/ basophil degranulation	Penicilin-anaphylaxis
Type 2	IgG against cell surface/ IgM-mediated cytotoxic reaction	Quinidine-hemolytic anemia
Type 3	Immune complex storage reaction	Cephalexin-serum disease
Type 4	Delayed type cell-mediated reaction	Neomycine-contact dermatitis

viral eruptions which are observed very commonly in this age group. Peripheral blood eosinophilia may sometimes be helpful in differentiation of drug reaction form viral infections. However, no diagnostic test is sufficient to make a definite diagnosis of drug allergy. Therefore, it is important to evaluate the temporal relation between administration of the drug and occurence of the reaction and the way of occurence of the reaction. In type B drug reactions, examination of the skin and mucosa, presence of fever and lymphadenopathy and laboratory evaluations including peripheral blood eosinophilia or increased liver enzymes are important.

While evaluating suspicious drug reactions the following points should be interrogated and elucidated in the history (2, 13):

- The drugs which were being used during the reaction, usage durations and doses, history of prior exposure to these drugs
- The time between administration of the drug and occurence of the reaction
- Can other drugs administered simultaneously also be responsible of the reaction?
- Is there a history of prior similar reaction? Did the prior reaction regress with discontinuation of the drug?
- Does the patient has another medical problem including food allergy or viral infection which may be related with the clinical finding?
- Does the patient have a genetic predisposition to drug allergy?

The answers of these questions may be helpful in classification of drug hypersensitivity reactions as immediate, accelerated and delayed reactions. Some signs and symptoms may be warning signs for drug allergy (Table 6).

Many drugs may cause to multiple types of drug reactions. In patients with drug reactions, drugs which may frequently lead to immediate and delayed reactions should be considered during evaluation. For example, beta-lactam antibiotics frequently lead to IgE-mediated reactions, while pseudo-allergic reactions are frequently related with administration of aspirin, NSAEDs and radiocontrast substances. Pseudo-allergic reactions are differentiated with occurence in 1-3 hours following administration of the drug and frequent occurence with higher doses compared to IgE-mediated reactions (1, 2).

Although NSAED hypersensitivity reactions are observed more rarely in children compared to adults, they are in the second

Table 4. Rearrangement of Gell and Coombs classification and subgroups of type 4 reactions (6)

Type	Mechanism	Example
Type 4a	TH1 lymphocytes activate monocytes/macrophages by releasing interferon-ϒ	Tuberculin reaction
Type 4b	TH2 lymphocytes release IL-4, IL-5 and IL-13 and activate eosinophils	MPE (with eosinophilia)
Type 4c	Cytotoxic T cells (CD4+ and CD8+) migrate to the tissue and lead to cell death	Maculopapular and bulleous eruptions
Type 4d	T-cell-mediated neutrophilic inflammatory response	Acute diffuse exanthematous pustulosis

MPE: maculopapular eruption

Table 5. Clinical classification of allergic reactions (10)

Systemic reactions	Organ-specific effects	
Anaphylaxis	Skin:	Lung:
Fever triggered by medication	Allergic contact dermatitis	Lung involvement
Autoimmune reactions	Expholiative dermatitis	Fibrotic reactions
Serum disease	Fixed drug erupiton	Hepatic:
Urticaria-angioedema	Morbilliform/maculopapular rash	Hepatocellular
DRESS	Photodermatitis	Cholestatic
	SJS	Renal:
	TEN	Glomerulonephritis
	Urticaria-angioedema(non-systemic)	Nephrotic syndrome
	Blood:	Interstitial nephritis
	Eosinophilia	Reactions not always related with drugs:
	Hemolytic anemia	Erythema multiforme
	Neutropenia	Vasculitis
	Thrombocytopenia	

SJS: Steven-Johnson syndrome; TEN: toxic epidermal necrolysis; DRESS: drug rash eosinophilia and systemic symptoms

Table 6. Early warning signs in drug allergies (2)

Type of reaction	Findings
Early reactions	Extensive pruritus
	Rhinoconjunctivitis, obstructive respiratory symptoms, nausea, vomiting
	Pruritus around the mouth, pruritus in the palms and soles
	Sudden erythema on the skin together with conjunctivitis and rhinitis
Delayed reactions	Fever, malaise
	Long-term findings after discontinuation of the drug
	Lymphadenopathy
	Pain and burning in the skin
	Bulleous lesions, epidermal separation (Nikolsky sign)
	Mucosal involvement
	Edema in the face and diffuse erythematous swelling
	Confluent lesions in extensive skin areas
	Eosinophilia (>1.5x10^9/L)
	Hepatic involvement

order among the most commonly reported drugs. The frequency of NSAED allergy reported in healthy children is 0.3%. The frequency confirmed with drug stimulation test is 5% in children with astma. Non-steroid antiinflammatory drug hypersensitivity develops with immune (type 1-4 hypersensitivity reactions) or non-immune (inhibition of cyclooxygenase enzyme and direct effect on mast cell) mechanisms. Since rhinits/astma induced by NSAED which develops with cyclooxygenase inhibition is observed in adults above the age of 30 years, it shows difference compared to drug allergies observed in children (9).

Diagnostic tests

Although the tests used in the diagnosis of drug reactions are limited, diagnostic tests are utilized according to effective immune mechanism and presence of organ-specific or systemic findings. Complete blood count, erythrocyte sedimentation rate, lung graphy in terms of lung involvement, hepatic and renal function tests, antinuclear and anticytoplasmic antibody tests, specific immunological tests and tissue biopsies in some cases may be directive.

Tests used in early reactions

In the retrospective diagnosis of anaphylaxis, serum total triptase or serum beta-triptase measurements are beneficial. The level of triptase has the highest value 30 minutes-1.5 hours after the beginning of the findings (1, 2, 4, 5). However, the sensitivity of this test is low and does not differentiate immune and non-immune mast cell activation (2).

Although clinical findings and the above-mentioned laboratory tests make a diagnosis of drug reaction, specific immunological tests should be performed to determine the drug which caused to drug reaction. Skin tests (prick and intradermal) are used for this purpose and they are generally recommended to be performed in 1-6 months following drug reaction. In severe anaphylaxis, prick and intradermal tests may be risky even though a long time has passed after the reaction (2, 14).

As *in vitro* tests, basophil activation test among specific IgE tests which evaluates CD63 and CD203c expression may be utilized following induction with allergen (2).

The drug stimulation test is the test with the highest sensitivity which is used in the diagnosis of early reactions when skin tests are negative. It may be performed after one month following drug reaction at the earliest. However, it should be kept in mind that severe reaction may develop while performing skin tests and drug stimulation test and all tests should be performed by an experienced specialist of allergy after ensuring the conditions for urgent intervention when necessary (15).

In drug reactions which develop with preperations containing multiple active ingredients, drug stimulation test should be performed with each drug separately. In addition, it should be kept in mind that preservatives may also be responsible of this reactions and tests with preservatives should also be performed (16).

Tests used in late reactions

Eosinophilia supports immune-mediated reaction. Increased transaminases shows hepatic involvement. Biopsy and histological examination may be helpful in presence of extraordinary skin lesions. The Coombs test is used in the diagnosis of immune hemolytic anemia. Complement levels (C3, C4, CH50) and evaluation of immune complexes support the diagnosis of serum disease, but a negative test does not exclude the diagnosis (2).

Specific tests used in late reactions include skin tests, in vitro tests and drug stimulation test. Skin tests are performed with the suspected drug as in intradermal test. The result of the test is evaluated after 48-72-96 hours. In vitro tests including patch test or lymphocytic transformation test should be performed primarily in acute generalized exanthematous pustulosis, DRESS, erythema multiforme, fixed drug eruption, SJS and TE. Skin tests may be risky in toxic epidermal necrolysis, SJS, bullous exanthemas, vasculitis and systemic reactions (for example: DRESS) even if a long time has passed after the reaction (1, 14, 17).

If all the above-mentioned tests are found to be negative, drug stimulation test with the suspected drug is performed, if there is no contraindication. 1/3 of the therapeutic dose is given primarily for beta lactam antibiotics. If the result is negative, 1/10 of the therapeutic dose is given 3 days-one week later (according to the

period between drug intake and reaction). If the test is negative again, full dose is given at the end of the same period (17).

Drug stimulation test should be performed under close observation and in allergy centers where appropriate conditions are ensured. Drug stimulation test should not be performed in severe reactions including DRESS, SJS, acute generalized exanthematous pustulosis or TEN (16, 17).

Treatment approaches

Prevention of drug reactions (1) can be summarized as determining the host's risk factors with detailed history (2), avoiding drugs which cause to cross reaction (3), performing tests which predict drug reactions if possible (4), avoiding unnecessary antibiotic prescription (5), prescribing oral antibiotics if possible (6), avoiding usage of multiple drugs (7) and indicating drug reactions in medical records.

The first step in treatment of allergic reactions is immediate discontinuation of the responsible drug and this may sometimes be sufficient. In IgE-mediated mild reactions, antihistaminic drugs are administered. If there are warning signs for anaphylaxis (angioedema, signs related with the respiratory or circulatory system, nausea, vomiting, diffuse pruritus), epinephrin should be immediately administered. Although the effect of glucocorticoids starts late (>45 minutes), they should be administered to prevent late reaction (5, 18).

In non-IgE-mediated reactions, additional treatment is administered, if the findings do not improve after the drug which is thought to be responsible is discontinued. Glucocorticoids are used in immune complex reactions, hematological reactions, early phases of SJS and erythema multiforme major and in contact dermatitis (5).

When choosing a different drug, cross-reactivity between drugs with a similar structure should be kept in mind. It should also be kept in mind that parenteral and topical administration is much more sensitizing compared to oral administration.

If a different drug which would not lead to cross-reaction can not be found, drug desentization (drug tolerance induction) is performed in the patient. Drug tolerance induction is changing of the patient's response to the drug. In this way, safe treatment is provided. Drug tolerance is provided with administration of the drug with increasing doses. It should be kept in mind that tolerance to the drug will be maintained as long as the patient continues to use the specific drug.

In prophylaxis of drug allergies, it is important to educate parents about the severity of drug allergies and drugs which cause to reaction and cross-reaction. The list of the drugs which the child should not use should be given to parents, urgent treatment of anaphylaxis and appropriate use of epinephrin autoinjector should be instructed and the child should be recommended to use a marking tag indicating drug allergy (5).

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