

Drug allergies in children

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Summary

Drug allergy when compared with other allergic diseases can be the cause of very serious reactions and can be life-threatening if neglected. In clinical practice, a wide range of symptoms from mild urticaria to anaphylaxis can be observed so that it can mimic the symptoms of all other allergic diseases. One of the significant consequences of allergic drug reactions is the use of less effective, more expensive or more toxic drugs in the future. A thorough history is essential to the management of drug allergy. Laboratory testing has a very limited role in the management of drug allergy. Confirmatory tests, if available, should be used to determine the allergic status of the patient. If these tests are not available, depending on the type of clinical reaction previously demonstrated, a graded challenge or desensitization may be considered. Education of the patient and primary care physician is an important component of management. (*Turk Arch Ped* 2012; 47: 86-91)

Key words: Drug allergy, diagnosis, management, pathogenesis

Introduction

Currently, in parallel to rapid increase in the use of drugs for diagnosis and treatment, adverse drug reactions are observed more frequently. The World Health Organization defines drug adverse reaction as an undesired and harmful response which occurs during use of a drug at the appropriated dose for the aim of diagnosis, treatment or prevention (1). Drug reactions develop by immune and non-immune mechanisms. The World Allergy Organization defines drug reactions which occur by IgE and T cell mediated hypersensitivity reactions as drug allergy (2).

Adverse drug reactions are divided into two main groups as type A (expected reactions or reactions which can occur in anyone without hypersensitivity) and type B (unexpected reactions which only occur in a small group of individuals who are sensitive) (Table 1). Type A reactions are related to the pharmacological effect and dose of the drug and constitute 80% of adverse drug reactions. Overdose, pharmacological side effects, indirect effects and drug-drug interactions are in this group. Type B reactions are not related with the known pharmacological effect of the drug, occur independent of the dose and constitute 20% of the reactions. Allergic, pseudoallergic and idiosyncratic drug reactions are in this group (3).

Drug allergies can be classified by the underlying immunopathogenesis or by occurrence time of reactions which is frequently used in the diagnostic approach. Reactions which occur in the first hour after drug intake are defined as "immediate" reactions and those which occur after one hour are defined as "nonimmediate" reactions. IgE mediated Type I and anaphylactoid mechanisms are responsible in immediate reactions. While Type II, III and IV hypersensitivity mechanisms are mainly responsible in nonimmediate reactions, the role of Type I reaction should also be investigated (2).

The rate of adverse drug reactions have been reported to be 10-20% in hospitalized patients and 25% in outpatients (4-6). Only 6-10% of drug reactions are related to allergic drug reactions. Although data about drug reactions are very limited in the pediatric age group, a study demonstrated that drug reactions were responsible in 2.09% of referrals to hospitals, in 1.46% of referrals to outpatient clinics and in 9.53% of hospitalized patients in the pediatric age group (7). Although there are no detailed data about the frequency of drug reactions and allergies in Turkey, the frequency of drug allergy reported by families was found to be 2.8% in children aged 6-9 years (8).

The drugs which most frequently lead to allergy include beta lactam antibiotics and non-steroid antiinflammatory drugs (9). In addition, other drugs which frequently lead to allergy include

radiocontrast materials, neuromuscular blocker agents and antiepileptics. Allergy is observed less commonly with local anesthetic agents and non-beta-lactam antibiotics.

Pathogenesis

Four types of immunological mechanisms which were classified by Gell and Coombs are involved in drug allergies (Table 2). Sometimes, more than one allergic mechanism are involved and even nonallergic mechanisms can be observed in combination with allergic mechanisms. IgE mediated Type I reactions constitute the most commonly observed group of reactions. Here, following combination of the drug and the specific IgE on the mast cell or basophil efficient mediators including histamine and leukotrienes are released and cause anaphylaxis, urticaria, laryngeal edema, angioedema, hypotension and bronchospasm symptoms. Type I and Type II mechanisms are mediated by complement and are observed less commonly. In Type II reactions, IgG antibody against the drug is present and findings including anemia and thrombocytopenia are present. In Type III reaction, complexes formed by the drug or its metabolite and specific IgG and IgM

antibodies developed against these are deposited in postcapillary venules. In Type IV reactions most of which are observed as skin findings are mediated by T lymphocytes which have gained sensitivity against the drug (10).

Type IV reactions are currently divided into 4 separate groups. In Type IVa reactions, Th1 cells are stimulated and they stimulate macrophages and monocytes by releasing IFN- γ and TNF- γ . In Type IVb reactions where Th2 cells are involved, eosinophilic inflammation occurs by IL-5. In Type IVc reactions, CD+8 cytotoxic T lymphocytes cause direct cell lysis by releasing enzymes including perforin and granzyme B. In Type IVd reactions which involve neutrophilic inflammation, CXCL-8 released by T lymphocytes prolong the life time of neutrophils, while GM-CSF contributes to inflammation by preventing neutrophil apoptosis (11).

How do drugs stimulate the immune system?

The antigenic properties of drugs are related to their chemical structures. Drugs with a molecular weight of more than 1000 D (for example, L-asparaginase, heterologous antisera and insulin) can trigger hypersensitivity reactions by

Table 1. Classification of adverse drug reactions

| Type A reactions | Samples |
|--------------------------------|---|
| High dose | Hepatic failure (acetaminophen) |
| Side effect | Headache, nausea (methylxanthines) |
| Indirect effects | Development of diarrhea after antibiotic use |
| Drug interaction | Increase of the level of theophylline by macrolides |
| Type B reactions | |
| Intolerance | Development of tinnitus with a single dose of aspirin |
| Idiosyncratic(pharmacogenetic) | Anemia with antioxidant drugs in G6PD deficiency |
| Immunological drug reactions | Anaphylaxis with beta lactams |

Table 2. Classification of hypersensitivity reactions (Gell and Coombs)

| Type | Mechanism | Clinical findings |
|------|--|--|
| I | Anaphylactic (IgE mediated) | Acute anaphylaxis Urticaria |
| II | Complement mediated cytotoxicity (IgG/IgM) | Hemolytic anemia, thrombocytopenia |
| III | Immune complex mediated | Serum sickness Drug fever Some skin eruptions and vasculitis |
| IV | Delayed or cellular hypersensitivity | Contact dermatitis "Morbilliform" eruptions Interstitial nephritis SJS/TEN Hepatitis |

stimulating the immune response directly. Most drugs are simple organic compounds with a molecular weight below 1000 D. They should become bioactive by being metabolized to have immunogenic action. Afterwards, they bind covalently to structures with large molecules on a high molecular weight carrier protein or on cell surface in the plasma. This is defined as "haptization" (12,13). The best example for this is penicillin group antibiotics.

However, haptization reaction does not occur directly for most drugs. Reactive intermediate products which form as a result of metabolism in the liver or in another place act as haptens and bind to high molecular weight proteins (3). The best example for this is sulphonamide group antibiotics.

Outside of these some drugs stimulate T cells directly by binding to T cell receptor (TCR) without a need for an introducer intermediate molecule and cause an immune response. In this condition which is called as PI (pharmacological interaction), there is no need for previous exposure to the drug. This mechanism is especially involved in T cell mediated skin reactions (14).

Risk factors in drug allergies

High molecular weight and complex structure of the drug increase the risk. The dosing frequency of the drug is also an important risk factor. Long-term use, intermittent or recurrent doses increase the risk of development of allergy compared to continuous use. In addition, the mode of administration is also important. Local administration leads to sensitization with a higher rate compared to intravenous administration and intravenous administration leads to sensitization with a higher rate compared to oral administration (3,4).

In terms of individual risk factors, the risk is lower in children compared to adults, since sensitization will increase as the exposure number increases. In women, drug allergies occur with a rate 2 fold higher than men. Genetic polymorphism in the enzymes which metabolize drugs, familial genetic predisposition, immune deficiency, some diseases including AIDS and EBV increase the risk of drug allergy. In addition, the risk of allergy increases in hepatic and renal failure, since the metabolism of the drug and excretion from the body will be disrupted (3,4).

Being atopic does not increase the risk in development of drug allergy (15). In people with non-beta-lactam antibiotic allergy, the possibility of development of penicillin allergy is higher. The risk of allergy against drugs which do not contain beta-lactam has been suggested to increase 10 fold in people with beta-lactam allergy (16).

Non-allergic (pseudo-allergic) hypersensitivity reactions

In this type of reactions, the findings fully suggest allergic mechanisms, but an immunologic cause can not be

demonstrated. These are immediate reactions characterized with mediator release from mast cells independent of IgE. These reactions can occur with the first dose of the drug without a need for a certain sensitization time in contrast to actual allergic reactions. Opiates, vancomycin, radiocontrast materials, aspirin and other non-steroid antiinflammatory drugs cause clinical pictures similar to urticaria, angioedema and even anaphylaxis (3,17).

Clinical findings in drug allergies

Findings related to drug intake may occur in a certain organ or systemic findings may be observed (Table 3). Among allergic reactions related to drugs, cutaneous findings are observed most commonly. Among cutaneous findings, the most commonly observed is maculopapular drug eruption. Urticaria and angioedema generally occur in the first few hours after drug intake. Maculopapular drug eruption generally develops after a few days. More severe forms of cutaneous drug reactions include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis and exfoliative dermatitis. These are life-threatening conditions if they are not treated (18,19). In drug allergies of hospitalized patients, cutaneous rash has been observed with a rate of 96% and systemic symptoms have been observed with a rate of 30%. The most severe drug reactions including SJS,

Table 3. Clinical findings in drug allergies

| Organ specific reactions | Clinical findings |
|---------------------------------|---|
| Skin | Exanthema, urticaria/angioedema, drug eruption, pustules, bulleous lesions, SJS, TEN, cutaneous lupus |
| Hematologic | Hemolytic anemia, thrombocytopenia, granulocytopenia |
| Liver | Hepatitis, cholestatic jaundice |
| Lung | Pneumoniae, fibrosis |
| Kidney | Interstitial nephritis, membranous glomerulonephritis |
| Multiple organ reactions | |
| Anaphylaxis | Urticaria/angioedema, bronchospasm, gastrointestinal system symptoms, hypotension |
| DRESS | Skin eruptions, fever, eosinophilia, hepatic failure, lymphadenopathy |
| Serum sickness | Urticaria, arthralgia, fever |
| SLE | Arthralgia, myalgia, fever, weakness |
| Vasculitis | Cutaneous or visceral |

SJS: Stevens-Johnson syndrome
TEN: Toxic epidermal necrolysis

toxic epidermal necrolysis (TEN) and exfoliative dermatitis have been observed with a rate of 5.2% (20).

Drug Rash with Eosinophilia and Systemic symptoms (DRESS) syndrome is another cutaneous drug reaction characterized by life-threatening inflammation in multiple organs. The difference of DRESS from other allergic drug reactions is that the reaction generally begins 2-8 weeks later after the beginning of treatment and symptoms can persist for weeks or months after the drug is discontinued (21).

Clinically, the most frightening condition is drug-related anaphylaxis and death. In a study in which 1790 patients who used monthly benzathine penicillin G, penicillin-related reaction was observed in 3.2% of the patients, anaphylaxis was observed in 0.2% and death occurred in 0.05%. According to injection numbers, reaction was reported in 19 of 10 000 injections, anaphylaxis was reported in one of 10 000 injections and death was reported in 3 of 100 000 injections (22).

Diagnosis in drug allergies

Diagnosis in drug allergies is a very troublesome process and the decision is difficult to make. The most important reasons for this are as follows: the patient may be using more than one drug, the similarity of clinical symptoms of the underlying disease with drug reactions, incorrect or deficient information given by the patient, limitation of diagnostic tests and unavailability of the tests in many centers. Especially in the pediatric age group, many viruses which lead to respiratory diseases cause confusion in the diagnosis of drug allergy causing skin eruption. Here, one of the determinant points is that eruption is not accompanied by pruritus. In addition, if eruption is accompanied by sore throat, lymphadenopathy and fever, this condition frequently suggests infection. In a study, actual drug allergy was found only in 23% of the patients who were referred to allergy clinic (23). In a study performed in children, diagnostic tests were performed in patients who gave a history of drug allergy and 94% of the patients tolerated the drug (24).

History

To determine if the clinical picture is related to drug allergy a detailed history is very important. To ease taking an appropriate and adequate history European Network for Drug Allergy (ENDA) prepared a special questionnaire form (25,26).

The main point in history is to decide which of the known hypersensitivity reactions is compatible with the reaction which has occurred in the patient. After this is determined the diagnostic test will be decided (3).

In vivo diagnostic tests

In selection of the test, the type of reaction and the time to its occurrence are important. "Prick" test and intradermal tests

should be performed in reactions which occur in the first hour and intradermal patch test should be performed in reactions which occur after one hour. While skin "prick" and intradermal tests demonstrate IgE mediated immediate reactions, skin patch test or intradermal tests which are assessed later determine T cell mediated reactions (27). The tests should be performed 4-6 weeks after the reaction at the earliest. During the test, recommended nonirritant doses of the drug should be used. A positive skin test can determine that the person is under risk in terms of IgE mediated reactions, but a negative skin test does not exclude the possibility of development of a reaction (28).

Drug stimulation tests (DST) are currently the most sensitive tests in the diagnosis of drug allergy. If a diagnosis can not be made with skin tests or in vitro tests, DST should be performed only in centers with intensive care services (29). DST are performed in patients in whom severe skin lesions including severe anaphylaxis, SJS and TEN have been developed (30). The beginning dose ranges between 1:10 000 and 1:10 of the therapeutic dose according to the severity of the previous reaction and the time between the doses should be at least 30 minutes. A negative test does not mean that the drug will be tolerated without any problem in the future and a positive skin test does not indicate a life-long sensitivity (29).

In vitro diagnostic tests

In the diagnosis of immediate type reactions, drug specific IgE can be measured as an alternative to skin tests. Specific IgE can be measured for limited number of drugs including penicillins, insulin, muscle relaxants and quinolones. Although its sensitivity is low, recent studies have reported that it is positive in patients with a history of anaphylaxis (31). Since not only the drug itself but also its metabolites can be allergen, the value of measuring specific IgE is low. Sensitivity for penicilloyl-IgE which is measured for the major determinant of penicillin (PPL) was reported to be 65-85% compared to skin test and 32-50% compared to the combination of skin test and drug stimulation test (31,32). Minor determinant penicillin IgE antibodies are not measured.

Flow-cytometric basophil activation test (FAST) is based on measurement of the markers including CD63, CD203c and CD69 which become surface markers when basophils are activated. FAST was studied in diagnosis of penicillin, aspirin/NSAI and neuromuscular drug allergies (33). In assessment of drug allergy, its sensitivity has been reported to be 36-97.9% and its specificity has been reported to be 90-95% (34).

Cellular allergen stimulation test (CAST) is based on measurement of LTC4-LTD4-LTE4 released by basophils following stimulation with allergen. The sensitivity of CAST method has been reported to be 43% for beta-lactam antibiotics and the specificity has been reported to be 79% (35).

In acute allergic conditions, serum mast cell β triptase (>1ng/ml) or plasma histamine (>10 nmol/L) levels which suggest mast cell or basophil activation can be determined (36). However, they may be false negative in mild anaphylaxies without hemodynamic changes (37).

Use of drug specific IgG, IgA and IgM measurements is not recommended in diagnosis of delayed type drug reactions. However, they can be measured in drug immunocytopenia which occurs by type II immune mechanism. When type III reaction is suspected, serum complement C3 and C4 or total hemolytic complement (CH50) can be tested. In type IV reactions, lymphocyte transformation test (LTT) can be performed. In this test, the growth of the lymphocytes in the patient exposed to a non-toxic amount of the suspected drug is measured and increase in growth of drug specific T cell clones is interpreted as sensitization to that drug (38). In a study performed in patients with delayed type reaction against beta-lactam antibiotics, the sensitivity of the test was found to be 78% and the specificity was found to be 85% (39). In recent years, better results have been reported to be obtained with T lymphocytes taken from skin lesions compared to T lymphocytes from the peripheral blood (40,41).

Consequently, there is no definite diagnostic method with a 100% sensitivity in drug allergy. In this difficult process of diagnosis, the flow chart below may be helpful (Figure 1).

Treatment

Acute treatment in drug allergy includes discontinuation of the accused drug and administering the necessary medical treatment according to the status of the active lesion. However, a long-term approach plan is very important in these patients.

Patients with drug allergy should be educated about rational drug use. Medical alarm jewels should be recommended to these patients and a list of the drugs which can cause cross-reaction with the drug defined to have caused reaction should be given. One of the most important points is that the patient gives the information about his/her drug allergy each time he/she refers to a healthcare facility.

These patients should be given an option of another drug. A drug with a different chemical structure which is known to be efficient and safe should be administered as gradual stimulation.

When a person must absolutely use a drug against which he/she was proved to have IgE mediated sensitivity,

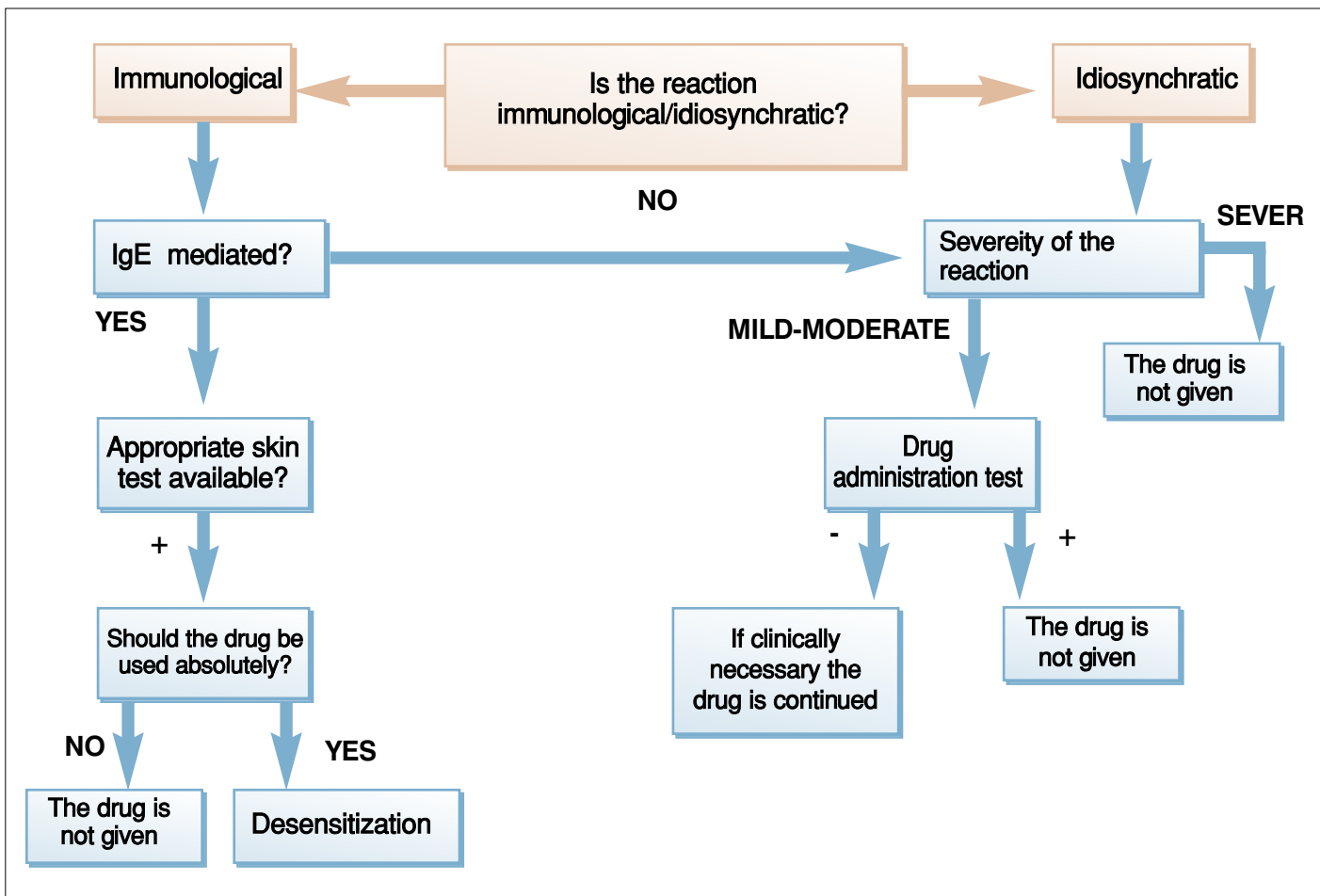


Figure 1. Approach to the patient with drug allergy

desensitization is performed to eliminate the sensitivity. In this process, a transient tolerance which lasts until the drug is discontinued is provided (42). Although the mechanism in desensitization is not known fully, it is explained as elimination of signal transmission ways as a result of saturation of the receptors on mast cell/basophil surface by introducing the drug with frequent intervals and increasing doses (43). Desensitization begins with 1/100 000-1/10 000 of the therapeutic dose. The dose is increased to 2 fold with intervals of 15 minutes and the target dose is achieved. Treatment should be continued uninterruptedly after reaching this dose. It should be kept in mind that desensitization will be eliminated 24-48 hours after the drug is discontinued (42).

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