Acta Biomed 2019; Vol. 90, Supplement 3: 44-51 DOI: 10.23750/abm.v90i3-S.8160

Review

Mechanisms of hypersensitivity reactions induced by drugs

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Summary. Adverse drug reactions include drug hypersensitivity reactions (DHRs), which can be immunologically mediated or non-immunologically mediated. The high number of DHRs unconfirmed and/or self-reported is a frequent problem in daily clinical practice, with considerable impact on future prescription choices and patient health. It is important to distinguish between hypersensitivity and non-hypersensitivity reactions by adopting a structured diagnostic approach to confirm or discard the suspected drug, not only to avoid life-threatening reactions, but also to reduce the frequent over-diagnosis of DHRs. (www.actabiomedica.it)

Key words: drug allergy, prevention, beta lactam hypersensitivity, NSAIDs hypersensitivity, hypersensitivity reactions, children, skin test, specific IgE, drug provocation test

Introduction

Adverse drug reactions (ADRs) affect 10-20% of hospitalized patients and over 7% of the general population (1). Data on prevalence and incidence of drug hypersensitivity reactions (DHRs) are limited, especially in pediatric age and varies around the world. Allergic reactions can manifest as immediate IgE-mediated or non-immediate T cell-mediated reactions.

About 10% of the parents reported that their children are allergic to drugs (2). Beta-lactam hypersensitivity is suspected in the majority of children, the most frequently suspected beta-lactams being amoxicillin and clavulanate, and, to a lesser extent, third-generation cephalosporins (3). A meta-analysis (4) found that just 3% of patients with penicillin allergy in their medical records had a confirmed diagnosis of hypersensitivity reactions by skin or drug provocation tests. The difference appears to be even more striking in the pediatric population, in whom penicillin allergy diagnoses based solely on clinical history are more common (5). According to the above-mentioned meta-analysis, the frequency of confirmed immediate reactions to penicillin is less than 2% in children (4). Overdiagnosis of beta lactams allergy is associated with a greater use of alternative antibiotics, which are usually less effective, less safe, and more expensive; they also usually have a broader spectrum of activity, which can increase the risk of infections by *Clostridium difficile* and multiresistant agents. There may also be economic and management consequences, including higher hospitalization costs, increased readmissions, and longer hospital stays (2). Hospitalizations of children labelled as allergic to penicillins are associated

with longer hospital stays, more comorbidities, and a tendency towards higher hospitalization costs. An accurate diagnosis of penicillin allergy based on clinical history and confirmatory tests is therefore essential in all paediatric patients (6).

Non-steroidal anti-inflammatory drugs (NSAIDs) are the second most frequent type of drug to cause hypersensitivity reactions in children. The overall prevalence of NSAID hypersensitivity has been reported as being between 0.6 and 5.7% in the general population (7). A questionnaire-based frequency of NSAID-induced reactions reported a frequency of 0.3% in children (8). However, in populations at risk (such as asthma or chronic urticaria sufferers) NSAID hypersensitivity prevalence may be higher (9, 10). In studies assessing tolerance for both NSAIDs and acetaminophen is reported that the prevalence of acetaminophen hypersensitivity in children reporting allergy to NSAIDs is 4-25% (11). The frequency of lgE-mediated anaphylactic reactions to NSAIDs in perioperative period was 1 in 2100 operations (12).

In the pediatric population, cutaneous reactions constitute 35% of adverse drug reactions and between 2% to 6.7% of cutaneous reactions can develop into severe and potentially life-threatening clinical syndromes. (2), The most common cutaneous reactions in children are maculopapular rashes (MPR; 20%-80%), urticaria/angioedema (20%-30%) (13), while eczema is rare (14). Serum sickness-like reactions (SSLRs) occur in 0.02%-0.2% of children, especially in young children treated with first-generation cephalosporins (15). Severe cutaneous adverse reactions (SCARs), including erythema multiforme major (EMM), Stevens-Johnson syndrome (SJS), acute generalized exanthematic pustulosis (AGEP), toxic epidermal necrolysis (TEN), and drug-induced reaction/rash with eosinophilia and systemic symptoms (DRESS) are rare, although they may represent up to 10% of the patients explored for suspected DHRs (16-18).

Classification

The classification of DHRs relies on the clinical presentation of typical symptoms and their timing, and were originally described by Gell and Coombs: namely Type I, IgE mediated reactions, Type II, antibody mediated cytotoxicity reactions, Type III, immune complex-mediated reactions, and Type IV, delayed hypersensitivity.

Recently phenotypes, endotypes, and genotypes for DHRs are being elucidated and applied to provide personalized approaches to treating and managing DHRs. Phenotypes in drug allergy focus on symptoms and timing of the reactions. The clinical presentations of each phenotype are mediated by different immunological mechanisms which are defined endotypes. Biomarkers are used to identify endotypes (Table 1) (19).

Phenotypes

DHRs phenotypes may be classified as immediate or nonimmediate/delayed reactions. Immediate reactions typically occur within one hour after the last drug administration and they are often caused by direct mast cell activation or IgE-mediated hypersensitivity. Delayed reactions occur from 1 hours after drug administration and may result from antigen-specific IgG production, complement activation or a T-cell mediated response. Reactions occurring between 1 and 6 hours after the last drug intake are called accelerate and can be caused both by an IgE-mediated and T-lymphocyte mediated response. There is an overlap between accelerate and delayed reactions (20).

However, the cut-off point of 1 h is arbitrary for different reasons. The exact occurrence of initial signs of a drug allergy might be hard to pinpoint in the clinical history, the route of administration can influence the time interval in which the reaction starts (e.g. antibiotics can elicit severe anaphylaxis within a few minutes after parenteral administration, but can take up to 1–2 h to do so after oral intake), drug metabolites may take some hours to be formed and therefore an IgE-mediated immediate reaction can start later than 1 h after drug intake (21).

DHRs phenotypes may be classified according to clinical presentation. Cutaneous Adverse Reactions are the most common manifestation of drug allergy and may be clinically classified in Mild Cutaneous Allergic Reactions (MCAR) and Severe Cutaneous adverse reactions (SCARs). The common culprit drugs to induce

Table 1. Drug hypersensitivity reactions: phenotypes, endotypes, biomarkers

Phenotype		Endotype	Biomarkers
Immediate:	Urticaria/angioedema, Anaphylaxis, Laringeal edema, Bronchospasm	I, IgE mediated Direct mast cell-basophil activation - Complement activation - Mrgx-2	Skin testing, Specific IgE, Basophil activation test, Tryptase
Immediate:	Aspirin exacerbated respiratory disease, Aspirin exacerbated cutaneous disease	COX-1 inibition	
Delayed:	Anemia, agranulocytosis Thrombocytopenia Autoimmunity (SLE, pemphigus)	II, IgG cytotoxic and complement	Patch test, LTT, HLA, Viral antibodies
Delayed:	Serum sickness-like reactions, Vasculitis, urticaria, Organ reactions	III, immune-complex, IgG mediated complement	
Delayed:	Contact eczema	IVa, Th1 (IFN-gamma), Infiltrated monocytes	
Delayed:	DRESS/DIHS	IVb, Th2 (IL-4, IL-5), Infiltrated eosinophils	
Delayed:	SYS/TEN, EM bullous/pustular	IVc, T cell cytotoxic	
Delayed: AGEP		IVd, T cell (IL-8, CXCL-8)	

SCARs include aromatic anti-epileptic drugs, allopurinol, NSAIDs, and antibiotics (22).

Endotypes

Multiple endotypes exist for DHRs, including immunologic reactions (mostly IgE-mediated reactions and T-cell mediated reactions) and non immunologic reactions (pharmacologic interactions, pseudoallergic reactions).

Immunologic Reactions. The term drug allergy refers to a specific immune response to a drug acting as an allergen, mostly linked to endogenous proteins or peptides. In majority of cases drugs or drug metabolites are too small (molecular weight <800 KD) to elicit a specific immune response on their own. Only if they bind *covalently* to endogenous proteins a new antigen is generated (apten-protein complex) (23). The covalent link is resistant on intracellular processing and transform an autologous protein to a novel drug modified protein (2). Autologous proteins may be soluble (e.g. albumin, transferrin) or cell bound protein (e .g. integrin, selectins). The typical immune response to such antigens is a T cell-dependent antibody formation. The sensitization takes time (>4 days). It occurs at therapeutic drug concentrations and it is often clinically unapparent. In T cell mediated reactions, however, symptoms may appear directly following sensitization, namely when the amount of reactive T cells is high enough and homes to the affected organs (mainly the skin) (18, 24). The fact that IgE mediated reactions con occur already al minimal doses does not mean the reaction is dose dependent. The final response is dependent on the type of sensitization. An immune-mediated mechanism linked to certain clinical phenotypes is the basis for the Coombs and Gell classification. The immediate appearing symp-

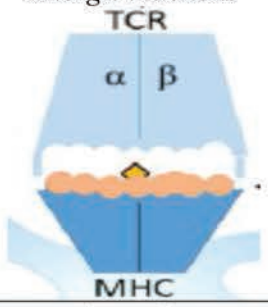
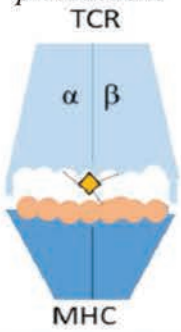
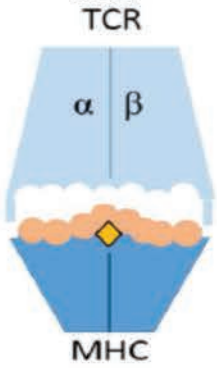
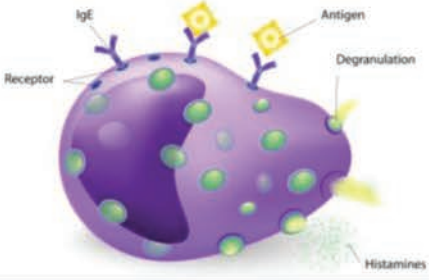
toms (urticaria, anaphylaxis) were classified as being due to IgE (type I) and the delayed appearing symptoms (e.g. exanthemas, eczema, hepatitis) as dependent on T-cell activation (and rarely antibody involvement, especially IgG) (25). In eczematous reactions it is possible to have increased inflammatory biomarkers (26) In immunologic reactions the extent of cross reactivity is dependent on structural similarity and affinity of the drugs to the available immune receptors, T cell receptor (TCR), human leukocyte antigen (HLA), IgE. (26). Immune reactions to drugs may be linked to an autoimmune reactions. The altered peptide repertoire model suggests that a drug could bind strongly and specifically to the HLA protein to alter the selection of self-peptides which in turn results in polyclonal T cell proliferation (26,27) (Table 2).

Non Immunologic Reactions. The pharmacological interaction with immune receptors (p-i concept) proposes that a drug/metabolite may directly, reversibly bind to the TCR and/or HLA protein but not the antigenic peptide (28). According to the "p-i" theory, the antigen-processing pathway in antigen presenting cells is bypassed. This drug binding to immune receptors is a typical off-target effect and is based on noncovalent bonds like van der Waals forces, hydrogen bonds, and electrostatic interactions. The interaction with HLA or TCR is often *selective* for a particular HLA molecule or a particular TCR, as only certain amino-acid sequences and 3D structures allow relatively strong, noncovalent drug binding (29). This is particularly well illustrated by abacavir and its association with HLA-B*57:01 allele. Individuals with this allele have approximately a 50% chance of developing abacavir hypersensitivity syndrome, while no one without this allele is predicted to develop an immunologically confirmed hypersensitivity reaction (30). This occurs only in *some* individuals, and persons at risk can be identified by carrying the risk allele. The majority of high risk alleles were HLA class I, but some less stringent associations were also found for HLA class II alleles (31, 32). In p-i reactions cross reactivity may be important and is based on pharmacologics properties of the drug. For example, the carbamazepine binding HLAB*15:02 protein binds carbamazepine, some carbamazepine metabolites and possibly even other anticonvulsants like lamotrigine and phenytoin (33). Clinical symptoms in p-i reactions typically appear > 5-7 days after the initiation of treatment and only after T cell expansion and migration into tissues. In p-i reactions drug concentrations are important for eliciting T cell reactions, but in some cases lower amounts of the drug may be sufficient to cause symptoms if a massive expansion of drug reactive T cells has already taken place (18).

The p-i concept implies important clinical consequences: reactions are dose dependent, if many clones are stimulated symptoms could appear rapidly, if few clones are stimulated symptoms appear days or weeks after. Moreover p-i concept justifies unelessness of skin tests in diagnosis of many delayed drug allergic reactions (29). In vitro analysis of T cells of patients suggests that p-i reactions may be involved MPR, but most frequently in severe hypersensitivity reactions like AGEP, drug-induced liver injury , SJS/TEN and DRESS (29-31).

Pseudo allergic reactions (PARs) do not require prior sensitization or cell expansion. Symptoms can appear after the first dose. The pathomechanisms of PARs are not yet completely clarified. PARs are characterized by the following properties which differentiate them from allergic reactions. (35). The symptoms of PARs are qualitatively different from the pharmacological response of a drug and are not related to adverse reactions connected with its pharmacological and toxicological profile. PARs are not specific with regard to the chemical structure of the triggering agent in contrast to allergic reactivity. The pseudo-allergic reactivity is not acquired but genetically predetermined. Symptoms of PARs are like those of allergic reactions and are typical of certain substances like NSAIDs, radiocontrast media, muscle relaxants, quinolones, and vancomycin. Reactions usually appear at standard or high doses, which is an important distinction to sensitized individuals having IgE reactions (36). Some of these effects appear to be linked to a single receptor on mast cells, known as MRGPRX2 (Mas-related G-protein-coupled receptor member X2). This receptor which recognize common chemical motif was found to be crucial for IgE independent, direct mast cell stimulation (37). Most PARs are mild (acute urticaria), but anaphylaxis even lethal may occur. In NSAID related pseudo allergic reactions

Table 2. Immune reaction to drugs

Immunologic reactions	***Pathogenesis***	***Need of sensitization***	***Dose dependence***	***Cross reactivity***
Allergic reactions 	Drug modified peptide derived from intracellular haptenated protein	YES	NO	Based on affinity of immune receptors
p-i reactions 	Drug bind to the TCR or to HLA molecules outside of the antigen-binding groove through noncovalent interaction	NO	YES	Based on pharmacol-ogic properties and type or HLA or TCR
Reactions by altered repertoire model 	Drugs bind within the antigen-binding groove of specific HLA molecules altering the repertoire of endogenous peptide ligands	NO	YES	Based on pharmacol-ogic properties
Pseudoallergic reactions 	Reactions related to mast cell or eosinophil activation	NO	YES	Based on ligands on mast cells or eosinophils

the underlying inflammation and effector cell hyperreactivity influences the clinical severity (38).

Cofactors

Most patients who suffer from urticaria and angioedema induced by NSAIDs are females and atopy predisposes to more severe reactions (39). DHRs are also frequently associated with viral infections and in most cases the drug is blamed for the exanthema that occurs. Sometimes this is true and the patient has a persistent delayed type allergy to aminopenicillins. However, the reaction does not often recur on re-administration of the drug. The rash in this case may be caused by a lowering of the T cell threshold for drug reaction during the infection, or from infection-induced alterations in drug metabolism or virally-induced polyclonal T cell activation. An interaction between viral infections and drug-induced hypersensitivity has been most often associated with ampicillin-induced exanthema in patients with infectious mononucleosis caused by Epstein Barr virus. Exanthematous eruptions occur in approximately 10% of patients with infectious mononucleosis, but this rate can increase to 70% in adults and 100% in children receiving ampicillin (40). Currently, there is on-going debate as to whether this is true hypersensitivity. The lymphocyte transformation test assay has helped to demonstrate the immune mechanism of the disease (41). Another well known example of a relationship between viral infection and an increased risk of developing drug-induced skin rashes, including SJS and TEN, has been observed in HIV-positive patients. Clinical observations and several studies showed that the incidence of severe adverse reactions to drugs such as co-trimoxazole was much higher in HIV patients than in the general population (42). Viral infections have been suggested as a potential trigger for hypersensitivity reactions. This is particularly the case with human herpes virus-6 HHV-6 infection and anticonvulsant-induced hypersensitivity (43). It has been suggested that since HHV-6 reactivation can only be detected in hypersensitivity syndrome and not in other drug reactions, it can be utilized as a diagnostic test for hypersensitivity. Indeed, in Japan, HHV-6 reactivation seems to be a gold standard test for drug-induced hypersensitivity syndrome (44). In addition, slow resolution of DRESS is thought to be linked to HHV-6 reactivation and hypogammaglobulinaemia which can occur during treatment with certain drugs, in particular anticonvulsants (45). The herpes group family of DNA viruses including EBV, cytomegalovirus, HHV-6, HHV-7 and herpes simplex virus, have not only been implicated in drug-induced hypersensitivity reactions but also in SJS, where viral DNA has been identified in the blood of patients (46). These viruses are important opportunistic pathogens, which can induce massive expansions of cross-reactive memory T-cells. Viruses can interact with the immune system at several points: during drug metabolism, during the presentation of a drug to lymphocytes by dendritic cells, and during the production of cytokine and chemokine in the effector response (47). On the other hand, certain microbes may prevent infection (48, 49). Furthermore, probiotics reduce Th2 cytokines and enhanced Th1 cytokines production and specific IgE and IgG1 (50). Therefore, it has been hypothesized that probiotics may reduce the risk for DHRs.

Conclusions

DHRs include immediate and delayed reactions that are potentially life-threatening. It remains to be understood the mechanisms of the reactions and the interactions between drug's pharmacological characteristics and variables related to the patients' health conditions and to patients' microbes. All these factors contribute to the occurrence of the DHRs.

Conflict of interest: None to declare

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Received: 24 January 2019
Accepted: 1 February 2019
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