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Adverse Drug Reactions: Mechanisms and Assessment

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Key Words

Adverse drug reaction · Drug allergy · Pseudo-allergy · IgE · Anaphylactoid reaction · Drug metabolism · Exanthematous drug eruption

Abstract

Adverse drug reactions (ADR) are an important clinical problem. They account for about 5% of all hospital admissions and cause death in approximately 0.01% of surgical patients. The mechanisms leading to ADR beyond IgE-mediated allergy are still poorly understood. The importance of chemically reactive drug metabolites and the involvement of T-lymphocytes in many drug hypersensitivity reactions have been highlighted in recent years. ADR are diagnosed on clinical grounds and the temporal relation between drug intake and the appearance of the symptoms. Allergy tests are required in the further assessment of the reaction. By means of skin tests, in vitro tests and provocation tests information about the culprit drug, the mechanism involved and possible alternatives can be obtained.

Introduction

According to a World Health Organization definition, an adverse drug reaction (ADR) is any noxious, unintended, and undesired effect of a drug, which occurs at doses used in humans for diagnosis, prophylaxis and therapy [1]. It has to be noted that errors in drug administration or compliance, therapeutic failures, accidental poisoning and drug abuse do not fall under this definition. ADR account for approximately 2–6% of all hospital admissions and they occur in about 10–20% of all hospitalized patients [2, 3]. Reliable estimates of the incidence of fatal drug reactions are difficult to obtain, however, it has been calculated that more than 100,000 patients die per year because of fatal ADR in the USA, which would make these reactions between the fourth and sixth leading cause of death [3]. When a new drug is marketed, only about 1,500 patients are likely to have been exposed to it [4]. Therefore, the most severe drug-induced reactions frequently are not uncovered in the adverse event profile of a drug and post-marketing surveillance is needed.

Classification

Although patients who have experienced ADR often refer to them as 'drug allergies', in fact, few ADR are truly allergic. About 80% of all ADR are common, predictable reactions that occur in any individual and are related to

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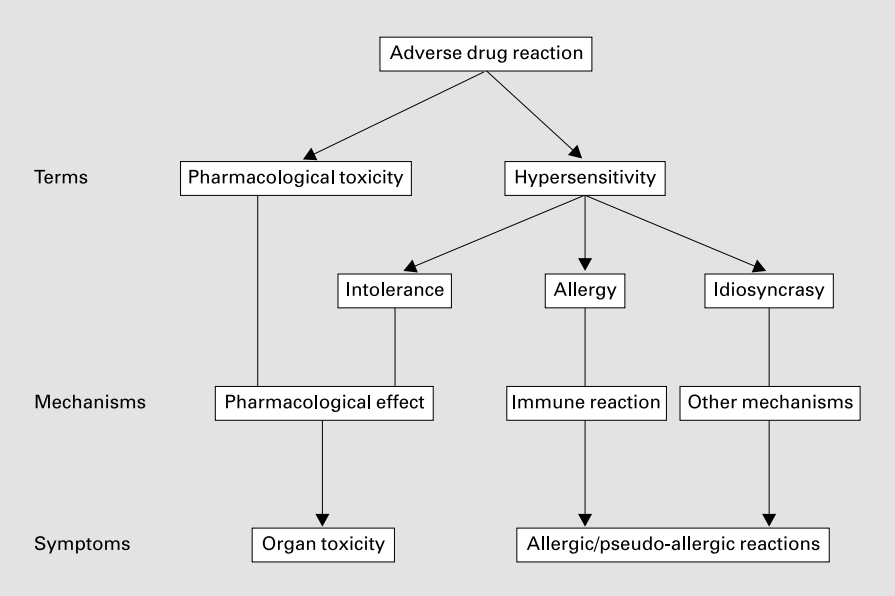

Fig. 1. Classification of adverse drug reactions [5].

the pharmacological toxicity of the drug (fig. 1) [5, 6]. These, also termed as 'A reactions' [7], are dose-related and readily reversible by dose reduction or withdrawal of the drug. Examples include (1) known side effects of a drug, such as sedating effects of antihistamines; (2) secondary events, such as pseudomembraneous colitis after antibiotic-induced alteration of the bacterial gut flora; or (3) drug interactions. Predisposing factors to pharmacological toxicity reactions include not only doses, but also the number of drugs prescribed, as it increases the likelihood for drug-drug interactions [8]. Also in patients with reduced renal function, decreased elimination of a drug makes this type of ADR more likely.

Hypersensitivity reactions, also termed 'B reactions' [7], are less common, but often severe and account for many deaths. They are not dose dependent and predictable and affect only predisposed individuals. Included in this category are drug intolerance (pharmacological toxicity of a drug given at therapeutic dosages), idiosyncratic reactions (non-immunological hypersensitivity that is not explicable by the pharmacological properties of a drug), and drug allergy (hypersensitivity with the involvement of one or more immunological mechanisms). When idiosyncratic reactions are under the clinical picture of an allergy, the term 'pseudo-allergy' may be used. Other pharmacologists and immunologists regard all 'type B' reactions as idiosyncratic reactions and restrict the term hypersensitivity to immunologically-mediated allergies, which is a reason for confusion in the literature [4, 9].

Mechanisms of Drug Hypersensitivity Reactions

Chemically Active Drug Metabolites

In recent years it has become increasingly evident that drug metabolism plays an important role in the pathogenesis of many drug-induced hypersensitivity reactions [10]. Metabolic processes may prevent accumulation of drugs in the body or within particular cells or cell compartments. A good example of an elicitor of drug intolerance is perihexilene, a drug used for angina pectoris. Perhexilene maleate causes hepatotoxicity and peripheral neuropathy only in patients deficient in the Cy P2D6 isoform of cytochrome P-450 [11].

In other instances, however, drug metabolizing enzymes may be used to bioactivate drugs to form chemically reactive or toxic metabolites leading to idiosyncratic or allergic drug reactions [12]. The chemically reactive metabolites for the majority of these reactions are unknown and it cannot be excluded that for many idiosyncratic reactions an immunological mechanism may be demonstrated, later when the diagnostic tools will be available. Other possible non-immunological mechanisms of drug hypersensitivity reactions are listed in table 1. Most drugs are chemically inert in their native state and must be metabolized in order to become immunogenic. Cytochrome P-450 appears to be the most important enzyme for drug metabolization. Drugs, such as sulfonamides, anticonvulsants and procainamide, contain aromatic

Table 1. Possible non-immunological mechanisms of pseudo-allergic reactions

Direct mediator release
Direct activation of the complement system
Activation of thrombocytes
Leukotriene/prostaglandin dysbalance
Activation of the coagulation system
Activation of endothelial cells
Activation of the prekallikrein-kallikrein system
Activation of eosinophils
Formation of fibrin split products
Psychoneurogenic reactions

amines and are oxidized by cytochrome P-450 or macrophage myeloperoxidase to form hydroxylamines and nitrosoamines, which are toxic, unstable and potentially immunogenic [13, 14]. These reagents are normally immediately detoxified by glutathione transferase and acetylation [15]. However, in susceptible patients, the balance between production of reactive metabolites and the detoxification systems may be perturbed by genetic factors or by host factors such as age, coexisting disease or enzyme depletion.

IgE-Mediated Drug Allergy

Most drugs are of low molecular weight <1,000 Da and in order to become immunogens they have to be bound to high-molecular-weight carrier proteins, a process termed haptenation. The best understood example for haptenation and induction of an IgE-mediated drug allergy are beta-lactam antibiotics. They do contain a reactive beta-lactam ring structure and do not have to be metabolized before haptenation can occur. In penicillin, the beta-lactam ring is unstable, and thus opens and acylates lysine residues form the penicilloyl determinant called the 'major' penicillin determinant [16]. Numerous other conjugates are also found, which as a whole have been termed the 'minor' determinant mixture. Specific IgE antibodies to penicillin and other beta-lactam antibiotics appear to recognize a multitude of antigenic determinants. Some beta-lactam-allergic individuals exhibit specific IgE antibodies to structures of the beta-lactam ring and may show cross-reactivity to other beta-lactam antibiotics, but others are highly selective in their recognition pattern and have IgE antibodies specific to side chains and thus react only to a single or few beta-lactam antibiotics [17–19]. Examples of other IgE-mediated drug hypersensitivities include reactions to immunoglobulins, insulins, chemotherapeutic agents and streptomycin [6, 20].

Involvement of T-Lymphocytes

Drug allergy can be mediated by drug-specific antibodies, drug-specific T-lymphocytes, or may share features of different types of immunological reactions. The finding that drugs might induce drug-specific activation of T-lymphocytes, particularly in exanthematous skin reactions, has been demonstrated already in the 1970s [21], and has been extended more recently [22, 23]. Similarly to the findings in IgE-mediated hypersensitivity, heterogeneity was noted with some penicillin-allergic patients having penicillin-specific T-cells in the peripheral blood proliferating only to the particular penicillin that elicited the reaction, while in others T-cells reacted also to other related penicillins [24]. There is evidence that drug haptens can be processed and presented to T-cells. CD8+ T-cells were demonstrated to be the predominant T-cell subset in betalactam- and in sulfamethoxazole-induced vesiculobullous exanthems [25, 26]. The epidermal T-cell clones from these patients were antigen specific and MHC class restricted [25]. T-cell clones derived from the peripheral blood patients with betalactam-induced maculopapular exanthems were demonstrated to be CD3+, CD4–, CD8+ and HLA-DR+ subset [27]. The cytokine gene expression and protein production has been compared in peripheral blood mononuclear cells (PBMCs) in patients with immediate and non-immediate drug-induced reactions. In patients with immediate reactions, the TH2-cytokine IL-4 was expressed and produced early in the PBMCs, whereas in patients with non-immediate reactions no expression of IL-4, but overexpression of the TH1-cytokines IL-2, IFN-γ and TNF-α was demonstrated [28]. Other studies have reported similar, but also contradictory results. In other maculopapular drug reactions predominance of CD4+ T-cells has been described in the dermal infiltrate [29, 30]. In some patients with immediate reactions to beta-lactam antibiotics high levels of IFN-γ, but little IL-4 were found, indicating that in this interesting area still more research is needed [31].

Assessment of Adverse Drug Reactions

Symptomatology of Adverse Drug Reactions

ADR can affect every organ system with a multitude of symptoms. Common reactions due to pharmacological toxicity (type A) correspond to the well-known effects described in drug information inserts and published refer-

Table 2. Grading system for scoring of anaphylactoid reactions (according to Ring and Messmer [33])

Grade	Symptoms			
	skin	abdomen	respiratory tract	circulation
I	Pruritus Flush Urticaria Angioedema			
II	Pruritus Flush Urticaria Angioedema (not obligatory)	Nausea Cramping	Rhinorrhea Hoarseness Dyspnea	Tachykardia ($\Delta > 20$/min) Hypotension ($\Delta > 20$ mm Hg syst.) Arrhythmia
III	Pruritus Flush Urticaria Angioedema (not obligatory)	Vomiting Defecation Diarrhea	Laryngeal edema Bronchospasmus Cyanosis	Shock
IV	Pruritus Flush Urticaria Angioedema (not obligatory)	Vomiting Defecation Diarrhea	Respiratory arrest	Circulatory arrest

ence manuals. Drug hypersensitivity reactions (type B) are classified according to the clinical symptoms and/or to the kinetics of the reaction [5]. Acute (0–1 h after drug application), subacute (1–24 h), or accelerated (>24 h) reactions can be distinguished, however, recently it has become more common to divide into immediate versus late or delayed type reactions. Immediate drug hypersensitivity reactions are generally characterized by anaphylactoid symptoms [32], and the severity of the reaction may be scored from grade I to grade IV (table 2) [33]. Non-immediate reactions most often affect the skin, manifesting as exanthematous skin reactions (exanthematous drug eruptions, EDE). Toxic epidermal necrolysis (Lyell's syndrome) is the maximal life-threatening variant of a cutaneous drug reaction. In some cases, anaphylactoid features may occur several hours to days after application of a drug. Radiocontrast media, for example, do cause anaphylactoid immediate type reactions, but in some patients delayed reactions after 6–12 h like angioedema, dyspnea, EDE, cardiovascular reactions, gastrointestinal complaints, headache and flu-like symptoms may occur [30, 34, 35].

History

Drugs and diagnostic reagents often have a specific profile of hypersensitivity reactions. Therefore, it is important to become familiar with this profile, when the probability that a reaction is caused by a specific drug has to be assessed. The doses of medications, concurrent medications and concurrent diseases at the time of the reaction should be asked, as they may predispose to ADR. Another crucial aspect is the temporal relation between the start of a drug treatment and begin of a reaction. A drug that is taken for years is unlikely to have caused a drug hypersensitivity reaction. In drug allergy, immunological reactions may require a sensitization period of several days, whereas idiosyncratic and pseudo-allergic reactions may occur at the first course of therapy.

Further Assessment

'Better safe than sorry' has been termed a simple approach to avoid all drugs that may have caused ADR in patients who present with such a history [36]. However, this cannot be regarded as the best management strategy for patients with ADR, as it may deprive patients needlessly of important drugs. For pharmacotoxic reactions (type A), the drug may be tolerated at a lower dose and dose modifications often help in drug-drug interactions. For patients with drug hypersensitivity reactions (type B), more caution is advised and allergy diagnosis in order to find the culprit drug as well as possible alternatives should be performed.

Allergy Diagnosis

Non-Specific Tests. Laboratory tests can be applied to assess organ involvement (e.g. creatinine, liver function tests, complete blood count). A biochemical marker of mast cell involvement in ADR is the neutral serine protease tryptase. This enzyme exists in an α- and β-form [37]. Whereas levels of α-tryptase are believed to be a reflection of the total body burden of mast cells [38], the β-form is released in immunologically-mediated as well as in non-immunologically-mediated anaphylactoid reactions [39]. It has been recommended to obtain serum for tryptase determination 1–2 h after the onset of an anaphylactoid reaction [39], but increased levels also have been found several hours later, e.g. in a case of a fatal anaphylactoid reaction [40].

Allergen-Specific Tests. Drug-specific diagnostic tools are limited as the metabolites of many suspected drugs are unknown or the reaction mechanisms responsible for a reaction have not been elucidated. In vitro diagnostic tests are sufficiently validated in the case of penicillins where specific IgE antibodies can be detected to confirm sensitization. In most other cases, in vitro tests are less reliable and less validated and results should be regarded with caution.

Skin Tests. A positive skin test or detection of specific IgE antibodies are an indication for a specific immunological reaction (sensitization) of an individual to a specific drug. However, a negative test reaction does not exclude a hypersensitivity reaction as inappropriate immunogens may have been used or an idiosyncratic reaction may be present. In vitro lymphocyte tests (LTT or cytokine secretion) may – in selected cases – prove helpful in exanthematous drug eruptions especially after coincubation with mouse liver microsomes in order to facilitate metabolite production [41].

Nevertheless, although widely neglected in the past, skin testing of drug hypersensitivity reactions has undergone a renaissance in the last years and general considerations for the use of skin tests have been published recently [42]. Skin prick tests and intradermal tests for the detection of IgE-mediated immediate reactions are widely used for beta-lactam antibiotics, but are also often indicative for a drug hypersensitivity reaction in other drugs, including immunoglobulins, insulins, streptomycins. With increasing evidence of specific T-lymphocytes being important in drug hypersensitivity reactions, patch tests and intradermal tests with delayed readings should be applied for late or delayed reactions. In fact, Barbaud et al. [43] found in a study of 72 patients with drug hypersensitivity reactions that positive skin test reactions were positive in 72% of patch, skin prick or intradermal tests. Others have reported similar encouraging results [44]. The use of test concentrations at non-irritative concentrations is crucial [42].

Provocation Tests. In cases where the culprit drug cannot be identified by these measures, provocation tests have to be considered. The controlled challenge with increasing doses of a drug should only be performed by an experienced allergist under in-patient or emergency conditions. In cases of very severe life-threatening reactions where no reliable therapeutic modality exists (e.g. toxic epidermal necrolysis, cytotoxic reactions), provocation tests are not indicated. In certain cases with increased cross-reactivity to possible alternative drugs, as it is the case with analgesics or insulins, provocation tests may also be indicated. In 128 patients with anaphylactoid reactions to analgesic preparations, blinded oral provocation tests to several analgesics were positive in 157 out of 531 provocation tests (31%) [45]. The often uncritically recommended alternative paracetamol (acetaminophen) is not generally a 'safe' drug for every patient, since anaphylactoid reactions have been observed also after acetaminophen [45].

Conclusion

If no reaction to a drug does occur to a provocation test, the drug may be continued, if medically indicated. If objective anaphylactoid symptoms or the previous symptoms are reproduced upon provocation test, the hypersensitivity is proven and generally the drug should be discontinued. The patient should carry documentation of this hypersensitivity (e.g. medic alert bracelet, 'allergy passport') at all times. In individual cases with a strong need for a particular drug, a hyposensitization may be attempted [46]. As in hyposensitization to allergens, in some types of symptoms and in some drugs, a drug is tolerated, if it is administered in slowly increasing dosages until reaching the therapeutic dose and on a continuous basis thereafter. Examples include the use of sulfamethoxazole in patients with HIV infection [47].

By means of allergy testing of drug hypersensitivity reactions the culprit drug can be detected, alternative drugs can be found, and information about the reaction mechanism can be obtained in the majority of cases.

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