Etiology and Pathogenesis of Adverse Drug Reactions

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Abstract

In clinical routine, adverse drug reactions (ADR) are common, and they should be included in the differential diagnosis in all patients undergoing drug treatment. Only part of those ADR are immune-mediated hypersensitivity reactions and thus true drug allergies. Far more common are non-immune-mediated ADR, e.g. due to the pharmacological properties of the drug or to the individual predisposition of the patient (enzymopathies, cytokine dysbalance, mast cell hyperreactivity). In true drug allergies, T cell- and immunoglobulin E (IgE)-mediated reactions dominate the clinical presentation. T cell-mediated ADR usually have a delayed appearance and include skin eruptions in most cases. Nevertheless, it should not be forgotten that they may involve systemic T cell activation and thus take a severe, sometimes lethal turn. Clinical danger signs are involvement of mucosal surfaces, blistering within the exanthematous skin areas and systemic symptoms, e.g. fever or malaise.

Drug presentation via antigen-presenting cells to T cells can either involve the classical pathway of haptenization of endogenous proteins or be directly mediated via noncovalent binding to immune receptors (MHC molecules or T cell receptors), the so-called p-i concept. Flare-up reactions during the acute phase of T cell-mediated ADR should not be mistaken for true drug allergies, as they only occur in the setting of a highly activated T cell pool. IgE-mediated ADR are less frequent and involve mast cells and/or basophils as peripheral effector cells. Recent data suggest that certain patients with drug allergy have a preexistent sensitization although they have never been exposed to the culprit drug, probably due to cross-reactivity. Thus, allergic drug reactions on first encounter are possible. In general, the extent of cross-reactivity is higher in IgE- compared to T cell-mediated ADR. Based on a specific ethnic background and only for severe T cell-mediated ADR to certain drugs, a strong HLA association has been established recently.

Essentials in a Nutshell

- Type A adverse drug reactions (ADR) are due to a pharmacological property of the causative drug, considered as pharmacotoxicological effects, and thus predictable
• Type B ADR comprise about 10–15% of all ADR, and include enzymopathies, cytokine or mediator dysbalances, nonspecific mast cell degranulation and specific immune reactions (true drug allergies)
• The vast majority of true drug allergies are considered to be either Ig-E (type I) or T cell mediated (type IV)
• T cell-mediated hypersensitivity reactions may be explained by the hapten/prohapten concept and/or by a pharmacological interaction of drugs with immune receptors (p-i concept)
• The hapten/prohapten concept may be a valid explanation for contact dermatitis, whereas p-i concept may play a major role in the effector phase of ADR to systemically applied drugs
• Recent data suggest that certain drug-allergic patients have a preexisting sensitization, although they have never been exposed to the culprit drug; thus drug allergies on first encounter are possible
• For severe T cell-mediated hypersensitivity reactions to certain drugs, a strong HLA association has been established recently

Introduction

The World Health Organization defines an ADR as a noxious and unintended response to a drug that occurs at a dose normally used in man [1]. ADRs encompass all adverse events related to drug administration, regardless of etiology or pathogenetic mechanism. A new drug usually undergoes toxicological and pharmacological tests in animals, followed by clinical trials in humans before it is authorized for marketing by drug regulatory agencies for specific indication(s). However, the preclinical and clinical premarketing investigation of a new drug does not always reveal all possible effects, side effects or adverse reactions. Most drugs are studied in less than 4,000 patients before approval. Therefore, drug reactions that occur in less than 1 in 1,000 patients are difficult to detect. In addition, premarketing trials often exclude special populations such as women of childbearing age, and many adverse reactions can be detected only in the presence of multiple cofactors of real life. They may also occur during off-label drug use and inappropriate administrations.

In the clinical setting, ADRs are a common and important public health problem, and they always need to be included in the differential diagnosis of patients under treatment with drugs. There are different classifications of ADRs [2–5] (table 1). Currently, the classification which has been proposed by Rawlins and Thompson is the most commonly used [6]. It differentiates two major subtypes:
• type A reactions which are due to a pharmacological propriety of the causative drug, and are thus predictable
• type B reactions which occur only in predisposed individuals and which are thus hard to predict.
Type B reactions comprise approximately 10–15% of all ADR and encompass idiosyncrasies, other non-immune-mediated and immune-mediated reactions. Hypersensitivity reactions may be immune mediated and non-immune mediated [7], even though a few authors use the term hypersensitivity reaction synonymously with drug allergy. It is often stated that type B reactions are not dose dependent and unpredictable. Both statements are however wrong. Although certain type B reactions are elicited by low drug doses, the possibility of drug desensitization has demonstrated a clear dose dependency for such reactions as well; unpredictability is also no longer true, as some immune-mediated ADR can be predicted by genetic markers (e.g. abacavir hypersensitivity and HLA B5701; cf. below ‘Genetic Factors’) and this is likely to be more frequently the case in the future.

Pathogenesis

Type A Reactions

Type A reactions include pharmacotoxicological effects resulting from medication errors such as e.g. overdose, exaggeration of a drug's normal pharmacological actions in sensitive patients, interactions with other drugs and/or underlying illness, impaired metabolism or excretion, and effects that are not directly related to
the desired pharmacological action of the drug. For their recognition, a complete history is essential. Sometimes, a thorough search for precedent medical treatment also with hidden xenobiotics is needed. Pharmacotoxicological effects and possible interactions of a certain drug are described in a pertinent summary of product characteristics or monographs. The search for interactions can be supported by computer-based drug interaction checkers. Unfortunately, drug monographs frequently do not clearly differentiate between adverse event (any undesirable event experienced by a patient whilst taking a medicine), ADR (event that is suspected to be caused by the drug), and different causes of ADRs (e.g. pharmacotoxicological or immune mediated). Thus, the diagnosis of an ADR and its cause can often only be assumed by the constellation of exposure, timing, and clinical features including the pattern of organ manifestations.

**Type B Reactions**

Defective or Absent Enzymes

Idiosyncratic reactions may be caused by an enzymopathy, congenital or acquired. In the affected patients, symptoms may arise due to slower or absent metabolism of the involved drug, causing an accumulation of the drug itself or of other substances to be processed.

Nonspecific Cytokine Dysbalance

Most cytokines are produced locally and have a predominant local activity. Thus, for most cytokines, only the local concentration is relatively high [8, 9]. If the cytokine is administered as a systemic therapy, the situation is reversed, with comparatively high systemic concentrations as required in order to achieve a sufficient local concentration at the site of interest. Such high systemic cytokine concentrations may lead to severe side effects limiting their use, for example, flu-like symptoms during interferon-α therapy. A different situation arises if a monoclonal antibody is directed against a potentially stimulatory receptor like CD3 on T cells (OKT3, muromunab) or CD28 on T cells (TGN1412). Under certain circumstances, the target cell releases a high amount of different cytokines. If those cytokines reach high systemic levels, they may cause various, occasionally severe symptoms [10] referred to as cytokine release syndrome (or cytokine storm). In the phase 1 clinical trial of TGN1412, the previously mentioned anti-CD28 antibody, this principle led to a near-fatal cytokine storm in the first 6 healthy volunteers investigated. Prior animal trials failed to reveal this ADR as the T cells of the animals chosen lacked CD28 on their surface [11]. The product was withdrawn from further trials.
Nonspecific Dysbalance of Inflammatory Mediators

Reactions to nonsteroidal anti-inflammatory drugs (NSAIDs) may comprise approximately 20–25% of all hypersensitivity reactions to drugs [12]. Hypersensitivity to aspirin and other NSAIDs may manifest similar to an immunoglobulin E (IgE)-mediated reaction with cutaneous symptoms such as urticaria and angioedema and/or with respiratory symptoms such as bronchospasm. There is good evidence that most of these reactions to NSAIDs are not IgE mediated, but caused by inhibition of the enzyme cyclooxygenase-1 (COX-1) in the skin and/or airways of hypersensitive patients. The inhibition of the COX-1 diminishes the production of prostaglandin E2 (PGE2) and, as a consequence, the production of the sulfidoleukotrienes LTC4, LTD4, and LTE4 is increased [13]. In addition, there is evidence that leukotriene C4 synthase is overexpressed in the bronchial mucosa of patients with respiratory hypersensitivity to NSAIDs [14].

Angiotensin-converting enzyme (ACE) inhibitor-induced cough or angioedema is another example of nonimmune-mediated hypersensitivity reactions caused by a dysbalance of inflammatory mediators. Bradykinin is degraded by kininase II (= ACE), and thus ACE inhibition reduces the catabolism of bradykinin, which accumulates in tissues [15, 16]. More recently, low levels of aminopeptidase P and dipeptidyl peptidase IV, enzymes known to catabolize bradykinin, have been suggested to be predisposing factors for the development of angioedema in patients treated with ACE inhibitors [17, 18].

Nonspecific Mast Cell Degranulation

Hypersensitivity to opiates such as codeine and morphine are common and usually limited to the skin (urticaria). These reactions are again not IgE mediated but probably caused by interaction with the endorphin receptor on mast cells and subsequent release of histamine and other mediators. As this is only partially inhibited by opiate receptor antagonists, components independent of opiate receptor binding may be also involved [19, 20]. Human mast cell opiate sensitivity may also vary, since in vitro cutaneous mast cells release inflammatory mediators after stimulation by morphine, whereas mast cells residing in lung, heart, and gastrointestinal tissues do not [21].

Formerly, neuromuscular blocking agents (NMBAs) and radio contrast media (RCM) were also considered to induce a non-IgE-mediated mast cell degranulation [22]. However, more recently several investigators found positive skin tests in vivo and basophil activation tests in vitro in patients with hypersensitivity reactions after NMBAs and RCM exposure. The tests were often positive only for the incriminated NMA and RCM, and negative for the others. These findings suggest the involvement of immune mechanisms in a substantial part of such reactions.
Interestingly, approximately 50% of patients with positive skin tests were found to have reacted on primary exposure, which may be best explained by pre-existent sensitization to drug-independent cross-reactive antigens (see section on cross-reactivity below).

Specific Immune Reactions (True Allergies)

Sensitization
To induce a specific immune response, antigens have to be recognized by T cells presented on appropriate major histocompatibility complexes (MHC) by antigen-presenting cells (APCs). Most pharmaceutical agents are molecules of low molecular weight and not able to bind per se to MHC. The hapten/prohapten concept is the common explanation for primary sensitizations: drugs or their reactive metabolites gain immunogenicity by forming stable hapten carrier compounds with human proteins, mostly albumin [26]. These compounds are taken up as neoantigens by dendritic cells, processed and transported to the local draining lymphoid tissue and presented there. They may induce sensitization, if they are recognized by specific naïve T cells. The event of sensitization is usually clinically inapparent. It may involve T cells alone or both T and B cells with consecutive differentiation and generation of specific antibodies with determined isotype, depending on the cytokine pattern of the involved T cells [27]. Upon renewed exposure, concerned specific T cells and/or antibodies may mediate allergic reactions which can be divided into 4 categories corresponding to type I–IV reactions according Gell and Coombs [28]. The vast majority of real drug allergies are considered to be either Ig-E (type I) or T cell mediated (type IV).

IgE-Mediated Allergic Reactions
If the primary sensitization leads to the formation of drug-specific Ig-E, most of the specific primed B cells differentiate into plasma cells and secrete IgE antibodies that bind to high-affinity receptors (e.g. FcεRI) on the surface of mast cells and basophils. Upon renewed exposure, the causative drug binds to the Fab part of the IgE molecule. A current paradigm postulates that the antigen must be presented in multivalent form to induce an allergic reaction: binding of two or more cell surface-bound IgE molecules (crosslinking) leading to activation of the mast cell and the release of factors such as histamine, leukotrienes, prostaglandins and cytokines. These released molecules elicit vasodilatation, increased vascular permeability, enhanced mucus production, bronchoconstriction and contribute to eosinophil recruitment. IgE-mediated reactions to drugs often result in urticaria or angioedema. But they may include gastrointestinal and respiratory symptoms, shock and severe cardiac complications as well. The IgE/mast cell system is extremely sensitive, and even very small amounts of a causative drug may induce generalized and severe symptoms.
IgG-Mediated Cytotoxicity (Type II)
Type II reactions are based on IgG molecules predominantly directed against erythrocytes, leukocytes, platelets and probably also hematopoietic precursor cells in the bone marrow, and subsequent complement-dependent cytotoxicity of these cells. The antibody (and complement)-coated cells will be sequestrated to the reticuloendothelial system in the liver and spleen by Fc or complement receptor binding or, more rarely – intravascular destruction may occur by complement-mediated lysis. Different pathways of antibody recognition of target cells have been proposed [29–31]:
- Structures of cell membranes are modified by the hapten and drug, respectively, inducing an immune response directed against these target structures. Such development of an IgG immune reaction against the hapten-carrier complex is rather rare, and occurs after longer drug exposure times at high-dose treatment. Some antibody reactivity may be directed to the carrier molecule itself (= autoantibodies). This autoimmune form is less abrupt, but longer lasting after cessation of the drug.
- The drug induces conformational changes in structures of cell membranes resulting in nonspecific adherence with naturally occurring autoantibodies. Such a reaction may only occur as long as the drug is present in soluble form.

Immune Complex Deposition (Type III)
Formation of immune complexes is a common event during a normal immune response and does normally not cause symptoms. In type III reactions, the immune complexes formed activate endothelial cells with complement activation in small vessels and deposition due to Fc-IgG R interaction. Why and under which exact circumstances an immune complex disease develops is at present not clear. Clinical symptoms of a type III reaction comprise serum sickness, drug-induced lupus erythematosus and/or vasculitis.

T Cell-Mediated, Delayed Drug Hypersensitivity Reactions (Type IV)
Based on a large body of experimental, immunohistochemical and clinical data, there is strong evidence that most delayed immune-mediated drug hypersensitivity reactions with skin involvement are T cell mediated [32]. T cell-mediated hypersensitivity may result in the release of different patterns of cytokines with distinct functions. They can be further sub-classified as follows [33] (cf. fig. 1):
- Predominance of cytokines and chemokines that preferentially activate and recruit monocytes (type IVa)
- Predominance of cytokines and chemokines that preferentially activate and recruit eosinophils (type IVb)
- Predominance of cytotoxic functions by either CD4+ or CD8+ T cells (type IVc)
- Predominance of cytokines and chemokines that preferentially activate and recruit neutrophils (type IVd).
T cells react with the drug in two different ways. 'Immunologically', namely by ‘recognizing’ a hapten-modified peptide with their T cell receptor (TCR) in the frame of MHC molecules. This corresponds to a classical immune response and is highly relevant for contact dermatitis, and is due to haptons covalently bound to proteins and peptides. Alternatively, T cells may be stimulated ‘pharmacologically’ – the drug itself binds either directly to certain regions of the TCR, which results, together with MHC interaction, in a stimulation of this T cell with the particular T cell receptor, or the drug may modify MHC peptide complexes directly, making them immunogenic for T cells.