

REVIEW ARTICLE

Educational case series: Mechanisms of drug allergyJean-Christoph Caubet¹, Werner J. Pichler² & Philippe A. Eigenmann¹¹Department of Child and Adolescent, University Hospitals of Geneva and Medical School of the University of Geneva, Geneva, Switzerland;²Department of Rheumatology and Clinical Immunology/Allergology Inselspital, University of Bern, Bern, Switzerland

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Abstract

Once administered, a drug can activate the immune system by various mechanisms and lead to a large range of clinical manifestations closely related to the type of immune reaction elicited. Administration of the drug can classically result in an immunoglobulin E (IgE)-type sensitization, but can also result in more complex activation of the immune system potentially resulting in severe syndromes, such as the drug-induced hypersensitivity syndrome (DIHS). Although there has been a major increase in our knowledge over the last years, the exact mechanisms of drug allergy are not well understood for most clinical manifestations. A complex interaction between individual characteristics, environmental factors, and the drug itself is usually responsible for adverse reactions to drugs. In this educational review series, we described three cases of drug allergy: first, a child with a typical IgE-mediated drug allergy, second, a child with a non-immediate reaction to penicillin, and in the third patient, we will discuss the drug-induced hypersensitivity syndrome, which is rare but potentially fatal. These cases are correlated to the immune mechanism potentially involved.

Adverse drug reactions have a significant impact on public health, clinical practice, and drug development. A widely used classification divides adverse drug reactions into two major types (1). Type A reactions are common (80%) and are caused by the pharmacologic or toxic properties of a drug. Such reactions are predictable and may occur in anyone. Type B reactions ('bizarre') are considered to be uncommon and unpredictable and occur only in people with a certain predisposition. This last type of reactions includes hypersensitivity/allergic reactions, which represent 1/6 of all adverse reactions to drugs (2). Recent data on abacavir- or carbamazepine-induced severe hypersensitivity reactions show, however, that such reactions are highly associated with certain HLA alleles (HLA-B*5701 or B*1502 in Han Chinese) and are thus predictable. They actually represent one of the first successful examples of 'personalized medicine' (3).

Most drugs exert their effects in tissues and organs into which they diffuse or are transported by the blood circulation. If a sufficient drug concentration is reached in the tissue, drugs may not only have a pharmacologic effect but also interact with the adaptive immune system, in particular with the highly polymorphous receptors of T cells. One of the most important questions that is still to be answered is how a therapeutic agent can activate the immune system. Landsteiner et al. (4) first proposed that with few exceptions, an

antigen must be presented to the immune system in a stable and preferentially multivalent form to activate immunopathologic mechanisms.

Several drugs with large molecular weight intrinsically meet this requirement by containing multiple epitopes. A few drugs have multiple recurrences of a single epitope and thus qualify as 'complete' allergens, able to cross-link IgE molecules in the effector phase directly (5–7). The best-studied example of this is quaternary ammonium epitopes, which render drugs such as succinylcholine bivalent and related neuromuscular blocking drugs multivalent. However, most pharmaceutical agents are of small molecular weight and simple in structure and do not qualify as drug allergens. Nevertheless, these small molecules can also activate the immune system by three specific ways. First, the recognition of small molecules by B and T cells can be explained by the hapten concept (Fig. 1) (8, 9). Haptens (a typical example is penicillin) are chemically reactive small molecules (mostly <1000 D) that are able to undergo a stable covalent binding to larger proteins or peptides. This modification may render the small molecule immunogenic. Haptenation results in an alteration of autologous proteins by drug epitopes, and a drug-specific immune response can ensue. Many drugs are not chemically reactive but can still elicit allergic side effects. The prohaptens hypothesis aims to reconcile this phenomenon with the classic

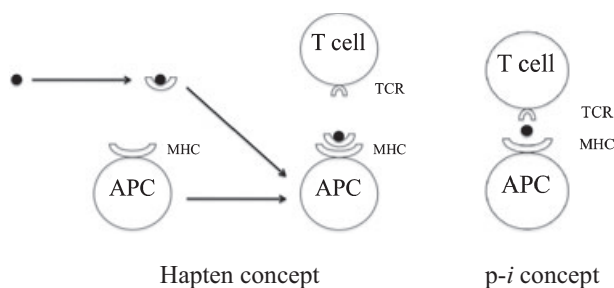


Figure 1 Schematic illustration of the hapten and p-i concept. According to Ref. (15, 14).

hapten hypothesis (10–13), i.e., a drug that is not chemically reactive, *per se*, may become reactive by being metabolized into a compound that is chemically reactive. Sulfamethoxazole is a prototype of the prohaptent hypothesis. Recently, a third possibility was proposed, namely a ‘pharmacologic interaction of drugs with immune receptors’ (p-i concept) (Fig. 1) (14, 15). According to this concept, a chemically inert drug in its native form without binding to a carrier molecule or being otherwise processed can nevertheless activate the immune system by binding directly to the immune receptors like T-cell receptor (TCR) of specific T cells or certain HLA molecules. If the drug fits with a sufficient affinity into such molecules, e.g., a certain TCR, the interaction via non-covalent bonds with proteins is strong enough to transmit a stimulatory signal via the TCRs leading to a stimulation of T cells resulting in cytokines production, proliferation, and/or cytotoxicity.

Whatever the initial mechanism of activation of the immune system, once recognized, the drug may initiate different types of allergic reaction. Similarly to other immune reactions, drug hypersensitivity reactions can be classified according to Gell and Coombs’ classification into four categories that reflect distinct immune mechanisms, explaining the heterogeneous clinical presentations (Table 1) (16, 17). In this educational review, we will illustrate different mechanisms occurring in drug allergic patients by three clinical cases.

Case 1

An 18-month-old boy, non-atopic and previously healthy, was treated by ceftriaxone i.v. because of an acute upper urinary tract infection. He developed anaphylaxis (urticaria, angioedema of the face, dyspnea, wheezing, tachycardia, and hypotension with a systolic blood pressure of 60 mmHg) within 10 min after receiving his first intravenous injection of ceftriaxone. His symptoms completely resolved within 6 h after emergency treatment with intramuscular adrenaline, 6-methyl-prednisolone, and clemastine administered intravenously.

Four months earlier, he had well tolerated a 10-day amoxicillin treatment for pneumonia. Two months after the clinical reaction, the child was referred for an allergy workup. Prick

Table 1 Gell and Coombs classification (16).

	Type I	Type II	Type III	Type IVa	Type IVb	Type IVc	Type IVd
Immune reactant	IgE	IgG	IgG	IFN gamma, TNF alpha (Th1 cells)	IL-5, IL-4/IL13 (Th2 cells)	Perforin/Granulysin B (CTL)	CXCL-8 CM-CSF (T cells)
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Soluble antigen	Soluble antigen presented by cells or direct T-cell stimulation	Soluble antigen presented by cells or direct T-cell stimulation	Cell-associated antigen or direct T-cell stimulation	Soluble antigen presented by cells or direct T-cell stimulation
Effector cells	Mast cell activation	FcR+ cells (phagocytes, NK cells)	FcR+ cells, complement immune complex	Macrophage activation	Eosinophils	T cells	Neutrophils
Examples of hypersensitivity reaction	Allergic rhinitis, asthma, systemic anaphylaxis	Hemolytic anemia, thrombocytopenia	Serum sickness, Arthus reaction	Tuberculin reaction, contact dermatitis (with IVc)	Maculopapular exanthema with eosinophilia	Contact dermatitis, maculopapular and bullous exanthema, hepatitis	AGEP Behcet disease

and intradermal skin tests were performed on the forearm skin, with penicilloyl polylysine (PPL) and minor determinant mixture (MDM) (Diater, Madrid, Spain) as well as amoxicillin (25 mg/ml) and ceftriaxone (3 mg/ml). Intradermal testing with ceftriaxone was positive after 15 min with a significant wheal (7 mm greater than that of the negative control). Serum-specific IgE measurements to ceftriaxone and amoxicillin were negative.

Discussion of the case

The symptoms reported here, rapid onset urticaria followed by an acute respiratory distress including wheezing, within minutes after the injection of ceftriaxone, followed by rapid recovery after anaphylaxis treatment, are suggestive of an IgE-mediated drug allergy. It is to be noted that urticaria is a symptom commonly observed in IgE-mediated drug allergy, but potentially also indicative of non-IgE-mediated drug allergy (18–20). The presence of airway reactions, the participation of several organs in the anaphylactic reaction, and the use of a drug, normally not implicated in anaphylactoid reactions, suggest that the reaction was IgE mediated. In our patient, positive skin tests to ceftriaxone, in conjunction with the suggestive history, confirm an immediate-type, IgE-mediated drug allergy.

In a severe anaphylactic reaction, it is advisable to perform skin tests to pinpoint the relevant drug. Four main groups of betalactams (BL) are described (Fig. 2). They include low molecular weight structures that share the same BL nuclear ring. The side chains contribute to the name of the specific penicillin and might be of immunologic relevance, contributing to the epitopes' structure (21–28). After administration under physiologic conditions, BL antibiotics have the capacity to bind easily to serum and cell membrane proteins. Binding occurs by the spontaneous opening of the BL ring to form stable covalent drug–protein conjugates, according to the hapten concept described earlier (Fig. 3). For penicillin, it results into the penicilloyl epitope, which is considered immunodominant in penicillin-specific

immune responses. Other molecular rearrangements allow BL to haptenate covalently through carboxyl and thiol groups, resulting in a variety of less dominant or 'minor' determinants. However, the contribution of those minor determinants in inducing specific response has not been totally defined.

In cephalosporins, the heterocycles are formed by 4 and 6 carbon atoms, resulting in lower tension in the BL ring (Fig. 2) (29). Haptenization of proteins by cephalosporins is thus slower and less efficient than by penicillins. However, the *in vivo* binding is sufficiently rapid to induce symptoms within 1 h of drug intake (17). Similarly to penicillins, it is supposed that a cephalosporoyl determinant, derived from the nucleophilic attack to the BL ring of the cephalosporin by the amino group (lysine) of proteins, may be formed (Fig. 3) (30, 31). The resulting compound, unlike penicilloyl derivative, is unstable and undergoes multiple fragmentations in the dihydrothiazine ring. This leads to several degradation products and makes isolation and characterization of the different antigenic elements of cephalosporins very difficult. Very little information exists about allergenicity of cephalosporins, especially regarding the structural differences between these compounds. Different *in vitro* studies have shown that IgE antibodies reacting with cephalosporins can detect a wide range of specificities, ranging from a small structure, such as a portion of a side chain, the full side chain, and part of the BL ring or even the whole cephalosporin molecule (32–36). However, the exact structure of the possible antigenic elements is not known yet. The different peculiarities linked to recognition of a cephalosporin molecule are also seen in different clinical studies. Thus, patients have been described as presenting with selective reaction to one cephalosporin or to cephalosporins with identical or similar side chains, and with cross-reaction to other BL molecules (36–40). It was recently shown that *ca.* 75% of subjects who are allergic to cephalosporin can tolerate penicillins and more than 95% can tolerate aztreonam, imipenem/cilastatin, and meropenem (41). Having reacted to cephalosporins with side chain structures similar or identical to those of

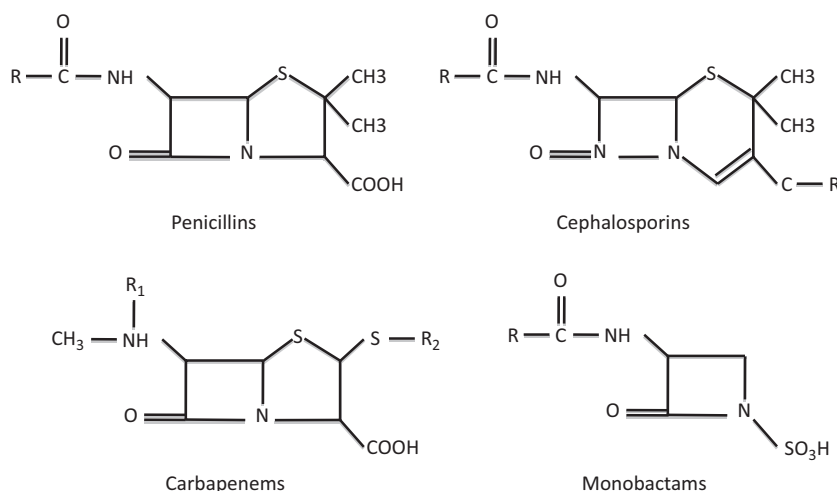


Figure 2 Chemical structures of the four major types of betalactam antibiotic, with the common betalactam ring.

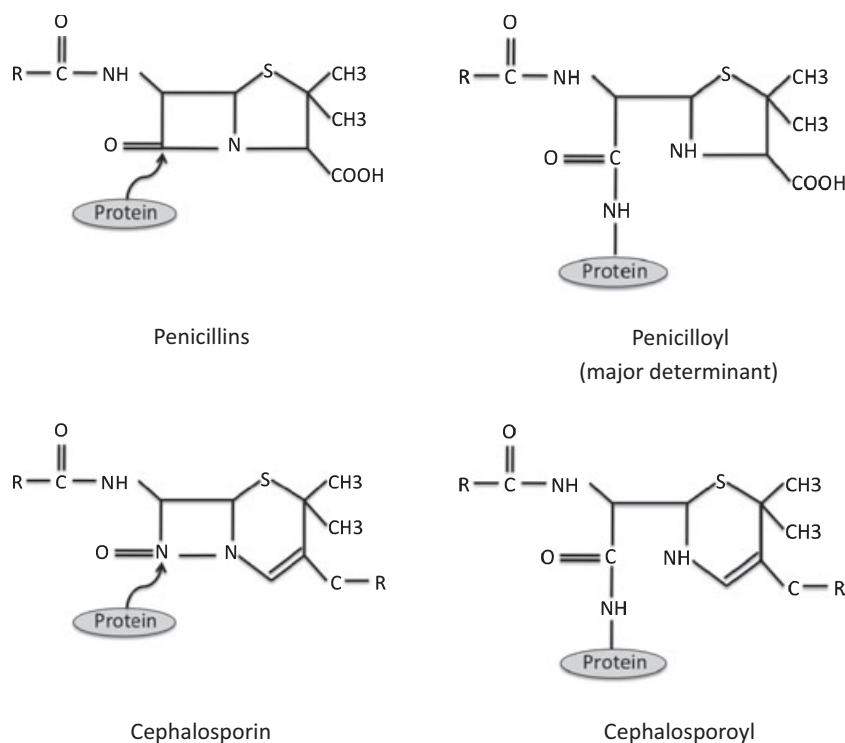


Figure 3 The penicilloyl determinant formation as a stable, isolable, well-defined chemical structure. The intermediate cephalosporoyl is not a stable, isolable and well characterized structure.

penicillins seems to be a significant predictor of cross-reactivity. Cross-reactivity could be attributed to identical side chains in R1 (such as cefaclor and cephalexin, or cefotaxime and ceftriaxone) or similar chains (cefaclor and cefadroxil). It could also be present because of similarities in R2 (cephalexin and cephadrine, cephalotin and cefotaxime) (42). However, as mentioned earlier, the degradation process of cephalosporins causes a multiple fragmentation of the dihydrothiazine ring. In consequence, the substitution of R2 can be lost, and the R1 acyl side chain remains unaltered. It is considered unlikely that the substitution of R2 causes antigenic factors of cephalosporins, nor be responsible for their cross-reactivity (36).

When direct haptation alters the protein, a drug-specific immune response can ensue. IgE-mediated reactions to drugs are usually thought to depend on the prior development of an immune response to a hapten/carrier complex: B cells need to mature into IgE-secreting plasma cells, and T cells help in this process by interacting with B cells (i.e., CD40–CD40L interaction) and by releasing IL-4/IL-13, which are switch factors for IgE synthesis. This sensitization phase may have occurred during an earlier drug treatment.

Upon reexposure to the drug, a hapten–carrier complex is formed again, which, when a sufficient density of drug epitopes were formed, then cross-links pre-formed drug-specific IgE antibodies located at the mast cell/basophil surface. The IgE antibodies will then bind to high-affinity Fcε-receptors on mast cells and basophils. These trigger an intracellular activation cascade that induces the release of multiple mediators (histamine, tryptase, leukotriens, prostaglandins, tumor necrosis factor-α, etc.).

However, it is to be noted that, like in our case, in 50% of patients with immediate reactions, no prior contact with the drug can be found by history and that 80% of the patients with lethal anaphylaxis had no prior treatment with the drug (43). This suggests that either (i) a silent sensitization to a cross-reactive compound had occurred, or (ii) pre-formed IgE existed that happened to react with the small molecular compound.

Case 2

A 2-yr-old girl presented with a history of fever, rhinitis, and sore throat for 1 day. She has been examined by her family physician who diagnosed an acute otitis media in the context of an upper respiratory tract viral infection. The child was started on amoxicillin, 250 mg three times daily. This was the first time she received this antibiotic. On the seventh day of treatment, she developed an itchy rash over the whole body. The child was brought to the emergency department where a generalized maculopapular eruption was noted. The rest of the physical examination was normal. Laboratory investigations showed a normal WBC and hepatic tests. Amoxicillin therapy was discontinued, and antihistamines were given to relieve the itchiness. The eruption cleared completely within 3 days.

The child received a complete allergy workup 5 months later. Following ENDA/European Academy of Allergy and Clinical Immunology guidelines for workup of subjects with a suspicion of non-immediate reaction to betalactam (44), delayed reading intradermal tests were performed on the forearm skin with PPL and MDM (Diater, Moolrid, Spain)

as well as amoxicillin (25 mg/ml). The patient also underwent a patch test with amoxicillin. All these tests were negative. In the next step, an oral challenge test (OCT) was carried out with amoxicillin. Six hours after the challenge, she developed the same benign rash, confirming a non-immediate allergy to penicillin.

Discussion of the case

Potential causes to explain a rash are multiple, particularly in children suffering from a common infectious disease treated by an antibiotic. In this young child, the diagnostic made by the allergologist based on a positive OCT is a non-immediate allergy to penicillin. Proof of an allergic reaction in children developing a rash during a BL treatment is rather rare. A relationship between the drug intake and skin rashes, tested by OCT in the absence of an acute infection, has been proven in only a low proportion of children developing a rash during a BL treatment (6.7%) (20). However, in common clinical practice, most of these children are falsely labeled as 'penicillin allergic' without appropriate testing, and drug allergy is clearly overdiagnosed in such patients.

Non-immediate reactions to penicillins are classified as non-IgE-mediated drug allergies (Table 1). Immunohistochemical studies have shown that cell infiltrates in drug-induced maculopapular rashes (MPR) are largely composed of CD3⁺ T cells (40–70%) (45–48). Both CD4⁺ and CD8⁺ are involved, with a predominance of CD4⁺ cells (48). The infiltrating T cells appear to be highly activated and express CD25, HLA-DR, and adhesion molecules such as the leukocyte function-related antigen 1 and L-selectin. It has been shown that expression of circulating cutaneous lymphocyte-associated antigen-positive T cells is increased in patients with non-immediate cutaneous drug reaction when compared to healthy controls (47). Up to 20% of the infiltrating T cells in drug-induced MPR express perforin and granzyme B (48, 49). Recently, Chung et al. (50) highlighted the important role of the cytotoxic molecule granulysin in severe cutaneous drug reactions, such as Steven Johnson and toxic epidermal necrolysis. Release of these cytotoxic granule proteins leads to cell death by damaging and forming pores in the target cell membrane and induces degradation of their DNA (51). Elevated levels of FAS-L were also detected in lesional skin of patients with MPR. Determination of FAS-L serum concentration has been proposed as a discriminating tool between drug rashes and viral exanthemas (52), but a better discrimination is the presence of eosinophilia (in *ca.* 50% of patients with MPR). In addition to their cytotoxic functions, T cells as well as other leukocytes and resident cells may also orchestrate skin inflammation through the release and induction of different cytokines and chemokines. A heterogeneous cytokine profile including both type 1 (e.g., interferon-gamma, tumor necrosis factor-alpha) and type 2 (e.g., IL-5) cytokines as well as various chemokines (e.g., CCL11/eotaxin, CCL5/RANTES, CCL27/CTACK) has been found in these drug-induced skin rashes (48, 53, 54). IL-5 together with mediators such as eotaxin is involved in the recruitment, activation, and differentiation of eosinophils. It is to be noted

that although the presence of eosinophils in the infiltrate is suggestive of drug-induced skin rashes, eosinophils may also be absent.

Little is known about the initial steps in the hypersensitivity response, i.e., drug allergen presentation to the lymphocytes, which is thought to be mediated by the innate immune response, mainly by dendritic cells (DC) (55). DC are professional antigen-presenting cells, essential for initiating a T-cell response. The DC may induce delayed T-cell responses, by presenting the drug to autologous T lymphocytes leading to a drug-specific response. Moreover, amoxicillin plays a fundamental role in triggering the maturational process in DC from allergic patients but not in controls (56). Why amoxicillin is able to induce this effect only in allergic individuals is still unknown. Among the resident cells, endothelial cells are also activated and express various adhesion molecules such as E- and P-selectin, platelet endothelial adhesion molecule 1, and intercellular adhesion molecule-1 (48, 57).

The differential diagnosis of a rash during a BL treatment includes various viral infections known to elicit maculopapular or urticarial rashes in children, independently of any medication intake. Similarly to non-immediate allergic reactions, viral-induced exanthemas seem to be immunologically mediated, with T cells playing a central role. However, major differences have been shown in the immunologic mechanism (58). In virus-induced exanthema, only a moderate percentage of activated T cells has been shown, with a non-significant increase in the percentage of cutaneous lymphocyte-associated positive memory T cells, in clear contrast with drug-induced MPR. The cytokine pattern is also different with a T-helper 0 pattern for viral-induced MPR and a T-helper 1 pattern in drug-induced MPR.

Finally, and most likely, the rash may result from an interaction between the virus- and drug-induced immune activation. The best-known example is an Epstein-Barr virus (EBV) infection, known as risk factor for cutaneous drug reactions. The pathogenesis of cutaneous drug reactions during viral infections may be attributed to a lowering of the threshold of T cells to react to drugs during the immune activation in the frame of a generalized viral infection. Other possibilities are viral-induced polyclonal activation of lymphocytes or alterations of drug metabolism (59). These reactions were sometimes considered as non-allergic as they do not regularly reappear after reexposure to the drug. However, recent data showed that some patients have a persistent delayed-type reaction to amoxicillin, instead of the classical transient decrease in drug tolerance during EBV infection (60). These data should encourage further studies in patients with amino-penicillin-induced exanthema during EBV infection.

Case 3

An 8-yr-old boy is referred by his pediatrician to the emergency department with fever, a generalized MPR and enlarged lymph nodes. Three weeks earlier, he had started a lamotrigine treatment because of multiple seizures. On physical examination, the patient had a high fever, marked

enlarged lymph nodes at various sites, and extensive exfoliative erythematous MPR with a marked facial edema. Laboratory studies showed a white blood cell count of 5500/ μ l (normal range, 3500–8000/ μ l) with 8% atypical lymphocytes and 18% eosinophils. Serum aspartate aminotransferase and alanine aminotransferase levels were two times the normal values. The patient developed fulminant hepatitis with a fast increase (within 5 days) in transaminases. A liver transplantation was needed, despite adequate treatment with glucocorticoids. Histologic finding confirmed massive hepatic necrosis with dense inflammatory infiltrates containing lymphocytes and eosinophils. PCR analysis of DNA in a serum sample obtained before transplantation demonstrated a high level of Human Herpes Virus 6 (HHV-6) viremia. A skin patch and a lymphocyte stimulation test for hypersensitivity to lamotrigine were performed after the steroid therapy had been stopped for 2 months. Both tests were positive. Based on these findings, a lamotrigine-induced hypersensitivity was diagnosed.

Discussion of the case

Drug-induced hypersensitivity syndrome (DIHS) only occurs in a relatively small proportion of patients (one in 1000 to one in 10,000 to phenytoin) (61) but is associated with considerable morbidity and mortality (between 30% and 50%) (62). Thus, rapid diagnosis is essential to have a favorable outcome. The numerous names used to describe DIHS (anti-convulsant syndrome, drug rash with eosinophilia and systemic symptoms, pseudolymphoma, graft-versus-host-like illness, etc) reflect the diagnostic difficulty and cause a lot of confusion in the literature. As in our case, the skin, liver, and hematologic systems are most commonly involved, with cutaneous symptoms being the most prominent. In addition, a wide variation of manifestations is likely to occur in other organs. Facial edema, in particular in the periorbital region, is indicative of the diagnosis. Categorized as a delayed-type hypersensitivity reaction, DIHS usually occurs within 3 wks–3 months after starting the treatment (63). Several drugs including sulfonamides and allopurinol have been associated with an increased risk of inducing such a syndrome, but the aromatic anticonvulsants are still the main drugs implicated in eliciting DIHS. Recently, some cases of DIHS induced by lamotrigine, a non-aromatic anticonvulsant, have been described in the literature (64). Cross-reactivity has been widely described among the aromatic anticonvulsants and occurs at a rate as high as 80% (65, 66). A case report recently showed the possibility of cross-reactivity between aromatic and non-aromatic anticonvulsant drugs (67).

Although there are conflicting views on the pathogenesis of this syndrome in different parts of the world, recent studies suggest an intimate relationship between viruses and the development of DIHS (68–74). Multiple and sequential reactivation of various herpes viruses has been observed during the course of this syndrome by PCR analysis (72). These reactivations may contribute to the perpetuation and sometimes even the aggravation of symptoms after cessation of the incriminated drug. From existing data, two main hypotheses have been proposed (17).

First, DIHS could be started by an ‘allergic’ immune reaction to the incriminated drugs, which seem to have the capacity to stimulate T cells. This hypothesis results from positive patch tests and lymphocyte transformation tests, indicating that drug-specific T cells are the driving force behind this syndrome (65, 75). Drugs involved in DIHS may be chemically reactive and able to covalently bind to various molecules, including MHC peptides. According to the p-i concept described earlier, some chemically inert drugs (for example, lamotrigine) can also directly and non-covalently bind to MHC–peptide complex to stimulate a drug-specific T-cell response. In addition, several drugs associated with DIHS are metabolized to reactive oxidative intermediates (76–78). These toxic oxidative metabolites generated under certain circumstances might also bind to tissue macromolecules, thereby acting as haptens stimulating T cells (79). Some predisposing factors can reduce a patient’s capacity to detoxify reactive drug products and make them more susceptible to a toxic effect of these products (79). This massive T-cell stimulation may reactivate the viral genome within the cells and then leads to antibody production and T-cell mediated reactivation of the virus-specific immune response.

An alternative view would attribute a more causal role to viruses. By analogy with graft-versus-host diseases, Shiohara et al. suggested that the clinical symptoms seen during the course of DIHS are likely to be mediated not only by an oligoclonal expansion of drug-specific T cells but also by virus-specific T cells that can cross-react with the drugs (17). The administration of the drugs leads to an expansion of these drug (and virus)-specific T cells. This may trigger latent virus reactivation perpetuated after cessation of drug because of the persistence of the viral antigens. This hypothesis can explain (i) the occurrence of relapses following the discontinuation of the offending drug corresponding with the detection of viral reactivation; (ii) the involvement of multiple

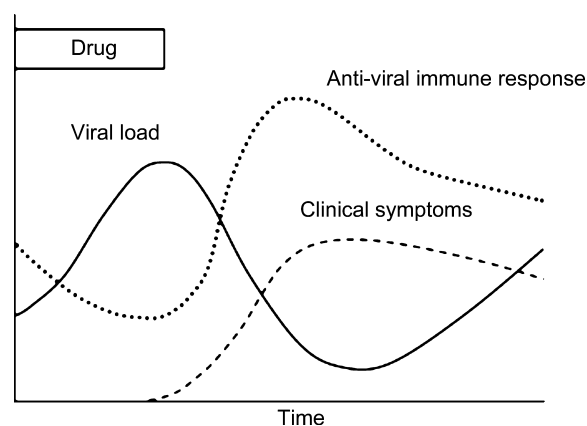


Figure 4 Schematic figure illustrating the relationship among viral loads, anti-viral immune responses and clinical symptoms before and after discontinuation of the causative drug in Drug-induced hypersensitivity syndrome. Reproduced with authorization from Shiohara et al. (69).

organs determined by the cellular tropism of each virus reactivated during the course of the disease; and (iii) the cross-reactivity to multiple drugs seen in patients with DIHS.

One point to be noted is that the viral genome was only detected 2–3 wks after the onset of syndrome but not at an early stage. In this regard, previous reports indicated that causative drugs shown to induce DIHS have in common intrinsic properties to potentially cause immunosuppression (71). It has also been demonstrated that there is a decrease in serum immunoglobulin (Ig) levels, including IgG and IgA and of circulating B cells at onset in patients with DIHS (Fig. 4) (69, 71). Thus, the absence of viral genome at the onset of the disease can be explained by assuming that clearance of the virus may take start only after withdrawal of the causative drug in patients with DIHS. This transient immune dysfunction is an interesting anomaly to explain, as proposed by Kano et al. (71), many characteristics of DIHS, i.e., the long interval until development of DIHS after the first drug intake, the spontaneous remission after drug withdrawal, the relapse with other drugs, and the reactivation of herpes viruses (HHV 6, EBV, cytomegalovirus (CMV). Moreover, clinical symptoms in DIHS are likely to be mediated by rapidly restored antiviral immune responses, such as those seen in immune reconstitution syndrome reported in HIV patients, but not by viruses themselves (69).

Thus, a complex interplay of multiple constitutional and/or acquired factors is likely to be present in DIHS. A

dynamic interplay of cofactors, personal and acquired, seems to be important in the occurrence and expression of DIHS. Recently, discovery of strong associations between specific HLA alleles and the development of DIHS has created the promise for prevention through screening (80).

Conclusion

In summary, drugs can activate the immune system in different ways, leading to a large variety of clinical reactions. Although our knowledge of the pathogenesis of drug adverse reactions has recently much improved, the exact mechanisms as well as phenomena leading to tolerance acquisition or to allergy are not completely understood for most of them yet. Nevertheless, a dynamic interplay of cofactors, individual and environmental, seems to be important in the occurrence and expression of drug adverse reactions. Importantly, certain dogmata are not valid in drug hypersensitivity: they may occur at the first encounter with the drug – without obvious sensitization to the drug itself. Mild reactions do often disappear over time, and in particular, severe reactions need often more time to develop than MPR. More studies are required for a better understanding of the mechanisms and to improve the diagnosis and the treatment of drug allergy.

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