

Danger Signs in Drug Hypersensitivity

Kathrin Scherer, MD^{*}, Andreas J. Bircher, MD

KEYWORDS

- Drug hypersensitivity • Adverse drug reaction
- Clinical danger signs • Immediate-type hypersensitivity
- Delayed-type hypersensitivity

Adverse drug reactions (ADRs) are a frequent problem in clinical routine; 10% to 15% of all patients receiving pharmacotherapy are affected. Predictable pharmacologic side effects (type A [eg, nonsteroidal anti-inflammatory drugs (NSAIDs) and ventricular ulcer]) are distinguished from chronic side effects that are associated with the duration of therapy (type C [eg, nephropathy caused by analgesics]) and from long-term side effects (type D [eg, carcinogenicity or teratogenicity]). Unpredictable side effects (type B, allergies/pseudoallergies/idiosyncrasia) are immunologic reactions, classified according to Gell and Coombs into 4 main pathophysiologic subtypes, or nonimmunologic intolerance reactions. They encompass approximately one-fifth to one-seventh of all ADRs.

In allergic adverse reactions, IgE-mediated immediate-type reactions (Gell and Coombs type I) as well as T-cell-mediated delayed-type reactions (Gell and Coombs type IV) are most frequent.

The skin is involved in approximately 20% of all ADRs in the sense of clinical findings or subjective symptoms on skin, mucosae, or adnex structures. Adverse cutaneous reactions to drugs affect 2% to 3% of hospitalized patients,^{1,2} which are frequently not severe, but some are fatal. The skin is not only a main target of drug allergies but also an important herald organ: it may reveal signs of a more severe cutaneous reaction or may point to the possible involvement of internal organs, or of a systemic hypersensitivity reaction.³ The early recognition of such herald signs may initiate immediate actions with the aim of preventing the development to more severe or even life-threatening reactions⁴ or a specific treatment may be started in some cases.⁵

This article discusses risk factors, early symptoms, and danger signs indicating a possibly severe course of an ADR and advises on early actions. In clinical situations, however, there may be a combination of overlapping symptoms and signs, some of which may be drug related, whereas others are related to the underlying disease.

Allergy Unit, Department of Dermatology, University Hospital Basel, Petersgraben 4, CH-4031 Basel, Switzerland

^{*} Corresponding author.

E-mail address: schererk@uhbs.ch

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Particularly in the acute stage, ADRs, which can mimic many diseases, are always an important differential diagnosis.⁶

PATIENTS AT RISK FOR DRUG HYPERSENSITIVITY REACTIONS

Some patients have an increased risk of developing a drug-hypersensitivity reaction. These patients need to be identified early and in some cases precautions may be taken.

P / D Reac /

A reliable history of a prior ADR, or even a documentation of such or a proved sensitization to a specific drug molecule, have to be noted. Drug-specific antibodies or drug-specific lymphocytes may already be present, potentially resulting in a fast recurrence (more or less severe) of the earlier reaction on accidental or intentional re-exposure. Potential cross-reactivity between related drug molecules has to be considered.

M / / le D T e a

Treatment with multiple drugs seems to elevate the risk for a hypersensitivity reaction, although the exact mechanism is unclear. Excessive demands on enzyme systems for oxidation or acetylation of multiple drugs may interfere with metabolism, lead to accumulation of drugs, and result in accumulation of reactive metabolites and drug interactions. The balance of metabolic bioactivation of a drug and detoxification is an important component of individual susceptibility for drug hypersensitivity.⁷ Also, intermittent or repeated administration of the same drug increases the likelihood of a patient developing a sensitization to the drug or one of its metabolites compared with continuous treatment.

R e f Ad / / a /

The route of administration is relevant because immunogenicity decreases from the topical > subcutaneous > intramuscular > oral > intravenous route. Topical administration of a drug is an important mode of sensitization, especially for antibiotics.

Apart from drug- and treatment-related risk factors, patient-related risks have to be considered.

C c / a / / e

Concomitant illnesses or an underlying disease may have an important influence on the likelihood of developing a drug-related hypersensitivity reaction. This is well known and has been shown repeatedly for viral infections, such as HIV,⁸ Epstein-Barr virus, cytomegalovirus, and other human herpesviruses as well as autoimmune disorders and blood cell malignancies. Current understanding of these reactions is based on the danger hypotheses, which state that a drug signal by itself is not sufficient to cause an immune response, but a second signal is mandatory, such as a danger signal or costimulatory signal.⁸ This would be provided by the generalized virus infection. Drug allergies themselves may also represent risk factors for subsequent drug allergies, and in severe forms a reactivation of virus-infections of the herpes group may occur.⁹

D e C a e

Elevation of drug doses during treatment may contribute to the elicitation of ADRs to a previously well-tolerated drug. Diseases of liver and kidney may interfere with transformation or elimination of potentially harmful reactive drugs or metabolites.¹⁰

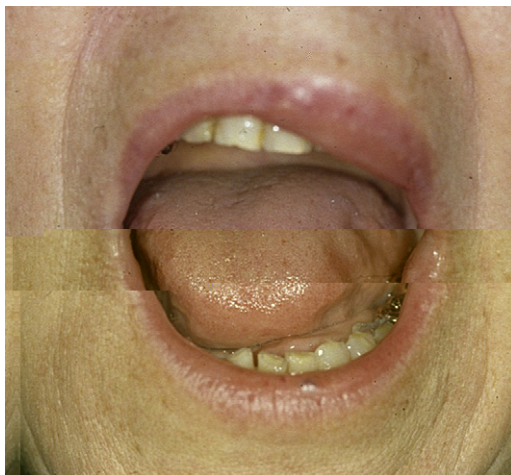


Fig. 1. Angioedema of the lips and tongue.

mortal fear.¹⁶ Other signs that should alert and result in therapeutic interventions are the development of extensive urticaria, especially if it evolves quickly; dyspnea and bronchospasm, especially in known asthmatics; and hypotension.

An anaphylactoid reaction with pruritus, flush and erythema of the trunk, angioedema, and hypertension—the so-called red man syndrome—has been ascribed to too rapid infusions of high doses of vancomycin. A direct histamine release has been shown.¹⁷ Early recognition of these symptoms and immediate action (drug withdrawal and treatment) are mandatory.

CUTANEOUS DANGER SIGNS IN DELAYED-TYPE REACTIONS

The disease entities mentioned below are discussed in more detail in the articles by Bischer; Harr and French elsewhere in this issue for further exploration of this topic.

Delayed-type, T-cell-mediated reactions frequently manifest on the skin with erythema, macules, and infiltrated papules and plaques predominantly on the trunk and the proximal extremities. For the interpretation of the severity of such a reaction, the type of putative causative drug and the time point of the first appearance of symptoms during the treatment course have to be taken into account, because some drugs are more likely to cause severe reactions (eg, allopurinol) than others (eg, amoxicillin). Infiltrated, palpable lesions are potential heralds of the severe drug-induced syndromes, such as drug rash with eosinophilia and systemic symptoms (DRESS) or drug-induced hypersensitivity syndrome (DIHS), used synonymously with DRESS for the purpose of this article. Atypical target lesions or widespread erythema, particularly in the upper chest and back, and development of epidermolysis or bullae are heralds of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

Not all infiltrated lesions herald severe hypersensitivity reactions, however. The general condition of a patient see below usually allows a decisive differentiation because patients with impending severe reactions are usually sicker, have higher temperatures, and complain about malaise compared with patients with mild cutaneous reactions. Such general symptoms should prompt a search for internal organ

involvement (differential blood count, liver and eventually kidney parameters) (discussed later). Uncomplicated pruritic maculopapular exanthems (MPEs) also do not normally develop into SJS/TEN. The primary lesions of MPEs are macules or papules, which, even in case of coalescence, are usually visible at the rims in contrast to atypical target lesions or plane erythemas in SJS/TEN. Patients with MPEs also do not exhibit severe mucosal involvement.

Important cutaneous alert signs (Box 2) for these severe drug hypersensitivity reactions are a central facial erythematous edema (Fig. 2) which is different from the usually pale asymmetric angioedema, as well as involvement of extended body surfaces with confluent lesions and diffuse erythematous swellings developing into erythroderma. Atypical target lesions (Fig. 3)² are a sign of impending development of severe bullous drug reactions, such as SJS and TEN.¹⁸ Another typical and early sign of SJS/TEN in patients with confluent macular exanthema is burning of the skin or painfulness of the skin on touch. Bullous lesions may be about to develop¹⁹; if lateral, tangential pressure on macular lesions leads to epidermal detachment—the so-called Nikolsky sign (Fig. 4)—it is an indication for intraepidermal blister formation.⁵ Confluent vesicles, bullous lesions, and even widespread detachment of necrolytic epidermis are signs of an advanced stage.

Mucosal involvement, in particular stomatitis or balanitis, could represent isolated, localized drug reactions, such as fixed drug eruptions but have to be taken seriously if more than one mucosal area is extensively affected and erosions and ulcerations occur (Fig. 5). In SJS/TEN, severe mucositis of more than one mucosa usually appears early and is followed by epidermal blister formation and necrolysis. Conjunctival involvement, in particular, warrants early cooperation with ophthalmologists because persistent ocular complications are frequent.

Exanthematic purpura (nonblanchable erythematous lesions) represents vasculitis of cutaneous blood vessels (Fig. 6) or a problem in the coagulation cascade. Hemorrhagic or palpable lesions are a sign of perivascular inflammation after destruction of blood vessels and should prompt a search for systemic vasculitis with involvement of internal organs or thrombocytopenia. Bullous transformation and necrosis may follow, which can be extensive and deep, depending on the size of vessel affected. Drug-induced thrombocytopenia (eg, from heparin) or warfarin necrosis presents with a black deep-reaching necrosis of extended skin areas.²⁰

Drug-induced pseudolymphoma typically has a late onset, has a less severe course, and presents with protracted infiltrated lesion.²¹

Box 2

Cutaneous danger signs for severe delayed-type reactions

- Centrofacial edema (diffuse erythematous swelling)
- Involvement of large body surfaces or erythroderma
- Painful skin, skin tender to touch
- Atypical target lesions
- Nikolsky sign positive, vesiculobullous lesions, epidermolysis
- Erosive stomatitis; mucositis, especially if affecting more than one mucosa
- Hemorrhagic necrotizing lesions
- Purpura

GENERAL SIGNS AND INTERNAL ORGAN INVOLVEMENT

Sudden onset of high fever ($>39^{\circ}\text{C}$), otherwise unexplained, disseminated lymphadenopathy, arthralgias, and arthritides may present herald signs for severe hypersensitivity reactions, such as DRESS or serum sickness-like reactions. Facial edema

exanthemas (systemic drug-related intertriginous and flexural exanthema syndrome [SDRIFE-syndrome],²² erythema multiforme, and acute, generalized exanthematous pustulosis [AGEP]). The speed of the evolution of the symptoms over time allows an estimate of the severity of an ADR, because rapidly developing exanthems are more dangerous. For more details see the article by Bircher elsewhere in this issue for further exploration of this topic.

than 90% of the reactions occur within the first 63 days of drug use. There are, however, drug-specific differences in the mean latency between start of intake and first symp-

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