



Immediate type drug hypersensitivity: clinical signs, danger signs and pitfalls

Allergie immédiate aux médicaments : signes cliniques, signes d'alerte et pièges

Andreas J. Bircher *

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

Received 30 December 2005; accepted 5 January 2006

Abstract

Drugs and drug allergens may elicit a wide variety of clinical manifestations and also a variety of pathogenetic mechanisms are involved. Therefore the diagnosis of a drug hypersensitivity reaction is often a major challenge for the diagnosing physician. Early recognition of danger signs of drug allergy may help to reduce sequelae. The knowledge of morphological signs helps to differentiate drug-induced manifestations from other disorders or mimics of drug allergy. Due to the often not specific manifestation of drug-induced allergic reactions, it is important to evaluate a morphological differential diagnosis. Here the emphasis is on immediate type manifestations particularly urticaria and angioedema including anaphylaxis. The typical clinical manifestations, danger signs, and some pitfalls are presented.

© 2006 Elsevier SAS. All rights reserved.

Résumé

Médicaments et allergènes médicamenteux peuvent induire des réactions adverses très variées répondant à des mécanismes différents. Le diagnostic d'hypersensibilité à un médicament peut donc poser problème au médecin. Les signes d'alarme précoces peuvent contribuer à diminuer les séquelles. Il faut savoir distinguer les manifestations d'intolérance médicamenteuse, souvent non spécifiques au plan sémiologique, de celles dues à d'autres affections. Ce travail met l'accent sur les manifestations de chronologie immédiate, en particulier urticaire, angioœdème et anaphylaxie. Les manifestations cliniques typiques, les signes d'alarme mais les difficultés et risques d'erreur y seront présentés.

© 2006 Elsevier SAS. All rights reserved.

Keywords: Drug hypersensitivity; Immediate type reactions; Clinical manifestations; Alert signs; Danger signs; Pitfalls

Mots clés : Hypersensibilité aux médicaments ; Réactions immédiates ; Symptômes ; Signes d'alerte ; Risques d'erreurs

1. Introduction

Drug hypersensitivity reactions often involve the skin. Cutaneous manifestations may be the only presentation of an adverse drug reaction, but the skin can also act as a herald organ, e.g. in systemic hypersensitivity reactions such as anaphylaxis or the drug hypersensitivity syndrome or DRESS.

Particularly the hypersensitivity reactions of type B (bizarre) present with symptoms and signs which are typically not related to pharmacologic effects and doses of the eliciting drugs. The skin is also an early and important organ for the manifestation of a severe cutaneous reaction or the involvement of circulating blood cells or internal organs [1]. For practical purposes clinical symptoms and signs can be grouped as follows: immediate onset reactions, i.e. beginning within minutes to hours, delayed onset or protracted reactions, i.e. manifesting within hours to days, general signs, and signs of internal organ involvement [2]. Here we put emphasis on immediate clinical

* Corresponding author. Tel.: +41 61 265 4359; fax: +41 61 265 4885.

E-mail address: andreas.bircher@unibas.ch (A.J. Bircher).

manifestations particularly urticaria and angioedema including anaphylaxis.

2. Clinical manifestations

Urticaria, angioedema and anaphylaxis can result from a type I (IgE-antibody) or rarely from a type III (immune complexes) reaction according to Coombs and Gell, but also from non-antibody-related, so-called pseudoallergic mechanisms as e.g. in aspirin intolerance. Eliciting drugs include antibiotics, NSAID's, radio contrast media, general anesthetic drugs and many others. Also a vast array of factors can directly trigger the release of histamine such as drugs, foods, food additives and infections [3] rendering the etiologic differential diagnosis sometimes difficult.

2.1. Urticaria

Urticaria is a disseminated skin eruption characterized by rapidly emerging, migrating and itching wheals. Histamine is one of the principal mediator of urticaria: it leads to itching and increased vascular permeability. A wheal is a flat or elevated, pale-red maculae caused by edema and vasodilation in the upper part of the dermis. It may measure from a few millimeters pinpoint wheals up to several centimeters. Wheals mainly affect trunk and extremities more rarely the face, after clearing they leave intact skin without desquamation behind. Pruritus is practically always associated with urticaria. The lesions typically appear within minutes and usually persist less than 24 hours at one location, however, a bout of urticaria may last several days to weeks. If an urticarial lesion persists more than 24 hours without changes at the same spot, leucocytoclastic vasculitis has to be excluded [4].

2.2. Angioedema

Angioedema is a tense non-pitting oedema of the deeper dermis, affecting mainly the face, lips, oral mucosae and male genitalia [5]. Rarely it affects extremities, hands and feet. Life-threatening situations occur when the larynx and pharynx are involved. Patients with angioedema of the lower gastrointestinal tract with colics, vomitus and diarrhea have been reported. Angioedema has a slower evolution than urticaria and may last up to several days. It causes less pruritus but often hypoesthesia or a feeling of pressure [4]. Among other mediators bradykinin [6] may play a more important role, therefore antihistaminic drugs do not reliably work in angioedema.

2.3. Anaphylaxis

Pruritus, urticaria and angioedema may present as initial or partial symptoms of full blown anaphylaxis. Sudden pruritus of palmar, the inguinae, or the capillium may be an early symptom of anaphylaxis. Also facial flush and erythema of the upper trunk, rhinitis and conjunctivitis may be an initial symptom of anaphylaxis. Anaphylaxis is typically IgE-mediated,

however, for some drugs also a not immunologic or so-called pseudoallergic pathomechanism exists, in such a case the term anaphylactoid reaction is used. Independent of the pathomechanism severe immediate type symptoms including bronchospasm and hypotension and lethal outcome may occur [7]. Typically, somewhat depending on the way of administration (oral, parenteral, rarely topical) first symptoms and signs begin within minutes up to a few hours after exposure to the drug.

3. Danger signs

The following immediate (cutaneous) signs may be signal for anaphylaxis or severe bronchospasm which may result in asphyxia, hypoxia or death. Therefore, early recognition and immediate action (drug withdrawal and treatment) are mandatory [2]. Such alert symptoms and signs include (Table 1) [8]:

- sudden onset of severe generalized pruritus or localized itching of the perioral area, the inguinae, palms or soles;
- sudden flush (particularly if accompanied by conjunctivitis or rhinitis);
- acute urticaria (wheals and hives);
- angioedema of mucosae, particularly if the tongue or the pharynx and larynx are affected;
- dysarthria, dysphagia and evidently;
- dyspnoea, bronchospasm or hypotension.

4. Pitfalls

The clinical manifestations of cutaneous hypersensitivity reactions may be manifold. They include a wide spectrum such as pruritus, erythema, erythroderma, urticaria, angioedema, macular, papular, pustular, vesicular, bullous, vasculitic and hemorrhagic exanthems. Members of the same drug group, e.g. the penicillins, may induce via different pathogenetic pathways different clinical manifestations [4]. Therefore, drug allergy is often a diagnostic challenge because pathognomonic clinical morphological reactions are unfortunately rare. Although the above-mentioned clinical signs may be typical manifestations of a drug-induced allergic reaction, other causes may induce similar or even identical clinical signs. Some disorders may mimic allergic reactions and may then be misinterpreted as drug allergy. Finally, because pathomechanisms are not always clear, the time latency of drug reactions do not always follow the expected patterns.

Table 1
Danger signs in immediate hypersensitivity reactions [2]

+++ Flush (and conjunctivitis/rhinitis)
+++ Dyspnoea, bronchospasm
+++ Hypotension
++ Angioedema (particularly tongue, larynx)
++ Severe pruritus (particularly of face, palms, soles)
+ Urticaria

+++ = Immediately stop and treat; ++ = stop and treat as required; + = consider to stop as early as possible, treat as required.

4.1. Pitfalls of time patterns

Although angioedema is a typical manifestation of an immediate type reaction with an occurrence typically within minutes to hours after intake of the eliciting drug, there are some exceptions. For a long time ACE-inhibitors have been recognized to be associated with recurrent angioedema [9]. There is no clear time pattern neither for the induction nor the reaction latency. Some patients suffer from a severe laryngeal angioedema upon the first intake of an ACE-inhibitor, others start to suffer from recurrent angioedema after years of tolerance of the drug. The pathogenesis is unknown, there is some evidence that bradykinin metabolism is involved (Fig. 1). However, some of these patients suffer also angioedema from sartanes, which according to newer data also seem to increase bradykinin levels [9]. Therefore, an individual disposition seems to play an important role, e.g. deficiency in another bradykinin-metabolizing enzyme carboxypeptidase has been proposed. Obesity, former bouts of angioedema, neck surgery, and particularly hereditary angioedema have been proposed or identified as risk factors. Rarely ACE-inhibitors acted as cofactors, i.e. a drug e.g. an antibiotic or local anesthetic only elicited angioedema as long as the patient was also treated with an ACE-inhibitor [10].

4.2. Pitfalls of morphological signs

Rarely corticosteroids may elicit immediate type reactions [11], and occasionally delayed exanthems [12]. Some cases

of immediate reactions are due to the steroid molecule itself, whereas several cases from the additive carboxymethylcellulose have been reported [13]. On the other hand facial flush from systemic corticosteroids is a phenomenon mainly observed in postmenopausal women [14]. It is a pharmacologic adverse effect due to a reactive vasodilation. In these patients no hypersensitivity is present and they can usually be treated with corticosteroids.

Another pitfall may be the centropal edematous swelling which is typical for the drug hypersensitivity syndrome or DRESS [15]. Patients with DRESS have also fever, an exanthematous rash, often eosinophilia and internal organ involvement, e.g. hepatitis.

Swellings in the neck area are sometimes misinterpreted as angioedema. The differential diagnosis after drug administration includes subcutaneous emphysema [16], and the rare sialadenopathy or iodine mumps due to iodine containing compounds [17]. Apart from the upper oral cavity angioedema may also affect the lower gastrointestinal tract resulting in colical pain, vomitus and diarrhea [18].

In some instances an exanthema may manifest in a symmetrical flexural distribution. A sharply delineated erythema of the perigenital and perianal area is associated with the affection of the large folds, such as the axilla, the elbows and the knee folds. Recently the acronym SDRIFE for this particular manifestation of a delayed type hypersensitivity has been proposed [19]. The time pattern usually follows a delayed type hypersensitivity reaction, i.e. the manifestation starts 12–24 hours after drug exposure in a previously sensitized patient.

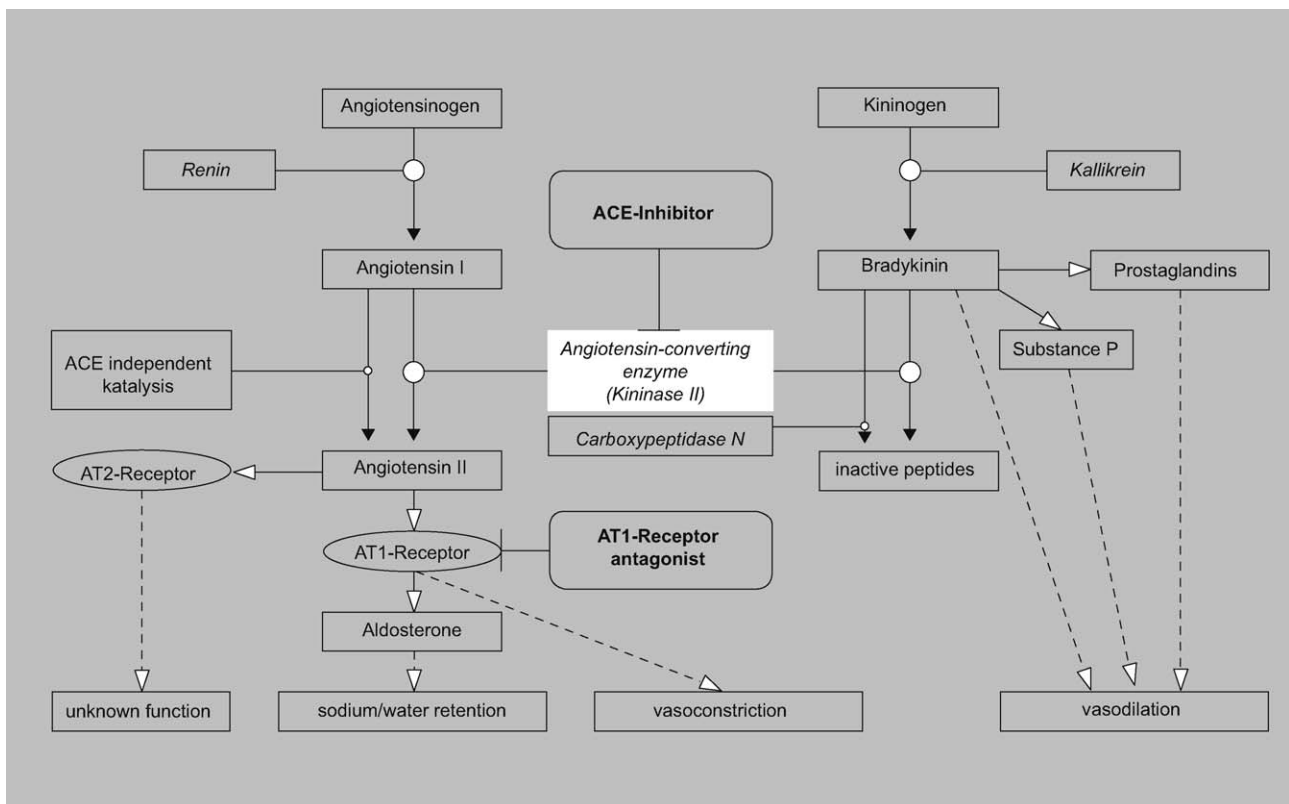


Fig. 1. Proposed mechanism in the pathogenesis of ACE-inhibitor induced angioedema.

4.3. Pitfalls of etiological differential diagnosis

Angioedema and urticaria belong to the most common skin disorders. Elicitors may be manifold, as mentioned above a large variety of triggers such as drugs, foods, food additives and infections may be involved [4,20]. This often complicates the identification of the eliciting factor, particularly in patients with acute infections who are treated with several drugs. Sometimes-confounded phenomena are the urticarias of physical origin. Particularly cholinergic urticaria, which may be triggered by fever is sometimes misinterpreted as drug-induced urticaria.

References

- [1] Roujeau JC. Clinical heterogeneity of drug hypersensitivity. *Toxicology* 2005;209(2):123–9.
- [2] Bircher AJ. Symptoms and danger signs in acute drug hypersensitivity. *Toxicology* 2005;209(2):201–7.
- [3] Moneret-Vautrin DA, Morisset M, Flabbee J, Beaudouin E, Kanny G. Epidemiology of life-threatening and lethal anaphylaxis: a review. *Allergy* 2005;60(4):443–51.
- [4] Bach S, Bircher AJ. Drug hypersensitivity reactions: from clinical manifestations to an allergologic diagnosis. *Allerg Immunol (Paris)* 2005;37(6):213–8.
- [5] Scherer K, Bircher AJ. Wenn's eng wird... oder das Angioödem des Oropharynx. *Ther Umsch* 2004;61(5):341–7.
- [6] Nussberger J, Cugno M, Amstutz C, Cicardi M, Pellacani A, Agostoni A. Plasma bradykinin in angio-oedema. *Lancet* 1998;351(9117):1693–7.
- [7] Brown SG. Cardiovascular aspects of anaphylaxis: implications for treatment and diagnosis. *Curr Opin Allergy Clin Immunol* 2005;5(4):359–64.
- [8] Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. *N Engl J Med* 1994;331(19):1272–85.
- [9] Campbell DJ, Krum H, Esler MD. Losartan increases bradykinin levels in hypertensive humans. *Circulation* 2005;111(3):315–20.
- [10] Schiller P, Langauer Messmer S, Haefely W, Schlienger R, Bircher AJ. Angiotensin-converting enzyme inhibitor induced angioedema. Late onset, irregular course and potential role of triggers. *Allergy* 1997;52:432–5.
- [11] Burgdorff T, Venemalm L, Vogt T, Landthaler M, Stolz W. IgE-mediated anaphylactic reaction induced by succinate ester of methylprednisolone. *Ann Allergy Asthma Immunol* 2002;89(4):425–8.
- [12] Bircher AJ, Levy F, Langauer S, Lepoittevin J. Contact allergy to topical corticosteroids and systemic contact dermatitis from prednisolone with tolerance of triamcinolone. *Acta Dermatol* 1995;75:490–3.
- [13] Bigliardi PL, Izakovic J, Weber JM, Bircher AJ. Anaphylaxis to the carbohydrate carboxymethylcellulose in parenteral corticosteroid preparations. *Dermatology* 2003;207(1):100–3.
- [14] Cicala RS, Westbrook L, Angel JJ. Side effects and complications of cervical epidural steroid injections. *J Pain Symptom Manage* 1989;4(2):64–6.
- [15] Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (Drug Rash with Eosinophilia and Systemic Symptoms: DRESS). *Semin Cutan Med Surg* 1996;15(4):250–7.
- [16] Fruhauf J, Weinke R, Pilger U, Kerl H, Mullegger RR. Soft tissue cervicofacial emphysema after dental treatment: report of 2 cases with emphasis on the differential diagnosis of angioedema. *Arch Dermatol* 2005;141(11):1437–40.
- [17] Bach S, Anner Y, Arnold A, Hohenstein E, Häusermann P, Bircher AJ. Delayed hypersensitivity reactions to iodinated contrast media in 2 patients: unusual manifestation as iodine mumps and flexural exanthem (SDRIFE). *Swiss Med Wkly* 2005;135(Suppl. 144):S14.
- [18] Schmidt TD, McGrath KM. Angiotensin-converting enzyme inhibitor angioedema of the intestine: a case report and review of the literature. *Am J Med Sci* 2002;324(2):106–8.
- [19] Häusermann P, Harr T, Bircher AJ. Baboon syndrome resulting from systemic drugs: is there strife between SDRIFE and allergic contact dermatitis syndrome? *Contact Dermatitis* 2004;51:297–310.
- [20] Sackesen C, Sekerel BE, Orhan F, Kocabas CN, Tuncer A, Adalioglu G. The etiology of different forms of urticaria in childhood. *Pediatr Dermatol* 2004;21(2):102–8.