



Clinical heterogeneity of drug hypersensitivity

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Abstract

Skin is the most frequent target of drug reactions that are reported, may be because they are easily detected. Most (probably more than 90%) are related to drug hypersensitivity, i.e. an individually tailored, unexpected effect mediated by a drug specific activation of the immune response.

The clinical presentation of “drug eruptions” is highly variable, from the most common transient and benign erythema that occurs 6–9 days after the introduction of a new drug in 1 to 3 % of users to the most severe forms, that fortunately affect less than 1/10,000 users.

Even though there are some overlapping or unclassifiable cases, it is important for clinicians to recognize and categorize severe cutaneous adverse reactions/SCAR (bullous fixed drug eruptions/bFDE, acute generalized exanthematous pustulosis/AGEP, drug reaction with eosinophilia and systemic symptoms/DRESS, Stevens-Johnson syndrome/SJS, toxic epidermal necrolysis/TEN). First they must suspect rapidly that an unusual eruption with high fever and severe constitutional symptoms is caused by a medication and not by an infection. Second they have to look for involvement of organs that differ according to the type of reaction. Third they can determine a prognosis, the mortality rate being virtually 0 for bFDE, 5% for AGEP, 10% for “hypersensitivity syndrome”/DRESS and 25% for SJS or TEN. In addition if some medications are “usual suspects” for all types (e.g. anticonvulsants), some other are more specific of a given pattern (pristinamycine, hydroxychloroquine, diltiazem for AGEP, minocycline for DRESS, anti-infectious sulfonamides, allopurinol for epidermal necrolysis).

The “phenotypic” diversity of the final expression drug reactions can be explained by the engagement of a variety of cytokines and inflammatory cells and by regulatory mechanisms. For example, memory cytotoxic T-Cells are key effectors in both localized blisters of bFDE and in extensive blisters of epidermal necrolysis.

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According to Dorland’s Medical Dictionary, hypersensitivity is a “state of altered reactivity in which the body reacts with an exaggerated immune response to a foreign substance”. This definition implies: unexpected, immunologically mediated, and

individual predisposition. This obviously applies to many idiosyncratic drug reactions, but not to all.

Many frequent adverse drug reactions (ADRs) are not hypersensitivity. This is the case for most CNS alterations, e.g. headache, drowsiness, sleepiness, convulsions, many symptoms of gastro-intestinal involvement such as diarrhoea after antibiotics or gastric bleeding and NSAIDs, frequent kidney related

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ADRs such as diuretic related hypokaliemia, NSAIDs induced renal failure or cytopenia from cancer drugs.

Also many kinds of cutaneous ADRs are definitely not immunologically mediated, including phototoxic reactions, hyperpigmentation, anticoagulant skin necrosis, toxicity towards hairs or skin of anticancer (and many other) drugs, antiretroviral agents related lipodystrophy, effects on skin and appendages of corticosteroids and hormones, etc. In recent years, however increasing evidence has indicated that most acute drug rashes are probably of immunological origin.

Skin is one of the most common targets of adverse drug reactions. Eruptions are observed in 0.1–1% of treated patients in pre-marketing trials of most drugs. A number of drugs of current utilisation are associated with higher rates of skin eruptions: 5–7% for aminopenicillins, 3–4% for antibacterial sulfonamides, 5–10% for many antiepileptics. In reported series 90% of these drug eruptions are benign (Hunziker et al., 1997). Because underreporting is expected to be more frequent for benign reactions, one may assume that severe cutaneous ADRs account for about 2% of all skin reactions.

It is our opinion that the different clinical patterns of severe drug eruptions should be distinguished, while others prefer mixing all of them under the denomination of “hypersensitivity reactions”. Both conceptions are based on mechanistic considerations. The “mergers” emphasize the key role of “reactive metabolites” of drugs as common initiators of all types of reactions (Knowles et al., 2000). The “splitters” underline the differences in clinical presentation, pathology of skin and visceral lesions, and biologic markers that suggest that the effector mechanisms are probably different (Roujeau and Stern, 1994).

1. Heterogeneity of skin lesions

1.1. Common “drug rashes”

Exanthematous or maculo-papular eruptions, often reported as “drug rashes” or “drug eruptions” are the most common adverse drug reactions affecting the skin. Prospective cohort studies have shown that these benign rash account for more than 90% of all cutaneous ADRs (Hunziker et al., 1997). The eruption usually occurs between 4 and 14 days after the beginning of

a new medication, and even 1 or 2 days after it has ceased (“eruption of the ninth day”). However, it can develop sooner, especially in case of rechallenge. The eruption consists of erythematous macules or papules, often symmetric. They begin on the trunk, upper extremities, and progressively become confluent. The eruption is typically polymorphous: morbilliform or sometimes urticarial on the limbs, confluent on the thorax, purpuric on the feet. Mucous membranes are usually not involved. Pruritis and low-grade fever are often associated to the eruption, which usually disappear in a few days. The clinical pattern of the eruption often changes with the body site and duration.

This explains why these eruptions may be reported as “polymorphic” or “multiforme”, creating confusion with Erythema Multiforme.

The differential diagnosis of exanthematous drug reactions includes viral eruptions (EBV, CMV, HHV6, Parvovirus B19, etc.), toxic eruptions, acute Graft-versus-Host reaction, Kawasaki syndrome, Still’s disease, etc. Viral infections are the cause of most drug eruptions in children, while drugs are more frequently responsible in adults.

Most drugs can induce an erythematous eruption in about 1% of users. The following drugs have higher risks (more than 3% of users): allopurinol, aminopenicillins, cephalosporins, antiepileptic agents, and antibacterial sulphonamides.

1.2. Urticaria, angioedema, anaphylaxis

Urticaria is a common, transient eruption of erythematous and oedematous papules and plaques, usually associated with pruritus. When dermal and subcutaneous tissues are involved, this reaction is known as angioedema. Urticaria and angioedema are associated in 50% of cases. They can be complicated by a life threatening anaphylaxis. Urticaria, angio-oedema and anaphylaxis are generally a type I hypersensitivity reaction mediated by IgE antibodies. Other “anaphylactoid” mechanisms leading to direct and a non-specific liberation of histamine or other mediators of inflammation are also common for drug reactions.

Clinically, itchy erythematous, oedematous papules and plaques develop in variable number and size. They last a few hours and disappear within 24 h, leaving the skin with a normal appearance. Angioedema is often associated to urticaria, consisting of pale or pink

swellings which affect the face (eyelids, lips, ears, etc.) but also buccal mucosa, tongue, larynx, pharynx, etc. Anaphylaxis can lead to respiratory collapse, shock and death.

Many drugs can induce urticaria. Antibiotics, especially penicillin, and general anaesthetics are classic causes of IgE mediated hypersensitivity reaction. The two most frequent causes of drug-induced non-IgE-mediated urticaria and angioedema are NSAIDs and angiotensin-converting enzyme (ACE) inhibitors. Angioedema occurs in 2–10 per 10,000 new users of angiotensin-converting-enzyme inhibitors, a rate probably higher than the risk associated with penicillins (about 1 per 10,000 courses).

Anaphylaxis has an incidence of 80–100 cases/million/year. It is much more often related to insect stings (59%) than to a drug allergy (18%). Even in case of circulatory failure the death rate is below 2% (Helbling et al., 2004). Drug related urticaria, angioedema or anaphylaxis begin a few minutes to a few hours after drug administration.

1.3. Acute generalized exanthematous pustulosis

AGEP is characterized by fever and a pustular rash (Beylot et al., 1980). Numerous, small, mostly non-follicular pustules arise on a widespread edematous erythema (Fig. 1). Edema of the face and the hands, purpura, vesicles, blisters, erythema multiforme-like lesions and mucous membrane involvement, has also been associated. The pustules are mainly localized on the mainfolds (neck, axillae, groins, etc.) trunk and upper extremities.



Fig. 1. AGEP. Dozens of non-follicular pustules arising on disseminated erythema.

Hyperleukocytosis with elevated neutrophils count, transient renal failure, hypocalcemia are frequently seen (Roujeau et al., 1991).

The time between the drug administration and the skin eruption is relatively short, less than 2 days. The eruption lasts a few days, and is followed by a superficial desquamation. AGEP must be differentiated from acute pustular psoriasis. The pustules in both diseases are clinically indistinguishable, the histopathology can be helpful.

Proposed diagnosis criteria include: (1) an acute pustular eruption; (2) fever above 38 °C; (3) neutrophilia with or without a mild eosinophilia; (4) sub-corneal or intraepidermal pustules on skin biopsy; (4) spontaneous resolution in less than 15 days (Sidoroff et al., 2001).

Antibiotics (aminopenicillins, pristinamycine, etc.) and diltiazem are the main drugs implicated in AGEP.

1.4. DRESS-hypersensitivity

The acronym of DRESS for drug reaction with eosinophilia and systemic symptoms has been proposed as more specific than “hypersensitivity” which would be an appropriate denomination for most types of drug reactions. DRESS points to two important characteristics: multi-systemic involvement and frequent eosinophilia (Bocquet et al., 1996).

It has been estimated to occur in about one in 10000 exposures with drugs such as antiepileptics and sulfonamides. It is typically characterized by a severe eruption (Fig. 2), lymphadenopathy, fever and hematological abnormalities. Visceral involvement differentiates hypersensitivity syndrome from common exanthematous eruptions, it may include hepatitis, arthralgias, pulmonary infiltrates, interstitial nephritis and affect other organs as well (Guillon et al., 1992).

These reactions are more frequent among persons of African ancestry. They begin 2–6 weeks after the first drug use, later than most other skin reactions.

Prominent eosinophilia is common and a rather characteristic biological feature of this reaction is the appearance of atypical lymphocytosis in the circulation. Rash and hepatitis may persist for several weeks after drug withdrawal, and some of the manifestations may be life threatening, with a mortality rate of about 10%.



Fig. 2. DRESS. Persistent exfoliative dermatitis.

The differential diagnosis includes acute viral infections, idiopathic hypereosinophilic syndrome, and lymphoma. A special attention should be paid to HHV6, since several publications suggested a possible interaction between DRESS and reactivation of HHV6.

The aromatic antiepileptic agents (phenobarbital, carbamazepine, phenytoin), minocycline and allopurinol are the most frequent causes. Sulfonamides, gold salts, dapsone may also induce this syndrome.

1.5. Fixed drug eruption (FDE)

The lesions develop usually less than 2 days after the drug intake. They are characterized by one or few, round, sharply demarcated erythematous and edematous plaques, sometimes with a central blister (Fig. 3). The eruption can be located on every site of the body and may involve mucous membranes, principally the lips and genitalia. The eruption progressively fades in



Fig. 3. Fixed drug eruption.

few days, to leave a post-inflammatory brown pigmentation. With rechallenge with the causative drug, the lesions recur at the same sites. After several relapses the eruption may involve large areas of the body. This generalized fixed drug eruption may be difficult to distinguish from TEN. The absence of mucous membrane erosions and mild constitutional symptoms support a diagnosis of FDE. The prognosis is much better than for TEN with basically no mortality.

The drugs most frequently associated with fixed drug eruption are phenazone derivatives, barbiturates, tetracyclines, sulfonamides, and carbamazepine.

1.6. Stevens-Johnson syndrome and toxic epidermal necrolysis

The incidence of TEN is evaluated to 0.4–1.2 cases per million person-years and of SJS from 1 to 2 cases per million person-years (Rzany et al., 1996).

With others we proposed to consider SJS and TEN as severity variants of the same drug-induced disease, and to distinguish SJS from erythema multiforme major, the later being mostly related to infections, especially with herpes (Auquier-Dunant et al., 2002).

In our experience erythema multiforme is rarely drug-induced. Most of the cases that are reported as drug-induced EM are either cases that we would label as SJS or cases of erythematous drug eruptions, because of confusion between “multiforme” and the polymorphous patterns of many erythematous eruptions.

Stevens-Johnson syndrome is characterized by small blisters arising on purple macules. Lesions are



Fig. 4. Overlap SJS/TEN.

widespread and usually predominate on the trunk. Confluence of blisters on limited areas leads to detachment below 10% of the body surface area.

Toxic epidermal necrolysis is characterized by the same lesions than SJS but with confluence of blisters leading to positive Nikolski sign and to detachment of large epidermal sheets on more than 30% of the body surface area (cases with detachment between 10 and 30% are labeled overlap SJS-TEN, Fig. 4) (Bastuji-Garin et al., 1993). Exfoliative dermatitis, staphylococcal scalded skin syndrome, AGEP, paraneoplastic pemphigus may be misdiagnosed as SJS or TEN.

Patients with SJS or TEN have high fever. Severe erosions of mucous membranes are nearly constant. Systemic manifestations include mild elevation of hepatic enzymes (overt hepatitis in 10% of cases), intestinal and pulmonary manifestations (with sloughing of epithelia similar to what happens to the skin). Death occurs in 10% of patients with SJS and above 30% of patients with TEN, principally from sepsis or pulmonary involvement.

Medications are responsible for at least 70% of cases of both SJS and TEN. Antibacterial sulfonamides, anticonvulsants, oxicam-NSAIDs, allopurinol and nevirapine are drugs associated with the higher risks.

2. Heterogeneity of skin pathology

In the common “drug rashes” cutaneous pathological slides show normal or nearly normal skin in the majority of cases. They may exhibit a mild lymphocytic infiltrate around vessels of the dermis, and a few

necrotic keratinocytes within the epidermis. This pattern is not specific and cannot help to distinguish a drug eruption from an eruption of another cause.

The histopathology of AGEP is characteristic by showing spongiform pustules located under the stratum corneum, the most superficial layer of the epidermis. Papillary dermal edema and perivascular polymorphous infiltrate are usually present. Leukocytoclastic vasculitis and focal necrotic keratinocytes have also been reported.

The histopathology of DRESS lesions exhibits a rather dense lymphocytic infiltrate in the superficial dermis and/or perivascular, associated to eosinophils and dermal edema. Occasionally the lymphocytic infiltrate contains atypical cells or is dense enough to raise the diagnosis of cutaneous lymphoma.

Biopsies of FDE reveal a mild superficial and deep dermal and perivascular infiltrate (composed of lymphocytes, eosinophils, and sometimes neutrophils) associated to a various amount of necrotic keratinocytes. In most severe forms the extent of epidermal necrosis may mimic TEN. When present, dermal macrophages pigmented by melanin (melanophages) are considered an important clue to the diagnosis.

In SJS and TEN pathology shows necrosis of full-thickness epidermis, with a very mild lymphocytic infiltrate of the superficial dermis. Negative immunofluorescence findings are important to rule out an autoimmune blistering disease.

3. Heterogeneity of biological alterations

There are few biological alterations in “common” drug rashes. Mild eosinophilia is present in 20–40% of cases.

AGEP is characterized by hyperleukocytosis with elevated neutrophil count, transient functional renal failure.

In addition to biological alterations related to the involvement of each specific organ, patients with DRESS usually have blood counts alteration suggestive of “lymphocyte activation” with lymphocytosis and atypical basophil lymphocytes. Eosinophilia above 1500 mm^{-3} is present in 60–70% of cases.

Eosinophilia and atypical lymphocytosis are not observed in SJS and TEN whereas leucopenia is frequent and lymphopenia is nearly constant.

4. Heterogeneity of complications, prognosis and sequels

At first glance, similar organs e.g. liver, kidney or lung may be involved in all types of severe cutaneous ADRs. Looking more closely there are anyhow important differences in the frequency, severity and more importantly type of involvement.

Mild elevation of liver enzymes is frequent in SJS or TEN but definite hepatitis is present in only 10% of cases versus 50% in DRESS.

Interstitial nephritis is frequent in DRESS, with proteinuria, abnormal urinary sediment with occasionally eosinophils. Interstitial infiltration by lymphocytes, histiocytes and eosinophils have been repeatedly demonstrated by kidney biopsy. In SJS or TEN kidney involvement, when present, has the features of “pre-renal azotemia”. In addition there are frequently urinary changes suggestive of tubular cell alterations without effect on kidney function.

Lung lesions consist in interstitial and alveolar infiltration by lymphocytes and eosinophils in DRESS and in necrosis of epithelial cells in TEN (Lebargy et al., 1997).

The death rates of severe cutaneous ADRs range from 2% for anaphylaxis to 40% for TEN with intermediate figures of 5% for AGEP and 10% for DRESS and SJS.

The principal sequels are: skin discolouration for FDE, SJS and TEN, chronic exfoliative dermatitis for DRESS, synechiae of genital mucosa and chronic potentially very severe lesions of the eyes for SJS and TEN.

5. Heterogeneity of drug causes

Many medications are associated with “high risk” of inducing nearly all types of cutaneous ADRs. This is the case for anti-infective sulfonamides and antiepileptic drugs. But there are also many examples pointing to some specificity. Minocycline a frequent cause of DRESS, is not a “high risk” drug for AGEP, SJS or TEN. Other cyclines, frequently found in series of FDE, are not associated to a substantial risk of DRESS. Allopurinol and oxicam-NSAIDs are major causes of SJS or TEN, frequent causes of DRESS but not associated to AGEP. Diltiazem and a macrolide related antibiotic,

pristinamycine are frequent causes of AGEP but not of other SCARs.

6. Why so many clinical presentations?

Most reactions being related to delayed hypersensitivity to a medication, the variety of clinical presentation needs additional explanations. It has been suggested that it could result from distinct T-lymphocyte recruitment. CD8 cytotoxic cells largely predominate in the lesions of blistering reactions (FDE, SJS, TEN) when CD4 cells predominate in “common” rashes (Barbaud et al., 1997), AGEP and DRESS. Different cytokine production may also contribute to different clinical features: perforin/granzyme, Fas-L, TNFalpha in SJS/TEN (Posadas et al., 2002); IL5 and eotaxin in DRESS (Choquet-Kastylevsky et al., 1998; Yawalkar et al., 2000); IL8 in AGEP (Britschgi et al., 2001). A role for regulatory T-cells has been proposed to explain the limited progression of blisters in FDE (Teraki and Shiohara, 2003).

It is anyhow obvious that the traditional Gell and Coombs classification of hypersensitivity reactions does not fit the various clinical features of hypersensitivity to medications. Therefore Pichler (2003) recently proposed a sub-classification of delayed hypersensitivity reactions (type IV).

Cytotoxicity (type IVc) from CD4+ or CD8+ T cells seems to participate in many drug reactions. The final pattern is modulated by the preferential activation and recruitment of monocytes (type IVa), eosinophils (type IVb) or neutrophils (type IVd). This classification will probably correspond well with the clinical heterogeneity of drug hypersensitivity.

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