

Physiopathology and treatment of severe drug eruptions

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This review will focus on recent advances concerning the most severe cutaneous drug reactions: the Stevens–Johnson syndrome, toxic epidermal necrolysis, and drug reactions with eosinophilia and systemic symptoms. The most significant progress concerned the demonstration that drugs more often than reactive metabolites are immunogenic and induced several kinds of responses. These findings provided the rationale for using new therapeutic approaches, which will be discussed.

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Abbreviations

DRESS	drug reaction with eosinophilia and systemic symptoms
IVIg	intravenous immunoglobulin
RCT	randomized controlled trial
SJS	Stevens–Johnson syndrome
SMX-NOH	sulfamethoxazole- <i>N</i> -4-hydroxylamine
TEN	toxic epidermal necrolysis
TNF-α	tumour necrosis factor alpha
CLA	cutaneous lymphocyte-associated antigen

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Introduction

According to the current definitions of the World Health Organization, drug eruptions are severe when they are life threatening and need hospitalization or result in some disability. Many drug eruptions fit this definition, some being subacute or chronic. We will focus here on a few acute reactions: the Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and ‘hypersensitivity syndrome’/drug reaction with eosinophilia and systemic symptoms (DRESS). Our definition criteria of these reactions are presented in Table 1.

It is our opinion that these different patterns of severe drug eruptions should be distinguished, whereas others prefer to group them all under the denomination of ‘hypersensitivity reactions’ [1]. 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 severe reactions. The ‘splitters’ underline the differences in clinical presentation, pathology of skin and visceral lesions, and biological markers that suggest that the effector mechanisms are probably different [2].

Recent advances in the mechanisms of severe drug eruptions

In the last decade our understanding of the immunogenicity of drugs progressed a lot.

The reactive metabolites hypothesis

The hypothesis was presented 15 years ago that patients suffering from severe drug reactions (hepatitis or cutaneous reactions) were exposed to increased amounts of reactive (oxidative) metabolites, because of a decreased production of normal soluble atoxic metabolites and also because of a decreased ability to detoxify reactive metabolites [3].

At both steps the alterations in detoxification enzymes could be explained on a genetic basis (e.g. slow acetylation genotype) or on a functional basis (e.g. deficit in glutathione in AIDS patients).

The reactive metabolite hypothesis has been supported by several pieces of evidence for drug-induced hepatitis, but still lacks definite proof for drug eruptions. Several series [4,5] found that a slow acetylation phenotype or genotype was associated with an increased risk of reactions to sulfonamides, but other series [6,7,8*] observed no significant association. The same equivocal results were obtained for epoxide hydrolase and

Table 1. Criteria used in the classification of severe drug eruptions

	SJS	TEN	'Hypersensitivity'/DRESS
Mucous membrane	> 90%	> 90%	< 30%
Erosions	Several sites	Several sites	Mouth and lips
Detachment of epidermis	Yes	Yes	No
	< 10% of BSA	≥ 30% of BSA ^a	
Hyperkeratosis/desquamation	No	No	Usual
Neutropenia	No	30%	No
Eosinophilia	No	No	90%
Atypical lymphocytes	No	No	30–40%
Respiratory tract	Bronchial erosions/ARDS	Bronchial erosions/ARDS	Interstitial pneumonitis
Liver	Hepatitis 10%	Hepatitis 10%	Hepatitis 60%
Heart	No	No	Myocarditis
Lymph node enlarged	No	No	Usual

ARDS, Adult respiratory distress syndrome; BSA, body surface area; DRESS, drug reaction with eosinophilia and systemic symptoms; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

^a When detachment involves 10–29% of BSA, we classify the case as SJS–TEN overlap.

Reproduced from Roujeau and Stern [2], with permission.

reactions to anticonvulsant agents [1]. Initial reports that AIDS patients were depleted in glutathione were not confirmed by further studies [8•,9]. *N*-acetylcysteine at a dose of 3 g twice a day could not be shown to prevent trimethoprim–sulfamethoxazole hypersensitivity reactions in patients with HIV infection [10]. A few recent publications are of interest on this point. One demonstrated that epidermal cells (keratinocytes) metabolized sulfamethoxazole to *N*-acetyl (non-reactive) and also to *N*-4-hydroxylamine [sulfamethoxazole-*N*-4-hydroxylamine (SMX-NOH) reactive metabolite]. When keratinocytes were incubated with 0.1–1 mmol SMX-NOH covalent adducts to membrane protein were obtained. On the other hand, when keratinocytes were incubated with 1 mmol of the parent drug (sulfamethoxazole) no covalent adduct was detected, probably because the production of SMX-NOH was too low (0.000005 mmol) [11••].

A prospective study of a cohort of 136 HIV-infected patients treated with sulfonamides [8•] found no association of drug eruption with acetylation genotype or glutathione levels, but it raised a new metabolic hypothesis of the potential role of a null mutation of glutathione transferase.

A third paper checked the immunological reactivity of T lymphocytes clones derived from patients with previous eruptions to sulfamethoxazole [12••]. The clones were obtained after in-vitro stimulation of blood lymphocytes by sulfamethoxazole and two reactive metabolites SMX-NOH and nitroso-sulfamethoxazole. More than 80% of 222 clones, even when obtained by stimulation with a reactive metabolite, recognized the parent drug only [12••]. These results challenge the current opinion that reactive metabolites are more important than sulfamethoxazole itself in initiating the immunological

reaction that results in eruption. The paper reassesses the usual distinction between the immunogenicity of sulfonamides and beta-lactams, two frequently sensitizing drugs. Penicillin G and its derivatives have long been known to be reactive *per se* [13], whereas sulfonamides were thought to need a transformation in reactive metabolites.

Immunology of severe drug eruptions

Much innovative research on the immunology of drug eruptions has come from Pichler's team in Bern, Switzerland.

Presentation and role of T cells

In the past 6 years they obtained T lymphocyte clones that reacted with a variety of drugs in several types of drug eruptions. Studies with these clones demonstrated that drugs differed from common peptide antigens by their ability to stimulate T cells in several ways, including an original non-covalent link with MHC molecules on the surface of antigen-presenting cells. *In vitro* different drug reactive clones produce different cytokines. This probably contributes to different clinical expressions of the reaction [12••,14–17].

Chemokines

Increased perforin and granzyme B containing T cells and peripheral blood mononuclear cells may contribute to the damage in epidermal cells [18,19]. The production of eotaxin and IL-5 is a main determinant of the eosinophilia that characterizes the DRESS/'hypersensitivity' syndrome [20,21]. The blood lymphocytes of patients who developed delayed hypersensitivity were restricted to T helper type 1 responses when specifically stimulated, in contrast to the cells of patients with immediate hypersensitivity who had both T helper types 1 and 2 responses [22].

Apoptosis

With regard to SJS and TEN, it has recently been proposed that the widespread apoptosis of keratinocytes that leads to the detachment of large sheets of epidermis was principally mediated by the interaction of Fas-CD95 and its ligand, Fas-L [23]. The death receptor Fas is normally present on epidermal cells. Fas-L can also be detected at very low levels. During TEN there is an overexpression of Fas-L, which may explain a 'collective suicide' of keratinocytes. Recent studies [18–24], however, confirmed previous observations that mediators of apoptosis other than Fas-L, e.g. perforin and tumour necrosis factor alpha (TNF- α), were also present and activated in the skin lesions of TEN. It therefore seems probable that several pathways may be activated at the same time, and that some additive effect leads to the destruction of the epidermis.

The ultimate non-specific activation of apoptosis pathways probably depends on activated T lymphocytes present at the site of lesions. For example, many activated CD8 T lymphocytes were found in the blister fluid accumulated under the necrotic epidermis. These cells shared phenotypic markers of natural killer and of cytotoxic T cells. They also expressed a membrane marker (cutaneous lymphocyte-associated antigen-CLA) allowing the homing of lymphocytes in the skin [25].

Not surprisingly, an overexpression of CLA on skin-infiltrating lymphocytes is a common finding in many cutaneous diseases, including drug reactions [26•]. The paper by Blanca *et al.* [27] suggested that CLA+ T cells and delayed skin reaction to drugs have parallel evolution.

It remains to be determined whether the lymphocytes present *in situ* are actually drug specific and whether the stimulation of these drug-specific lymphocytes is initiated locally or in lymphoid organs with a secondary direction towards the skin because of CLA expression.

Treatment of severe drug eruptions

We will review below the most important supportive measures and discuss the interest of more specific approaches.

Withdrawal of the suspect drug(s)

Because of the frequent practice of treating AIDS patients 'through' mild drug eruptions, we looked at the impact of the date of drug withdrawal in a large retrospective series of patients with SJS or TEN in our institution. We observed that the death rate was lower in patients who stopped the administration of causative drugs with short elimination half-lives early (no later than the day when blisters or erosions first occurred) in comparison with patients who used the suspect drugs after the onset of blisters [28].

We concluded that withdrawal of the suspect drug(s) should be carried out as soon as possible in patients with SJS or TEN. Whether this conclusion also applies to other types of severe drug eruptions is not known, but would seem logical.

Supportive therapy

In the case of 'acute skin failure' (DRESS with exfoliative dermatitis, TEN), management of patients must be undertaken in specialized intensive care units or in burns units [29•]. The main principles of symptomatic therapy are the same as for major burns, and include: fluid replacement, anti-infectious therapy, aggressive nutritional support, warming of the environmental temperature, and skin care with appropriate dressings [30].

Treatments aimed at halting disease progression

The duration of disease progression in SJS and TEN is unpredictable but is often short (4–5 days as a mean). Because patients are hospitalized a mean of 2 days after the onset of the reaction, there is little time to stop the disease. Any ineffective intervention should be expected to stop the progression in 2–3 days.

The recent elaboration of a scoring system (SCORTEN) that reliably predicted the outcome of patients with SJS or TEN may help to evaluate the results of non-controlled treatments in homogeneous series of patients [31]. Because of the rarity of SJS and TEN, the realization of randomized controlled trials (RCT) will be difficult.

Systemic corticosteroids

The use of systemic corticosteroids remains controversial. The best available data, although uncontrolled,

Figure 1. Toxic epidermal necrolysis



Purpuric macules coalesce to form blisters.

suggest that corticosteroids should be avoided in the most severe cases [32].

Immunosuppressive agents

Cyclophosphamide in high intravenous doses has been administered to a few patients, with claimed benefits.

A recent publication from a burns unit in Spain [33•] reported the treatment of 11 consecutive patients with cyclosporin A (3 mg/kg twice a day). Treatment with cyclosporin was safe and was associated with a more rapid re-epithelialization rate and a lower mortality rate (0/11 versus 3/6) than historical treatment with cyclophosphamide and corticosteroids.

Anti-cytokine drugs

With the rationale of inhibiting TNF- α production, we tested thalidomide in a double-blind placebo controlled trial [34]. The trial was interrupted after the inclusion of 25 patients because of an unexpectedly high mortality rate, significantly related to thalidomide and suspected to result from a paradoxical increase in TNF- α production.

Enthusiasm has recently been expressed about the use of high doses of human intravenous immunoglobulin (IVIg) [35–37]. This was based on an in-vitro demonstration that IVIg can inhibit Fas-FasL-mediated apoptosis, but not on firm clinical evidence. This treatment has been used in single cases and in a series of 10 patients with TEN of moderate severity [23]. The expected number of deaths in this small group was no more than two. The observation that all 10 patients survived provides strong encouragement for further studies, but cannot yet be considered as evidence of efficacy.

In conclusion, we consider that to date no other treatment than symptomatic should be proposed for patients with SJS or TEN unless tested in a formal clinical trial.

Hypersensitivity syndrome drug reaction with eosinophilia and systemic symptoms

Steroids are the first line therapy for idiopathic hypereosinophilic syndrome. There are many case reports of a dramatic improvement of visceral manifestations of drug 'hypersensitivity syndrome'/DRESS after the administration of moderate to high doses of systemic steroids. This may be life-saving. However, we also observed several patients who experienced relapses when steroid doses were tapered, and therefore needed continuation of steroids for many months. A chronic human herpesvirus type 6 activation promoted by systemic steroids could explain these relapses [38].

While awaiting better evidence on the therapeutic effect of systemic steroids in patients with 'hypersensitivity

Figure 2. Hypersensitivity syndrome or DRESS



Oedematous infiltrative papule coalescing into plaques.

syndrome'/DRESS, we recommend using systemic steroids only for patients with life-threatening visceral manifestations. In milder cases, topical steroids improve the skin manifestations. A case report of successful IVIg has been also reported [39].

IFN- α , a second line therapy for idiopathic hypereosinophilic syndrome could be tested in long-lasting cases of 'hypersensitivity syndrome'/DRESS.

Treatment of sequels

This applies principally to the chronic eye lesions that may follow SJS or TEN and sometimes result in serious disability. Wearing gas-permeable scleral contact lenses resulted in improved quality of life in 90% of patients, by reducing photophobia and discomfort. It also improved visual acuity and healed corneal epithelial defects in half of the patients [40].

Autologous germinal cells taken from the limbus and grafted on a support of amniotic membrane may be efficient in the most severe cases [41•].

Prevention, future use of drugs

Patients should be advised to avoid re-exposure to the suspect drug(s). Published cases of recurrences were all attributed to the same generic drug or to compounds closely related chemically (e.g. aromatic anticonvulsants). Therefore there is no rationale for restricting the use of all classes of 'high-risk drugs'. Because some familial cases have been reported, first-degree relatives should be alerted to their elevated risk of such reactions to the same drug(s). Cases should be notified to regulatory agencies.

When a high risk of drug eruption can be expected, e.g. in HIV-infected individuals, several methods were

proposed for preventing the reaction. In an RCT [42•] the incidence of rash complicating the first few weeks of treatment with nevirapine, an antiretroviral agent, was significantly diminished by adding corticosteroids (50 mg every other day) for 2 weeks, or by using a slowly escalating dose.

Another RCT [43•] demonstrated a lower incidence of adverse reactions to sulfamethoxazole in the prevention of pneumocystosis in HIV-infected individuals, with the utilization of slowly escalating doses.

These two RCT indirectly support the frequent practice of 'desensitizing' patients with a history of drug eruption when the treatment is needed again [44]. These empiric 'desensitization' procedures were not submitted to formal controlled trials, but seem to be associated with an acceptably low risk of severe reactions.

Conclusion

The main advances made recently concerning severe drug eruptions are: (i) the discovery that drugs are able to stimulate T lymphocytes, and the many different pathways of T cell activation may explain the different clinical expression of drug eruptions; (ii) the concept that the reactive metabolites of drugs, especially sulphonamides, are the main immunogenic factors should be reconsidered; and (iii) the expression of the skin homing marker on T lymphocytes may contribute to the predominant cutaneous expression of adverse drug reactions.

With regard to treatment, rapid withdrawal of the suspected drug and supportive therapy are still the main principle of treatment. Cyclosporin and IVIg were credited with halting disease progression in TEN-SJS in small open studies, and were evaluated more carefully.

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