Adverse cutaneous reactions to drugs

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Drug eruptions are probably the most frequent of all manifestations of drug sensitivity. They occur in about 2% of treatment courses and are commoner in women, the elderly and in patients with the acquired immunodeficiency syndrome (AIDS), especially from sulphonamides such as in co-trimoxazole[1]. Drugs most often incriminated are listed in Table 1. The prevalence of a history of penicillin allergy has been estimated as up to 10%, and reactions to sulphonamides may affect 5% of those treated. Potentially fatal conditions such as Stevens–Johnson syndrome and toxic epidermal necrolysis are fortunately rare (0.5–1.8 cases per million per year)[2]. Adverse drug reactions may reflect immunological drug allergy or, more usually, non-immunological mechanisms. Idiosyncratic reactions are independent of dose, unrelated to the pharmacological action of the drug and may have a genetic basis[3]. This article lists the commonest clinical patterns of drug eruptions (excluding contact dermatitis) and reviews their management.

Types of clinical reaction

The skin has only a limited repertoire of morphological reaction patterns in response to a variety of stimuli (Table 2). (The reader is referred to comprehensive texts listing drugs causing specific drug eruptions[4,5].)

Exanthematic (maculopapular) reactions

Symmetrical scarlatiniform, rubelliform or morbilliform eruptions, sometimes purpuric, are the commonest cutaneous drug reactions. They occur up to two weeks after the administration of almost any drug, may be accompanied by mild fever, pruritus and eosinophilia, and usually recur on rechallenge. The eruption may subside despite continuing the medication, but there is a risk of exfoliative dermatitis. Exanthematic eruptions regularly occur in patients with infectious mononucleosis treated with ampicillin (Fig 1).

Urticaria and angio-oedema

Urticaria is the second commonest type of drug reaction. There are circumscribed, raised, oedematous, erythematous weals widely scattered on the body (Fig 2). Urticaria may accompany systemic anaphylaxis or 'serum sickness' reactions. Angio-oedema, oedema of the deep dermis or subcutaneous and submucosal areas, is more rare. Aspirin and other non-steroidal anti-inflammatory drugs, penicillin, blood transfusions, radiocontrast media and angiotensin-converting enzyme inhibitors are potential causes.

Fixed drug eruptions

Fixed eruptions recur in the same site(s) each time the drug is administered as round plaques of erythema and oedema, sometimes with bullae (Fig 3). The limbs, genitalia and perianal areas are favoured sites. Post-inflammatory hyperpigmentation may be all that is visible between attacks.

Table 1. Drugs frequently implicated in drug eruptions.

- Antimicrobial agents:
  - amoxycillin
  - ampicillin
  - penicillin
  - trimethoprim-sulphamethoxazole
- Non-steroidal anti-inflammatory agents
- Blood products
- Drugs acting on the central nervous system:
  - anticonvulsants
  - hypnotics
  - tranquillisers
- Diuretics:
  - frusemide
  - hydrochlorothiazide
- Miscellaneous:
  - desensitising vaccines
  - muscle relaxants
  - intravenous anaesthetics
  - radiological contrast media

Table 2. Types of mucocutaneous drug reactions (excluding allergic contact dermatitis).

- Exanthematic (maculopapular)
- Purpura
- Erythemato-squamous:
  - annular erythema
  - pityriasis rosea-like eruptions
  - psoriasiform eruptions
- Erythroderma and exfoliative dermatitis
- Urticaria, anaphylaxis and serum sickness
- Fixed eruptions
- Vasculitis
- Lichenoid eruptions
- Photosensitivity
- Pigmentary abnormalities
- Acneiform and pustular eruptions
- Eczematous eruptions
- Erythema nodosum
- Bullous eruptions:
  - erythema multiforme and the Stevens–Johnson syndrome
  - toxic epidermal necrolysis
  - porphyria and pseudoporphyria
  - drug-induced bullous pemphigoid
  - drug-induced pemphigus
- Connective tissue reactions:
  - lupus erythematosus-like syndrome
  - drug-induced dermatomyositis
  - scleroderma-like
  - eosinophilia-myalgia syndrome
- Pseudolymphomatous eruptions
- Erythromelalgia
- Drug-induced hair abnormalities:
  - alopecia
  - hypertrichosis
- Drug-induced nail abnormalities
- Drug-induced oral conditions

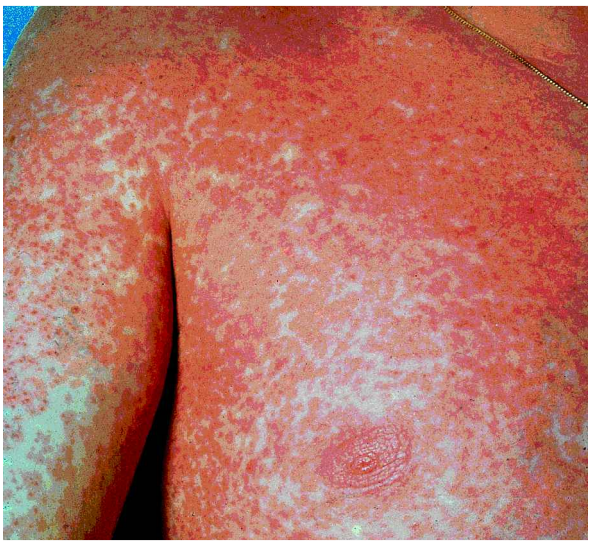

Fig 1. Florid erythematous maculopapular eruption in a patient with infectious mononucleosis treated with ampicillin. Figs 1–7 reproduced with permission from Breathnach and Hintner, 1992[14]. Oxford: Blackwell Science Ltd.

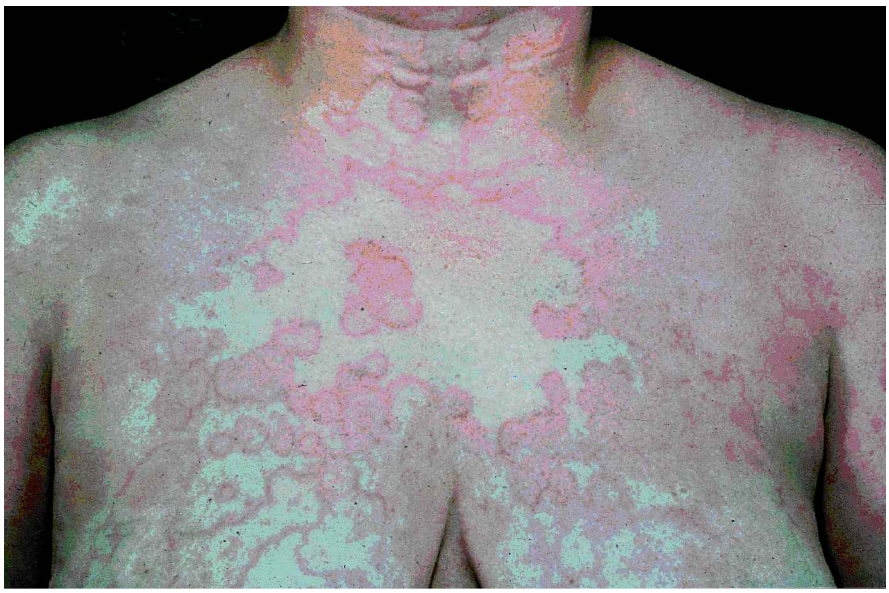

Fig 2. Urticarial eruption secondary to acetylsalicylic acid (aspirin).

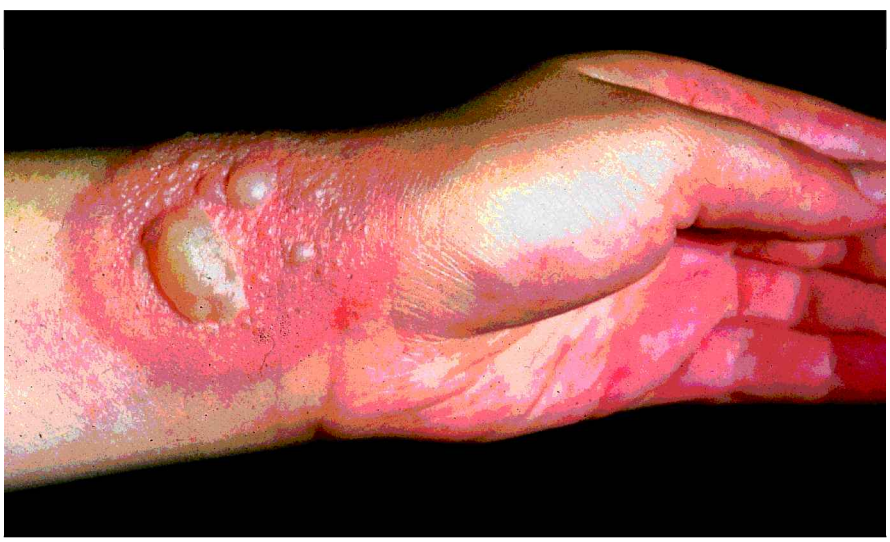

Fig 3. Bullous fixed drug eruption.

Photosensitivity

Drug-light reactions may be phototoxic or photo-allergic. Phototoxic reactions are commoner and occur in almost everyone given a high enough dose of drug and light irradiation. They develop within 5–20 hours and resemble exaggerated sunburn in exposed areas. Photo-allergic reactions require a latent period for sensitisation, usually appearing within 24 hours of re-exposure to drug and light. Unlike phototoxic reactions, they may spread beyond irradiated areas.

Vasculitis

Drug-induced cutaneous necrotising vasculitis, a manifestation of immune complex disease, presents with palpable purpuric lesions primarily on the legs. Urticarial lesions, ulcerated areas and haemorrhagic blisters may be present (Fig 4). The heart, liver and especially the kidneys may be involved, with fatal results.

Drug hypersensitivity syndrome

There may be a serious hypersensitivity reaction pattern 3–6 weeks after certain drugs, particularly anticonvulsants and antimicrobials, with fever, facial oedema, generalised papulopustular or exanthematous rash, lymphadenopathy or hepatitis. This may sometimes be accompanied by nephritis, pneumonitis, myocarditis and hypothyroidism, with eosinophilia and mononucleosis[6].

Erythroderma and exfoliative dermatitis

A potentially fatal widespread confluent erythema (erythroderma), often with desquamation (exfoliative dermatitis) (Fig 5), may follow exanthematic eruptions or the drug hypersensitivity syndrome, or develop *de novo*. Complications include hypothermia, fluid and electrolyte loss, infection, cardiac failure, stress-induced gastrointestinal ulceration and haemorrhage, malabsorption and venous thrombosis.

Erythema multiforme and the Stevens-Johnson syndrome

Erythema multiforme is characterised by macular, papular or urticarial lesions and classical 'target lesions' with central vesicles, bullae or purpura, distributed preferentially on the distal extremities and mucous membranes. The Stevens-Johnson syndrome comprises fever, malaise, myalgia, arthralgia and extensive erythema multiforme of the trunk, with severe involvement of mucous membranes (Fig 6).

Toxic epidermal necrolysis

Persistent fever accompanies extensive mucous membrane involvement and generalised epidermal blistering and sloughing (Fig 7). There is an appreciable mortality (up to 30%)[7]. Stomatitis and mucositis lead to impaired oral intake, malnutrition and dehydration, and urethritis progressing to urinary retention. Ocular complications, including blindness, develop in 50% of survivors. Wound infections, pigmentary changes, nail dystrophy, hypohidrosis, scarring alopecia, hypertrophic scarring, xerostomia, oesophageal strictures, phimosis and chronic oro-genital erosions occur.

Management of drug eruptions

Drug reactions, apart from fixed drug eruptions, usually have non-specific clinical features. Experience with the type of reaction most commonly caused by particular drugs may narrow the range of suspects[1,2] but it is often impossible to identify the culprit with certainty. The investigations follow four main lines:

1 Drug history.
2 Skin testing.
3 *In vitro* tests.
4 Challenge tests.

(The reader is referred to a comprehensive review of the detailed management of drug eruptions[2].)

Drug history

Patients should be questioned on when each drug was first administered, prior drug sensitivity or contact dermatitis, and use of laxatives, oral contraceptives, vaccines, homeopathic medicines, etc. Allergic drug reactions do not usually develop for at least four days after initial drug administration. A drug reaction may first become evident after cessation of the offending medication. Resolution of an eruption following drug withdrawal is suggestive but not diagnostic, while persistence despite drug withdrawal may simply reflect a long drug half-life.

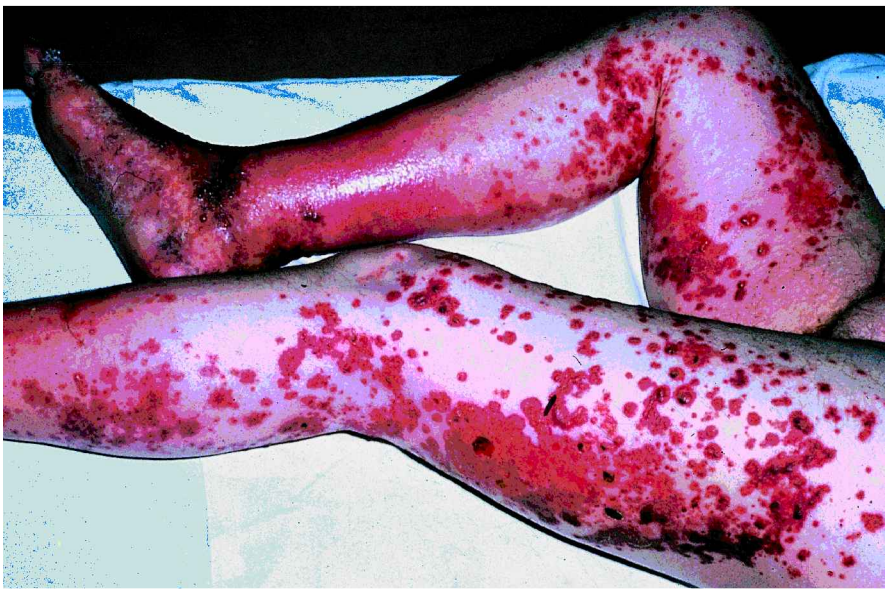

Fig 4. Purpura and skin necrosis in drug-induced immune complex-mediated vasculitis.

Skin testing

Skin prick testing and intradermal testing may identify patients with immediate hypersensitivity reactions to penicillin and other beta-lactam antibiotics[8], agents used in general anaesthesia, tetanus toxoid, streptokinase, chymopapain, heterologous sera or insulin, and may prevent anaphylaxis. However, the significant antigenic determinants are unknown for most drugs and false positives and negatives occur. Moreover, intradermal testing is not always safe. For penicillin sensitivity, the major determinant antigen (benzylpenicilloyl polylysine) used alone misses up to 25% of subjects at risk for anaphylaxis, and addition of benzyl penicillin G as the sole minor determinant antigen misses up to 10%. Comprehensive skin testing is therefore practicable only in specialised centres. Patch testing may help in systemic contact-type dermatitis medicamentosa, in photosensitivity (photo-patch testing) and fixed drug reactions[9].

Key Points

Always ask about previous adverse drug reactions, and substitute non-cross-reacting alternative drugs where indicated

Mark the patient's notes clearly with any known drug allergies

Despite a detailed drug history, skin testing, and *in vitro* tests, it is frequently impossible to identify with certainty the cause of a drug eruption

Most drug eruptions settle rapidly on drug withdrawal, and with use of emollients, topical corticosteroids and systemic antihistamine therapy

Drug-induced exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis are potentially fatal conditions. They require intensive inpatient therapy, with attention to fluid and electrolyte balance, nutrition and control of temperature and infection

KEY WORDS: CPD, drug eruptions

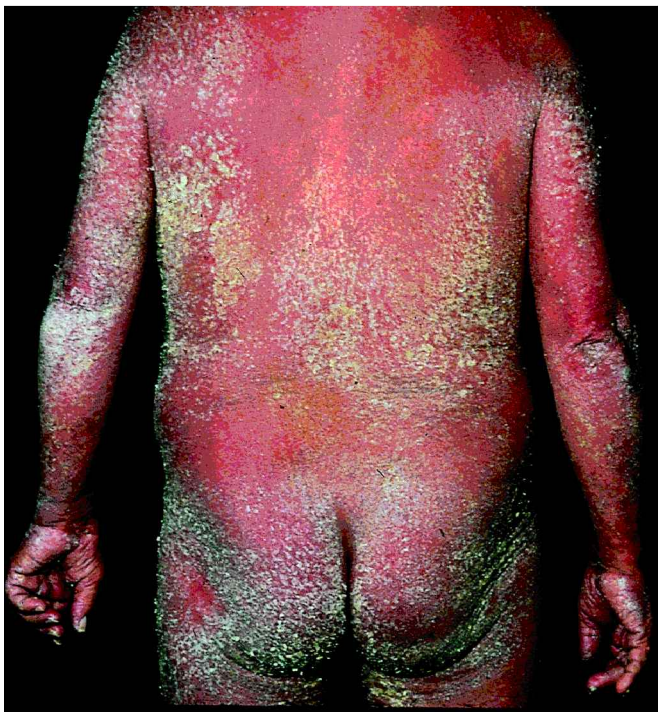

Fig 5. Drug-induced exfoliative dermatitis.

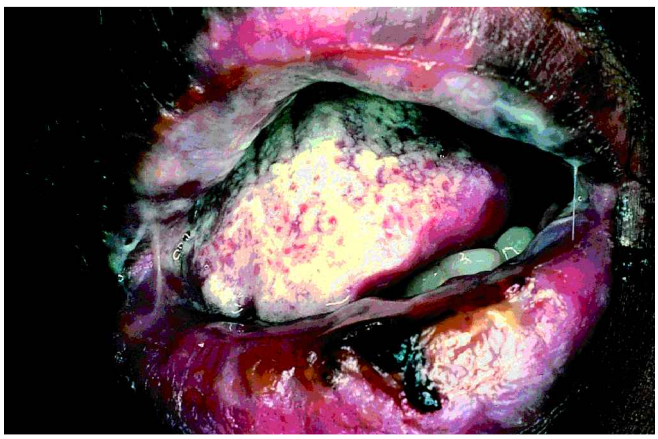

Fig 6. Erosion and crusting of lips in Stevens-Johnson syndrome.

In vitro *tests*

Radioallergosorbent (RAST) tests for drug-specific immunoglobulin (Ig) E class antibody are available for penicillin (major determinant antigen only), insulin and ACTH. The histamine release, basophil degranulation, passive haemagglutination and lymphocyte transformation tests, with or without liver microsomes to enable generation of drug metabolites[10], are of strictly limited use. The leukocyte and macrophage migration inhibition tests and the lymphocyte toxicity assay are essentially research tools.

Challenge tests

Provocation tests have resulted in fatalities and should be avoided except in the case of fixed drug eruptions.

Treatment of drug eruptions

All but essential medications should be withdrawn, and alternative non-cross-reacting drugs substituted for the remainder. Minor drug eruptions can be managed by withdrawal of the suspected drug(s) and symptomatic therapy with emollients, mild to moderately potent topical corticosteroids and systemic antihistamines.

Patients with lichenoid eruptions, drug-induced vasculitis or serum sickness reactions require investigation, including skin biopsy, and probably also therapy with systemic steroids and/or other immunosuppressive agents. The drug-induced hypersensitivity syndrome responds to systemic corticosteroids[11].

Prospective skin testing, under cover of oral corticosteroids, antihistamines and adrenaline, may identify safe alternative therapy in patients with a history of an adverse reaction to essential drugs such as radiographic contrast media or general anaesthetic agents. Rapid desensitisation may reduce the risk of IgE-mediated reactions if there is no acceptable alternative drug.

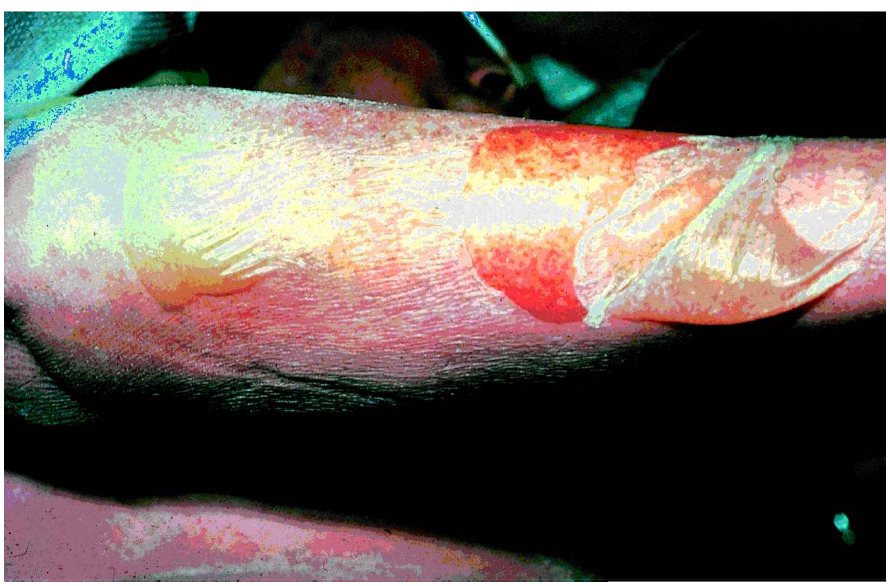

Fig 7. Cutaneous sloughing and bulla formation in a patient with toxic epidermal necrolysis.

Anaphylaxis

Adrenaline (0.5–1 ml of a 1:1,000 solution) should be given intramuscularly. The airway should be checked and blood pressure and pulse monitored. Chlorpheniramine maleate (10–20 mg, diluted in up to 5 ml water for injections) should be given intravenously slowly over one minute. Hydrocortisone sodium phosphate (250 mg), should be injected intravenously immediately. Aminophylline (250 mg over 5 min) should be given intravenously for bronchospasm. An alternative approach is to give nebulised terbutaline or salbutamol.

Exfoliative dermatitis/erythroderma[4,12]

Patients with exfoliative dermatitis or erythroderma are poikilothermic and must be maintained in an optimal environmental temperature. Potent topical or systemic steroids (prednisolone 40–60 mg daily) should be started, together with measures to combat infection and treatment of cardiac failure. Hypoalbuminaemia may require intravenous albumin replacement.

Toxic epidermal necrolysis[4,7,12,13]

Toxic epidermal necrolysis is a potentially fatal condition. It requires intensive therapy with nursing on an air fluidised bed, use of topical antiseptics and appropriate dressings, constant ophthalmic care and maintenance of fluid and electrolytes, body temperature and nutrition. Routine use of prophylactic broad spectrum antibiotics and oral steroid therapy remain controversial. If immunosuppressives, including steroids, cyclophosphamide and cyclosporin, are to have any effect, they should be given as early as possible and as only a short course. Intravenous Ig may be beneficial.

Conclusion

Adverse drug reactions are the price that has to be paid for the benefits of modern drug therapy, but happily the overall incidence is low. Prevention necessitates extensive pre-marketing clinical trials and comprehensive post-marketing surveillance, and doctors should ask patients about allergies before prescribing any drug. In the UK, only about 10% of serious reactions are notified to the Committee on Safety of Medicines. Clinicians should be encouraged to make full use of the 'yellow card' reporting scheme.

Acknowledgements

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