Drug eruptions

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Abstract

Drug eruptions occur in up to 2% of hospitalized patients; most are minor irritations, but rarely they are life-threatening. This article outlines a logical approach to identifying drug eruptions, their triggers and management. Classification of the morphological type and the timing of their onset relative to initiation of the culprit drug are the most important factors in their recognition. The features that mark potentially life-threatening eruptions (Stevens–Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms) are highlighted. Emerging problems such as the pustular eruptions associated with epidermal growth factor receptor antagonists used in malignancy, drug-induced ulcers, and skin tumours associated with BRAF inhibitors are covered.

Keywords Drug reactions; eosinophilia; pustular eruption; Stevens–Johnson syndrome; toxic epidermal necrolysis

Key points

- About 2% of hospitalized patients develop a rash arising from a drug exposure
- Most are relatively benign and self-limiting, but about 1 in 1000 hospitalized patients experience a severe, potentially life-threatening eruption
- Hospital in-patients are often on numerous medications, some of which are life-saving. It can be difficult to determine whether a particular rash is drug-related, as well as which particular drug is responsible. The benefits and risks of stopping that particular drug must be carefully weighed up
- It is important to be able to distinguish potentially life-threatening severe cutaneous adverse reactions from less severe reactions

Factors influencing drug reactions

Host factors

The best comprehensive prospective data relating to the incidence of drug reactions were collected in the 1970s and 1980s by the Boston Collaborative Drug Surveillance Program (BCDSP).[1] Every in-patient was assessed at discharge to determine whether or not they had sustained an adverse effect of a drug, and the suspect drug was identified. Adverse cutaneous reactions were more common in women with increasing age, and their incidence could be as high as 50 per 1000 drug exposures (for ampicillin). Sadly, such a comprehensive study has never been repeated.

Drug reactions are more common in patients with viral infections who are exposed to antibiotics, patients with systemic lupus erythematosus and HIV infection (particularly with co-trimoxazole) and patients with chronic lymphocytic leukaemia. Ampicillin rashes are more common in individuals who have infectious mononucleosis or are co-prescribed allopurinol.

Drug factors

Remember that a drug is any agent administered to a patient in the investigation or treatment of a disease. Proteins (including blood products) and drugs that are strong haptens are frequent inducers of drug eruptions. The BCDSP has produced reaction rate tables so likely and unlikely candidate drugs can be identified (Table 1). However, it should be remembered that these are data from in-patients and may not reflect drug reactions seen in out-patients, and that some newer drugs may be omitted.

It is important to remember that some drugs cross-react with others and thus in a sensitized individual are more likely to produce a rash. Examples include sulphonamides, sulphonylureas and sulphones, as well as thiazides, penicillins and cephalosporins.

Reaching a diagnosis in patients with a suspected drug eruption

History

Patients can disregard over-the-counter agents and herbal therapies, eye drops, inhalers and topical skin preparations as

Adverse cutaneous reaction rates for drugs – in-patient population (after the Boston Collaborative Drug Surveillance Program)

Drug	%
Amoxicillin	5.1
Trimethoprim–sulphamethoxazole	4.7
Ampicillin	4.2
Semisynthetic penicillin	2.9
Blood (whole human)	2.8
Penicillin G	1.6
Cephalosporins	1.3
Quinidine	1.2
Gentamicin sulphate	1.0
Packed red blood cells	0.8
Mercurial diuretics	0.9
Heparin	0.7

Table 1

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suspects. They may also not be aware of agents they have been administered under anaesthetic (such as an antibiotic given at cystoscopy or before a joint replacement, and intravesicular instillation drugs such as mitomycin). It may be necessary to inspect several prescription charts, general practitioner records and even the patient's medicine chest to identify culprit drugs. In assessing an individual with a suspect drug eruption, it is important to perform the following steps.

- Determine whether there are any features suggestive of a severe cutaneous adverse reaction. These include:
  - involvement of the buccal mucosa or anogenital mucosal surfaces
  - palpable lymphadenopathy and/or hepatosplenomegaly
  - systemic disturbance: pyrexia/hypothermia, tachycardia, shock, significant derangement of renal or liver function
  - skin pain
  - complete exfoliation of the skin in response to mild digital pressure (Nikolsky sign)
  - generalized erythema and oedema affecting 90% or more of the skin surface area (i.e. erythroderma).
- Consider the timing interval between starting a possible culprit drug and the onset of the rash. In general, specific eruptions have characteristically different latent periods (Figure 1), although if a patient has previously been sensitized to a particular drug, a particular eruption can develop far more rapidly. In rare cases, an eruption may not arise for up to several weeks after stopping the causative medication. Angioedema induced by angiotensin-converting enzyme (ACE) inhibitors can occur years after their initiation.
- If possible, classify the morphological type of eruption — is it morbilliform (exanthema-like), urticarial or angioedematous, eczematous, vasculitic, psoriasiform, pityriasis rosacea-like, bullous, lichen planus-like, acne-like, photosensitive, pustular or a fixed drug eruption? The Medicines and Healthcare products Regulatory Agency (MHRA) website and other reference sources (e.g. Litt[2]) classify reported reactions and often rank the frequency of different reaction types.
- Consider the differing morphological reaction patterns of different drugs. For example, consider a patient with a fixed drug eruption exposed to ampicillin and phenolphthalein. Although phenolphthalein reactions are rare and penicillin reactions common, phenolphthalein is a much more common cause of a fixed eruption.
- Assess the patient generally — is there lymphadenopathy, hepatomegaly, fever, constitutional symptoms (see drug reaction with eosinophilia and systemic symptoms (DRESS), below) or mucosal disease? Is there extensive blistering or epidermal necrosis (see toxic epidermal necrolysis (TEN), below), or hypotension, shivering, hypovolaemia and hypothermia resulting from skin failure or sepsis (in erythroderma or TEN)?
- Assess the need for investigations — neutrophil and eosinophil count, liver function tests (in DRESS), serum urea and electrolytes, and skin microbiology (in TEN).
- Assess the need for specialist referral — always needed in the case of suspected TEN, Stevens–Johnson syndrome (SJS), DRESS and erythroderma (defined as >80% skin involvement).
- Consider reporting the reaction. In the UK, the Yellow Card reporting system is available online at the MHRA site — www.mhra.gov.uk.
- Remember that all manner of skin reactions (even pigmentation and ulceration) have been reported with drugs. If in doubt, consult the reference sources, have a high index of suspicion and remember this might even be a novel reaction!
- Discontinue suspect drugs and potential cross-reacting agents.
- Consider a MedicAlert badge or similar for potentially serious reactions, and inform other medical and dental providers to prevent re-exposure.

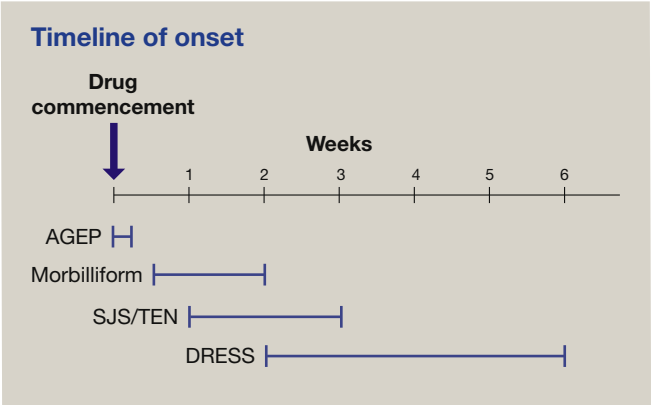

Figure 1 Usual timeline of onset of severe cutaneous adverse reactions and morbiliform eruption. AGEP, acute generalized exanthematous pustulosis; DRESS, drug reaction with eosinophilia and systemic symptoms; SJS, Stevens—Johnson syndrome; TEN, toxic epidermal necrolysis.

Life-threatening severe cutaneous adverse reactions

Stevens–Johnson syndrome and toxic epidermal necrolysis

This is characterized by full-thickness epithelial necrosis, which can affect the skin, as well as the oral, urethral and conjunctival mucosae. The eruption typically starts 7–14 days after exposure to the culprit drug. There is often a prodromal illness of several days' duration, with symptoms resembling a respiratory tract infection or flu-like illness. Target lesions, the hallmark of erythema multiforme, can be confined to the hands and feet in SJS, but can extend to produce diffuse and extensive erythema with TEN. Skin lesions are characteristically painful, which can be a useful diagnostic clue in the early stages. In TEN, the epidermis necroses, separating from the dermis and producing erosions and blisters (Figure 2). SJS and TEN describe the same disease process, but SJS involves less than 10% of the total body surface area, whereas TEN involves more than 30% (10–30% is termed an overlap syndrome).

The epidermis can fold and pleat like wrinkled, wet wallpaper. Epithelial necrosis of the oral, urethral and conjunctival mucosae can ensue. Constitutional upset is marked and can be an early warning of other problems: fever, leucopenia, tachycardia, hypotension and raised serum urea imply a poor prognosis. Respiratory tract involvement can develop, requiring ventilatory support: oxygen saturations should be regularly

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