Is this rash caused by my medicine?

Skin rashes are a common side effect of medicines. This article aims to help you identify a cutaneous drug reaction and give the most appropriate advice.

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AN ADVERSE drug reaction (ADR) has been defined by the World Health Organization as “an appreciably harmful or unpleasant reaction, resulting from the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen or withdrawal of the product”. This rather wordy explanation belies the fact that ADRs can present in a number of different ways and can seriously impact on the faith patients put in healthcare.

Cutaneous drug reactions (or “drug eruptions”) are probably the most common manifestation of an ADR, representing up to 30 per cent of such events and being responsible for 3 per cent of hospital admissions.1

Mechanisms

Although patients may automatically assume they are “allergic” to a medicine that appears to bring on a rash, drug eruptions can be allergic or non-allergic (ie, immune or non-immune mediated). Non-allergic cutaneous reactions include the common blue-grey skin discoloration that can follow amiodarone therapy and the photosensitivity caused by tetracyclines. These are described as type B ADRs. Type A (or “augmented”) ADRs are expected, due to their normal pharmacological actions (eg, bruising caused by anticoagulants) whereas type B (“bizarre”) reactions are idiosyncratic and usually unrelated to pharmacology and dose (eg, rash with amoxicillin). Reactions to aspirin and non-steroidal anti-inflammatory drugs can also be non-allergic. True allergic reactions are immune mediated and can be classified according to the Gell-

REFLECT

1 Would you be able to identify a rash caused by a drug?
2 Can you name three drugs that commonly cause skin reactions?
3 What symptoms indicate an urgent need to refer a suspected drug eruption?

Before reading on, think about how this article may help you to do your job better.

Goombs system, described in Panel 1 (p308). All true drug allergies require that the patient has been previously exposed to the same or a cross-reacting drug — it is only during subsequent courses of the drug that the reaction becomes evident. It should be noted, however, that allergic and non-allergic reactions can cause similar symptoms.

Risk factors

Various factors heighten the risk of drug eruptions. It seems that females are more likely to experience the problem than males (60 per cent versus 40 per cent in a recent five-year review of inpatients).2 And young adults are more prone to cutaneous reactions than the elderly or infants.
Rashes and skin reactions feature in nearly every summary of drug product characteristics but certain therapeutic groups are recognised as higher risk agents reported following the use of Chinese herbal medicines. Patients may also forget to mention medicines taken on a prn basis (eg, NSAIDs) and may need prompting. They might not have detailed information regarding what has been taken and, in some cases, it may not be possible to determine the active ingredients.

Bear in mind that the causative agent does not have to be something the patient has swallowed — cutaneous reactions have been reported following the use of eyedrops, inhaled medicines and suppositories.

An easy way of covering all potential causes is to remember the “7Ts”:
- Instilled (eg, eye and ear drops)
- Inhaled
- Ingested (eg, capsules, tablets, syrups)
- Injected (eg, suppositories)
- “Incognito” (ie, complementary medicines and vitamins)
- Intermittent (medicines taken on a prn basis)

Careful questioning and an assessment of the time-line over which a drug eruption has occurred, should help you to identify whether a rash is related to medication.

Timing
In many cases, a reaction will manifest fairly soon after the culprit drug has been started. However, eruptions can also occur long after a medicine was started and even stopped. Moreover, the rash can persist for weeks after the suspected drug is withdrawn. So do not assume that recently started medicines are the cause. For example, ACE inhibitor-induced angioedema (a variation of urticaria) typically involves the tongue and lips and can develop any time after a patient begins to take the medicine, even after many years. Incidence of ACE inhibitor-induced angioedema is between 0.1 and 0.68 per cent. People of Afro-Caribbean origin are at increased risk of ACE inhibitor-induced angioedema.

It can be difficult to establish whether a medicine is responsible for a rash, and, of course, skin-related events can occur independently as a result of other conditions, such as hepatic disease, bacterial or viral
infections and even allergies to foods such as shellfish. Nevertheless, drugs should always be considered as a possible cause of a new event.

Prolonged or frequent dosing of a drug is more likely to cause sensitisation than short static bursts of therapy so the causative agent may be something that the patient has taken or used many times before.

It is probably useful, in terms of taking a drug history, to start from a month before any symptoms develop. Other helpful facts to establish include:

- When and where the symptoms first appeared
- What the eruption looks like and if there has been any change over time
- Medical history
- Any current medical issues

Examples of reaction
Cutaneous reactions can range from mild discomfort (eg, simple urticaria and pruritus) to life-threatening conditions such as TENS.

Morbilliform rashes
Morbilliform rashes are the most common drug-associated skin eruption, presenting in up to 95 per cent of cases. Morbilliform rashes (see Figure 1) look similar to the rash caused by measles infection and can be described as fine pink macules or papules, which become confluent over time.

The rash typically starts on the trunk and spreads to the limbs, symmetrically. Rashes of this kind tend to occur within one or two weeks of starting the drug and are normally resolved one or two weeks after stopping.

However, they may develop up to a week after stopping a medicine and on the next exposure to the agent can appear in a matter of days.

Acute urticaria
Acute urticaria is characterised by weals (smooth, slightly elevated patches, commonly 1–2cm across, with pale centres), redness (erythema) and intense itching (pruritus). Each lesion (see Figure 2) lasts for less than 24 hours and leaves bruising. The lesions may be associated with systemic symptoms such as joint, abdominal or chest pain and fever. Urticarial vasculitis is typically a type III allergic reaction although diagnosis requires referral to a dermatologist and a skin biopsy to look for histological changes. On initial presentation the pharmacist would need to determine if the patient was systemically unwell, which indicates a more serious condition. Advice to see an emergency doctor within 24 hours is usually appropriate.

Regardless, urticarial vasculitis should always be investigated because it is often a sign of underlying autoimmune disease.

Fixed drug eruption
In a fixed drug eruption, well-defined, brown or red, round or oval patches appear on the skin (see Figure 4). Characteristically the patches recur at the same site each time a particular drug is taken although the number of sites may increase with repeated exposures. They are sometimes surmounted by blisters. Fixed drug eruptions typically cause a burning sensation and are associated with general malaise. They tend to occur within hours of drug administration and resolve within a few weeks of stopping.

Erythema multiforme
In erythema multiforme, there is an eruption of circular, target-like lesions starting at the extremities and spreading centrally (see Figure 5). Affected areas include the palms and soles of the feet, provoking burning pain. Blistering may occur, affecting less than 10 per cent of the body surface area.

Erythema multiforme is generally considered a type II allergic reaction and although not considered life-threatening, it shares characteristics with more serious presentations such as drug rash with eosinophilia and systemic symptoms (DRESS). Sulfonamides are considered to account for around 30 per cent of cases.

Life-threatening eruptions
DRESS, SJS and TENS are essentially a continuum of the same type of reaction, but with the involvement of a progressively larger body surface area. They are medical emergencies requiring hospital admission.

DRESS is a serious hypersensitivity reaction to a drug. The rash is associated with fever and eosinophilia occurring three to four weeks after starting a drug. The appearance of the rash can vary. It can involve extensive blistering and skin loss, but more often presents as an itchy redness which may contain papules, pustules or vesicles. There may be lymph node enlargement and internal organ involvement.
The mucous membranes

Lesions can occur anywhere, but most commonly affect the palms, backs of the hands and soles. The mucous membranes of the oropharynx and eyes may also be affected. Most patients are aged between 10 and 30 years.7

The culmination of SJS is skin sloughing or epidermal detachment which can involve 10–30 per cent of the body surface area. TENS TENS is similar to SJS but involves more extensive blistering affecting >30 per cent of body surface area. Some reports estimate 70 per cent mortality associated with this presentation.8

Drugs most commonly associated with SJS and TENS are allopurinol, carbamazepine (and other antiepileptics), sulfonamides, antiretrovirals, imidazoles and NSAIDs.7

When to refer

Although most drug eruptions are self-limiting and minor, the following symptoms should be referred:

● Systemic illness (ie, fever, sore throat) preceding or accompanying the rash
● Intensive rash or blistering
● Any detachment of the skin
● Any involvement of mucus membranes, eyes or genitals

Management

Treatment of patients presenting with a suspected drug rash largely depends on the type of reaction and its seriousness. The simplest action would be to stop the drug. This would mean weighing up the severity of the reaction against the need to treat the condition and whether there are alternative options. In some cases dose reduction may be appropriate. For example, an SPC for allopurinol (Māthān Ltd) states that skin reactions “may be pruritic, maculopapular, sometimes scaly, sometimes purpuric and rarely exfoliative” and can occur at any time during treatment. It advises that allopurinol should be withdrawn immediately should such reactions occur. After a mild reaction, allopurinol may be reintroduced at a small dose (eg, 50mg/day) and gradually increased. If the rash recurs, the drug should be permanently withdrawn because more severe hypersensitivity may occur, the SPC says.

In mild drug eruptions, no specific treatment is required but over-the-counter steroids, antipruritics or antihistamines may be used to provide symptomatic relief. Gold compresses may relieve pain. Menthol 1 per cent in aqueous cream is reported to soothe itching.9 Cool baths or showers may also help. Oral steroids (eg, prednisolone 30–40mg for three to five days) may be prescribed in severe cases of acute urticaria.

Patients with suspected life-threatening conditions, such as SJS, should be urgently referred to hospital. Prompt diagnosis and withdrawal of the offending drug is the main way to reduce mortality. These patients may also be given immunomodulation therapy with high-dose intravenous immunoglobulin. The use of systemic corticosteroids in these cases is controversial.10 Supportive treatment, ideally in an intensive care unit, may include antipyretics and topical steroids. In case of exfoliative dermatitis, the main principles of therapy are the same as for major burns.11

Regardless of the action taken it can be useful to provide the patient with information regarding all possible suspected drugs (including those that may have been stopped) and any action taken. Providing this information in writing may help patients when they present to a GP or emergency department. In addition, one of the most useful things a patient or pharmacist can do is take a photograph of the rash. This is because the evidence can fade and an image avoids confusion over descriptions. A well timed photo will enable a dermatologist or allergy specialist to make a more accurate diagnosis should the need arise. Note, however, that patient consent is needed before any photos are taken.

Following particularly troublesome or serious eruptions patients may be referred to a dermatologist or allergy specialist. Skin biopsies can detect superficial inflammation but histology can identify a precise cause and may simply be used to eliminate other conditions. The presence of lymphocytes, neutrophils and eosinophils may offer further clues.

Those with a history of drug eruptions should avoid further exposure to the culprit and related medicines where possible. Premedication with antihistamines is not routinely recommended and may mask early signs of anaphylaxis. Patients may benefit from Medic Alert jewellery or watches (www.medicalert.org.uk), particularly if an eruption was due to commonly used medicines, such as antibiotics and analgesics.

Desensitisation

A history of drug eruption does not preclude further use of the culprit drug. If deemed essential, drug desensitisation can be undertaken but only by specialists in an appropriate environment. Desensitisation protocols induce a temporary unresponsive state to certain allergens by gradual reintroduction of small doses of a drug at fixed time intervals. Eventually this may allow the use of full therapeutic doses without anaphylaxis.

Reporting

The cost of cutaneous drug reactions to the health service is substantial and their impact on patients can be immense. All incidents of new or serious drug reactions should be reported via the Medicines and Healthcare products Regulatory Agency’s Yellow Card scheme (https://yellowcard.mhra.gov.uk). Reports can be made by healthcare professionals as well as patients and can now be completed online as well as by post.

PRACTICE POINTS

Reading is only one way to undertake CPD and the regulator will expect to see various approaches in a pharmacist’s CPD portfolio.

1. Make a list of the products you could recommend for a mild drug eruption.
3. Explore the new MHRA Yellow Card reporting website.

Consider making this activity one of your nine CPD entries this year.