Cutaneous drug eruptions and drug toxicities

A drug-induced reaction should be considered whenever there is a cutaneous eruption of sudden onset in a patient who is taking a medication.

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Complications from drug therapy are a major cause of patient morbidity and account for a significant number of patient deaths. Drug eruptions range from common nuisance eruptions to rare, life-threatening, drug-induced diseases. Drug reactions can be limited to the skin or the eruption may be part of a systemic reaction, such as the drug hypersensitivity syndrome or the Stevens–Johnson syndrome.

There is a wide range of drug-induced cutaneous disease. Many drug eruptions are distinct disease entities, others closely mimic other conditions, and, occasionally, in susceptible individuals, cutaneous disease can be unmasked by drugs. Certain drugs are commonly associated with certain types of reactions and a precise description of the reaction pattern can help narrow possible causes. Conditions such as toxic epidermal necrolysis and acute generalised exanthematous pustulosis were described only after the more widespread use of medications, despite their dramatic clinical appearance suggesting most cases were drug related. Most cases of these diseases can be linked to a specific drug cause. Fixed drug eruptions are also almost always drug associated.

Although the categories of drugs most commonly implicated in drug-induced reactions are antimicrobial agents, NSAIDS and anticonvulsants, all drugs should be suspected if there is a sudden onset cutaneous eruption in a patient taking a medication. Patients presenting with drug-induced disease need to be evaluated as they would for any other medical presentation. Serious life-threatening reactions may, on the surface, closely resemble 'benign' transient self-limiting reactions. Exanthematous eruptions are a good example of this problem.

This article highlights some of the common reactions to drug therapy that may be seen in general practice and also mentions some other reactions should not be missed.

IN SUMMARY

- **Cutaneous reactions due to drug therapy are common and are an important cause of patient morbidity and mortality.**
- **Adverse reactions to drugs range from common nuisance eruptions to rare life-threatening drug-induced diseases.**
- **Although antimicrobial agents, NSAIDs and anticonvulsants are the most commonly implicated drugs in adverse drug reactions, all drugs should be suspected if there is a sudden onset cutaneous reaction in a patient taking a medication.**
- **The severity of systemic involvement is not necessarily indicated by the severity of the cutaneous reaction so all patients presenting with a cutaneous eruption due to a drug should be further evaluated for systemic symptoms and signs.**
- **Lives can be saved by appropriate drug dosing, consideration of intercurrent drug therapies and diseases, early recognition of potentially severe reactions and appropriate management.**

Table 1. Exanthematous eruptions

Simple

Morbilliform or macular rashes
Pruritus usually present
Common causes include:

- antibiotics, especially beta lactams, macrolides, quinolones and sulfonamides
- anticonvulsants
- allopurinol
- antiretrovirals, especially nevirapine and efavirenz
- NSAIDs, including COX-2 inhibitors

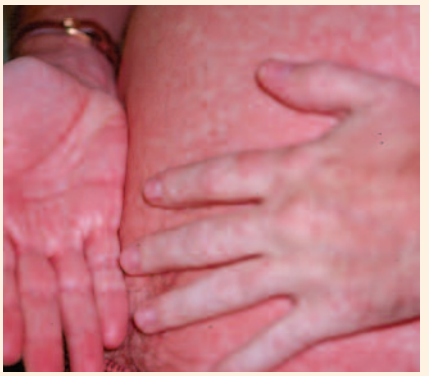
Severe

Occuring as part of a systemic reaction, the drug hypersensitivity syndrome
Common causes include:

- sulfonamide antibiotics
- anticonvulsants
- allopurinol
- minocycline
- antiretrovirals, especially nevirapine and abacavir

Case 1. Exanthematous eruption – celecoxib

A 42-year-old man with osteoarthritis of the knees developed a transient simple exanthematic eruption 10 days after starting celecoxib for the first time. There were no systemic features. The eruption was itchy but settled over seven days with topical mometasone furoate and continuation of celecoxib therapy.



Exanthematous eruptions

Simple exanthematous eruptions

Exanthematous eruptions occurring without any other symptoms or signs are known as simple exanthematous drug eruptions (Table 1). Also known as morbilliform or maculopapular rashes, they are the most common types of drug eruption, accounting for approximately 95% of skin reactions. These eruptions usually start on the trunk and spread peripherally in a symmetrical fashion; pruritus is generally present (see Case 1). The eruptions usually occur within one week of starting therapy, and resolve within seven to 14 days. They may settle even when the causative drug is continued. Causative drugs are listed in Table 1. The main differential diagnosis in these patients is a viral exanthema; other causes include collagen vascular disease and bacterial and rickettsial infection.

Severe exanthematous reactions

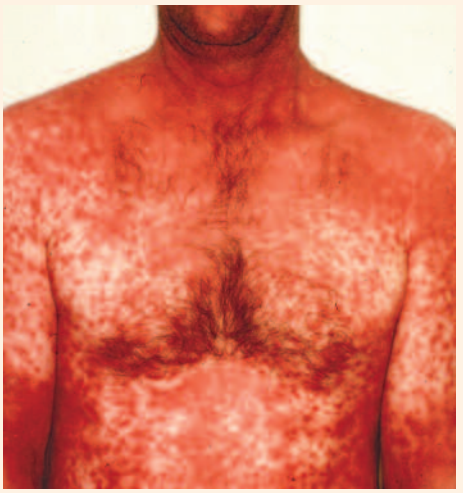
An exanthematous eruption in conjunction with fever and internal organ involvement (e.g. liver, kidney, central nervous system) signifies a more serious reaction known as the drug hypersensitivity syndrome (see Case 2). This reaction occurs most frequently on first exposure to the drug, with initial symptoms starting one to six weeks after exposure. Fever, pharyngitis and malaise often accompany the eruption as presenting symptoms. Although most patients present with an exanthematous eruption, more serious cutaneous manifestations may be evident. Internal organ involvement can be asymptomatic, with fever the only clinical manifestation initially. Atypical lymphocytosis with a subsequent eosinophilia may occur during the initial phases of the reaction in some patients. Some patients may become hypothyroid about two months after initiation of symptoms.

Common causes of severe exanthematous reactions are listed in Table 1.

Recognising severe drug reactions

Certain clinical features can provide clues that an exanthematous eruption is part of a serious reaction (Table 2). Early cessation of the causative drug can save lives. Even the most minor cutaneous eruption should trigger a clinical review of systems because the severity of systemic involvement does not necessarily mirror that of the skin. Hepatic, renal, joint, respiratory, haematological and neurological changes should be clinically screened for, and any systemic symptoms or signs investigated. Fever, malaise, pharyngitis and other symptoms or signs should be investigated. A usual screen would include a full blood

Case 2. Drug hypersensitivity syndrome – allopurinol



Eight weeks into therapy of gout with allopurinol, a 37-year-old man with hypertension developed an itchy eruption with prominent facial involvement associated with a puffy face, uncomfortable neck swelling, pharyngitis and fever. Initially his rash was exanthematous but it evolved to erythroderma with prominent redness, pustulation and desquamation. Investigations identified hepatitis, nephritis, atypical lymphocytes and neutrophilia. He quickly improved when started on prednisolone (50 mg/day). This was weaned over a month. Despite allopurinol withdrawal, the reaction took over six months to settle entirely. During weaning, his symptoms and rash would rapidly recur when his corticosteroid dose was below 10 mg.

count, liver and renal function tests and urine analysis.

Drug-induced disease

Distinct disease entities

Drug-induced diseases make up a distinct group of clinical disease entities. Many are named after diseases they mimic, including a range of idiopathic or infective diseases, but generally they show characteristic differences and their timing of onset after starting a new drug is usually characteristic (Table 3).

Table 2. Warning features of a severe adverse drug reaction

- Fever and/or other symptoms of internal organ involvement such as pharyngitis, malaise, arthralgia, cough and meningitis
- Prominent facial involvement and/or oedema and swelling of face and neck
- Mucous membrane involvement, particularly if erosive or involving conjunctiva
- Lymphadenopathy
- Skin tenderness or pain, blistering or shedding
- Purpura

Mimicking other disease

Diseases induced by drugs can mimic many infective and idiopathic diseases. It is, therefore, always important to consider whether a particular eruption could be caused or exacerbated by drug therapy, and whether it is possible to stop or change any potentially causative nonessential drugs.

Drug-induced diseases may show some similarities to idiopathic disease but also some distinct differences. For example, minocycline-induced lupus occurs in younger individuals than idiopathic systemic lupus, and is not usually associated with a cutaneous eruption, presenting more often with arthralgia, fever, malaise and hepatitis. Rashes in drug-induced lupus often simulate a viral exanthema rather than a more clinically distinct lupus associated eruption such as malar erythema or discoid plaques (see Case 3).

Unmasking of, or predisposing to, idiopathic disease

Drugs can increase the risk of a susceptible individual developing a usually idiopathic cutaneous disease. An example is pemphigus triggered by penicillamine or captopril. This condition presents with mucocutaneous erosion, ulceration and/or blistering. Fortunately, many cases of drug-induced pemphigus settle with drug withdrawal alone. Other cases may continue, however, and require long term immunosuppressive therapy, despite withdrawal of the drug trigger. Deaths have been reported.

Interactions between drugs, infections and disease

Interactions between drugs, infections and disease can predispose individuals to apparently idiopathic reactions to drugs. It is imperative that prescribing doctors are aware of potential drug–drug, drug–infection and drug–disease interactions to reduce the risk of severe life-threatening reactions.

Drug–drug interaction

When lamotrigine is given to a patient already taking valproic acid there is an increased risk of severe cutaneous drug reactions such as Stevens–Johnson syndrome or toxic epidermal necrolysis unless the starting dose of lamotrigine is appropriately reduced and introduced at a slow rate. Stevens–Johnson syndrome and toxic epidermal necrolysis are characterised by fever, pharyngitis, erosion and ulceration of the mucous membranes (including the eyes, nose, mouth and pharynx), along with blistering and detachment of the epithelium. These reactions are often associated with inflammation of internal organs, particularly the liver, kidneys, lungs and haematological system.

Table 3. Examples of drug induced cutaneous eruptions

Distinct disease entities
Toxic epidermal necrolysis
Acute generalised exanthemic pustulosis
Fixed drug eruption

Mimicking infective or idiopathic disease
Exanthematic eruptions
Drug induced lupus
Drug hypersensitivity syndrome

Triggering onset of normally idiopathic diseases in predisposed individuals
Pemphigus triggered by captopril
Psoriasis triggered by alpha interferon

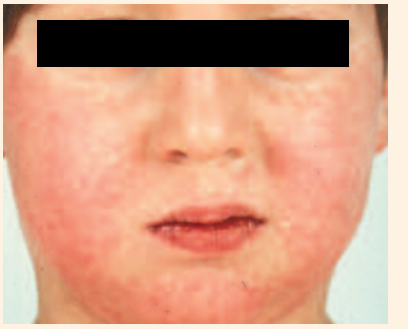
Drug–drug interactions
Lamotrigine and valproic acid – increased risk of severe cutaneous reactions such as Stevens–Johnson syndrome and toxic epidermal necrolysis

Drug–active infection interactions
Ampicillin and acute infectious mononucleosis – exanthemic eruption
Sulfonamide antibiotics and HIV infection – hypersensitivity reactions

Drug–systemic disease interactions
Allopurinol and renal disease – hypersensitivity reaction

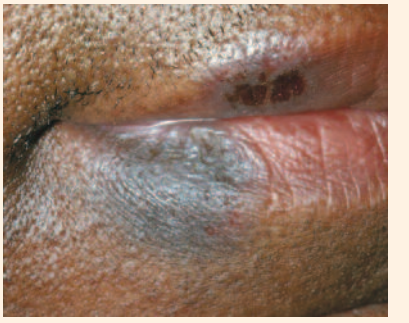
Case 3. Drug-induced lupus – minocycline

A 17-year-old woman was given minocycline for acne. Her acne improved but about 12 months into therapy she developed arthralgia and arthritis involving her ankles, knees and hands. She had a low grade fever and there was an associated exanthematic rash. She had a positive ANA with homogeneous pattern and hepatitis. Minocycline was stopped and her symptoms resolved over several weeks.



Case 4. Fixed drug eruption – paracetamol

A 27-year-old man developed two irritable oval lesions on his lips six hours after taking paracetamol for a headache. Initially these were red and oedematous, later developing to superficial erosions with crusting. They then settled over seven days, leaving prominent hyperpigmentation that took months to improve. Lesions recurred in a similar time frame on a later self-initiated rechallenge, helping confirm the diagnosis.



Drug–active infection interaction
Drugs can also interact with active infection, increasing the risk of drug eruption. Almost all patients with acute infectious mononucleosis develop exanthematous eruptions when exposed to ampicillin, thus these eruptions could almost be used as a diagnostic tool. This reaction fails to recur when the same patient is exposed again to penicillin or its derivatives in the absence of active Epstein Barr virus infection.

Up to 50% of patients with HIV have been reported to develop hypersensitivity reactions when administered high doses of sulfonamide antibiotics. These reactions do not necessarily recur on rechallenge, and these patients can often be successfully desensitised should further courses be required. However, patients with associated fever or internal organ involvement should not be rechallenged.

Drug–systemic disease interaction
Drugs can also interact with systemic disease, increasing the risk of idiopathic reactions should appropriate dose adjustments not be made. For example, if allopurinol is given at normal doses to patients with renal disease, there is an increased risk of a hypersensitivity reaction. Such reactions can range from mild to severe, prolonged and life-threatening, and include simple exanthematous rashes, allopurinol drug hypersensitivity syndrome, Stevens–Johnson syndrome and toxic epidermal necrolysis (see Case 2).

Fixed drug eruptions
Fixed drug eruptions usually appear as solitary or multiple, erythematous, bright red or dusky red macules that may evolve into oedematous plaques or even blisters. They are most commonly found on the genitalia, perianal and perioral areas, although they can occur anywhere on the skin surface. Some patients may complain of burning or stinging, and others

may have fever, malaise or abdominal symptoms. Fixed drug eruptions can develop within 30 minutes to up to eight to 16 hours after ingestion of the medication. After the initial acute phase, which may last days to weeks, residual greyish or slate-coloured hyperpigmentation develops. Upon rechallenge, lesions recur in the same location and new ones often also appear (see Case 4).

More than 100 drugs have been implicated in fixed drug eruptions, including NSAIDs, paracetamol, sulfonamide antibiotics and tetracyclines. A challenge or provocation test with the suspected drug may be useful in establishing the diagnosis. Patch testing at the site of a previous lesion can also be helpful in identifying the causative agent.

Management of drug eruptions and toxicities

It is important to manage carefully adverse reactions or complications of medical therapy to minimise negative consequences. Adverse reactions can severely undermine the doctor–patient relationship, and it is important, therefore, to instigate effective management strategies whenever such events occur. The patient and their family should be kept informed of the adverse reaction's cause, potential course and significance. For example, first degree family members are at increased risk of severe reactions to similar drugs in cases of drug hypersensitivity syndrome, Stevens–Johnson syndrome and toxic epidermal necrolysis.

First line therapy for cutaneous drug eruptions is supportive therapy and withdrawal of the causative drug. For most eruptions (i.e. mild cases), oral antihistamines, topical corticosteroids and moisturising lotions are used for symptomatic relief of pruritus. Hospitalisation, systemic corticosteroids and close monitoring for internal organ toxicities are appropriate for patients with hypersensitivity syndrome. Admission to a burns unit or ICU with expertise in burns dressings and administration of intravenous immunoglobulins are required for those with toxic epidermal necrolysis and Stevens–Johnson syndrome.

Conclusion

Drug eruptions are common and an important cause of patient morbidity and mortality. Adverse reactions are part of the price we pay for the increasing armamentarium of medical therapies for managing disease. At present, we cannot predict who will do well on a medication and who is at increased risk of an adverse event. Adverse drug reactions need to be considered in the differential diagnoses of a very broad range of cutaneous eruptions and diseases. Appropriate drug dosing, consideration of intercurrent drug therapies and diseases, early recognition of potentially severe reactions and appropriate management can save lives. MT

DECLARATION OF INTEREST: None.