5

Drug-induced skin reactions

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Introduction

Cutaneous drug eruptions are one of the most common types of adverse reaction to drug therapy, with an overall incidence rate of 2–3% in hospitalised patients.[1–3] Almost any medicine can induce skin reactions, and certain drug classes, such as non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics and antiepileptics, have drug eruption rates approaching 1–5%.[4] Although most drug-related skin eruptions are not serious, some are severe and potentially life-threatening. Serious reactions include angio-oedema, erythroderma, Stevens–Johnson syndrome and toxic epidermal necrolysis. Drug eruptions can also occur as part of a spectrum of multiorgan involvement, for example in drug-induced systemic lupus erythematosus (see Chapter 11). As with other types of drug reaction, the pathogenesis of these eruptions may be either immunological or non-immunological. Healthcare professionals should carefully evaluate all drug-associated rashes. It is important that skin reactions are identified and documented in the patient record so that their recurrence can be avoided. This chapter describes common, serious and distinctive cutaneous reactions (excluding contact dermatitis, which may be due to any external irritant, including drugs and excipients), with guidance on diagnosis and management.

A cutaneous drug reaction should be suspected in any patient who develops a rash during a course of drug therapy. The reaction may be due to any medicine the patient is currently taking or has recently been exposed to, including prescribed and over-the-counter medicines, herbal or homoeopathic preparations, vaccines or contrast media. Remember that the non-drug components of a medicine, i.e. the pharmaceutical excipients, may cause hypersensitivity reactions in some patients.

Classification and mechanism

Cutaneous drug reactions may be caused by several different mechanisms, but in many cases the precise mechanism is unknown. Many drug eruptions are the result of a hypersensitivity reaction with an underlying immune mechanism. Skin reactions as a result of non-immunological causes are more common and include cumulative toxicity, overdose, photosensitivity, drug interactions, and metabolic alterations.[5]

The term hypersensitivity is applied when the immune response to an agent (immunogen) results in an increased or exaggerated response. Drugs, or their metabolites, act as haptens by covalently binding to peptides and modifying them to become immunogenic, inducing a specific cell-mediated or humoral immune response. All of the four Coombs' and Gell immune mechanisms may be involved (Table 5.1). Recent immunological research suggests that combined involvement of different immune mechanisms may feature in some reactions, and that T cells are involved in all four types of reaction.[6] It has also been postulated that some drugs have structural

Table 5.1 Immunological (hypersensitivity) reactions

Type I reactions are caused by the formation of drug/antigen-specific IgE that cross-links with receptors on mast cells and basophils. This leads to immediate release of chemical mediators, including histamine and leukotrienes. Clinical features include pruritus, urticaria, angio-oedema and, less commonly, bronchoconstriction and anaphylaxis. The drugs most commonly responsible for type I hypersensitivity are aspirin, opioids, penicillins and some vaccines.
Type II or cytotoxic reactions are based on IgG or IgM-mediated mechanisms. These involve binding of antibody to cells with subsequent binding of complement and cell rupture. This mechanism accounts for blood cell dyscrasias such as haemolytic anaemia and thrombocytopenia.
Type III reactions are mediated by intravascular immune complexes. These arise when drug antigen and antibodies, usually of IgG or IgM class, are both present in the circulation, with the antigen present in excess. Slow removal of immune complexes by phagocytes leads to their deposition in the skin and the microcirculation of the kidneys, joints and gastrointestinal system. Serum sickness and vasculitis are examples of type III reactions.
Type IV reactions are mediated by T cells causing 'delayed' hypersensitivity reactions. Typical examples include contact dermatitis or delayed skin tests to tuberculin. Drug-related delayed-type hypersensitivity reactions include Stevens–Johnson syndrome and toxic epidermal necrolysis (TEN). Recent work has proposed that type IV reactions be divided into four subtypes based on the T-lymphocyte subset and cytokine expression profile involved.[5]

Ig, immunoglobulin.

features allowing direct interaction with T cells, a concept termed pharmacologic interaction with immune receptors (p-I concept).[5] The clinical manifestations of drug hypersensitivity depend on various factors, including the chemical or structural features of a drug, the genetic background of the affected individual, and the specificity and function of the drug-induced immune response.

Different types of immune effector mechanism can produce diverse clinical patterns of hypersensitivity reaction,[4] for example, penicillins, as the classic drugs acting as haptens, are reported to cause type 1 IgE-mediated (immediate-type) hypersensitivity reactions as well as non-IgE mediated reactions, including morbilliform eruptions, erythema multiforme and Stevens–Johnson syndrome.[7,8]

It is especially important that allergic skin reactions are correctly identified, as subsequent exposure to the drug may cause a more severe reaction. Patients with a reliable history of drug allergy should always be carefully monitored when any new medicine is started, as 10% of patients with drug hypersensitivity reactions react to more than one structurally distinct compound.[5] The route of administration is a factor in drug allergy; in general, topical application has the greatest propensity to induce allergy, followed by parenteral then oral administration.[9]

Certain patient groups appear to be predisposed to cutaneous adverse drug reactions (ADRs).[10] There is a high incidence of hypersensitivity reactions in patients with altered immune status, for example due to viral infections (Epstein–Barr virus or HIV). A well-documented example is the increased risk of co-trimoxazole hypersensitivity in HIV patients. As with ADRs in general, altered drug handling due to organ impairment or genetic factors may play a part; for example, slow-acetylator status may predispose to sulfonamide reactions. The role of atopy in predisposing to drug reactions is controversial.[11] It may be important in reactions to iodinated contrast material, but not in those to penicillins or during anaesthesia.[12] The term multiple drug allergy syndrome has been used to describe patients who have a propensity to react against different, chemically unrelated drugs.[13]

Diagnosis

It can be difficult to diagnose a drug eruption with confidence. Most drugs are associated with a spectrum of skin reactions, although some agents seldom cause skin reactions (Table 5.2).[6,14] Some types of skin rash are very rarely drug induced, for example eczema. Many drug reactions cannot be distinguished from naturally occurring eruptions, and so misdiagnosis is

Table 5.2 Drugs rarely causing cutaneous eruptions (rates estimated to be 3 cases per 1000)

Antacids	Muscle relaxants
Antihistamines (oral)	Nitrates
Atropine	Nystatin
Benzodiazepines	Oral contraceptives
Corticosteroids	Propranolol
Digoxin	Spironolactone
Ferrous sulphate	Theophylline
Insulin	Thyroid hormones
Laxatives	Vitamins
Local anaesthetics (other than topical)	

common. For example, there may be uncertainty about whether a morbilliform rash is due to a viral infection or an antibiotic, and this may unnecessarily limit the future use of a particular medication. Furthermore, patients may be taking several medicines, making it difficult to establish the one responsible. Some drugs are more likely to be the cause of a particular type of eruption than others. For example, if a patient taking both demeclocycline and chlorpromazine develops a photosensitivity reaction the chances are that demeclocycline is the cause, although both drugs are capable of producing the reaction. However, if the patient develops skin hyperpigmentation then chlorpromazine is more likely to be implicated.

The timing of skin reactions is often a useful diagnostic tool. In general, the onset occurs within a few weeks of the introduction of the causative drug. If a medicine has been taken for many years without a problem then it is less likely to be responsible. When examining a list of medicines taken by a patient with a rash, new drugs taken within the previous month are the most likely cause. There are some notable exceptions to this rule. Hypersensitivity reactions to penicillins can occur several weeks after the drug has been discontinued, and the typical psoriasiform skin eruption seen with the beta-blocker practolol (withdrawn in the 1970s) generally occurred after many months of treatment. Gold can also cause very late reactions.

Drugs suspected of causing skin reactions should usually be withdrawn and not used again in that patient, although the risk–benefit potential needs to be considered before discontinuing any necessary medicines. Symptomatic treatment may be needed. Calamine lotion or systemic antihistamines may relieve pruritus and topical corticosteroids may help inflammation and itch. For more serious reactions, systemic corticosteroids may be indicated. The main clinical features that are suggestive of a

severe reaction include mucous membrane involvement, blisters or skin detachment, high fever, angio-oedema or tongue swelling, facial oedema, skin necrosis, lymphadenopathy or dyspnoea. In most cases drug eruptions are reversible, resolving gradually after the causative drug is withdrawn. Knowledge of the half-lives of the implicated medicines can be important; for medications with long half-lives, the time to resolution may be several weeks or more.

Although skin-prick or blood tests may be used in the diagnosis of some reactions (e.g. those dependent on IgE, such as immediate-type reactions to penicillin), they are not usually helpful in skin manifestations of an allergy.[7,15] Skin-prick tests are not risk free and should only be carried out close to intensive care facilities. Rechallenge is not normally advised in the diagnosis of skin reactions because of the inherent risks to the patient.

Management points

When a patient may have experienced a drug eruption:

- Take an accurate medication history. Note details of all current and recent medication, including over-the-counter medicines, herbal (e.g. St John's Wort, echinacea) and homoeopathic preparations, and injections, including vaccines or contrast media.
- Note the times when each medicine was first taken relative to the onset of the reaction, and check whether the patient has taken these medicines previously.
- Some skin reactions, particularly urticaria, may be due to sensitivity to pharmaceutical excipients. If this type of reaction is present, it is worth noting the proprietary (brand) names of medicines taken as well as the generic name.
- Ask the patient if they have a previous history of drug sensitivity, contact dermatitis, connective tissue disease or atopic disease with asthma or eczema.
- Examine the rash to determine what type it is and whether it appears to be a drug eruption.
- Record clearly in the patient's notes any known or suspected ADR, with details of the presumed cause. Tell the patient or relatives, and preferably give a written note so that future exposure can be avoided.
- Take great care in prescribing for the patient subsequently. Check prescribing information (e.g. the *British National Formulary*) for

potential cross-reactions if you are not sure. Clarify that compound preparations do not contain potentially harmful constituents.
- Notify suspected ADRs to the relevant regulatory authority. This information is essential for identifying new drug safety hazards and enables the study of factors associated with ADRs.

Exanthematous (erythematous) reactions

Exanthema is an umbrella term for skin reactions that literally burst forth on the skin. Enanthematous reactions similarly occur on the mucous membranes. Typical characteristics of skin exanthemas include erythema (redness), or morbilliform (resembling measles) or maculopapular lesions. Macules are small, distinct, flat areas and papules are small, raised lesions. This is the most common type of drug-induced cutaneous reaction. The eruption often starts on the trunk; the extremities and intertriginous areas are often involved, but the face may be spared. The rash is usually bright red in colour and the skin may feel hot, burning or itchy.

These reactions can occur with almost any medicine at any time, usually up to a month after treatment is started, but they are most common in the first 10 days. If the causative drug is continued, exfoliative dermatitis may develop. These eruptions usually resolve rapidly when the causative drug is stopped, and occasionally while it is still being taken. Penicillins and sulfonamides frequently cause these rashes. With all the penicillins almost every type of exanthematous eruption may occur; a generalised morbilliform eruption is common with ampicillin and amoxicillin. Viral infections may increase the incidence of morbilliform drug reactions. Ampicillin almost always causes a severe morbilliform eruption when given to a patient with infectious mononucleosis. The exact mechanism involved is unknown. Ampicillin and its derivatives should be avoided in these patients.

Drugs that commonly cause exanthematous reactions are shown in Table 5.3.

Erythroderma and exfoliative dermatitis

A widespread confluent erythematous rash (erythroderma), often associated with desquamation (exfoliative dermatitis), is one of the most severe patterns of cutaneous drug reaction. There may be systemic symptoms, such as fever, lymphadenopathy and anorexia. Possible complications

Table 5.3 Some drugs that commonly cause exanthematous reactions

Allopurinol
Antimicrobials: cephalosporins, penicillins, chloramphenicol, erythromycin, gentamicin, amphotericin, antituberculous drugs, nalidixic acid, nitrofurantoin, sulfonamides
Barbiturates
Captopril
Carbamazepine
Furosemide
Gold salts
Lithium
Phenothiazines
Phenylbutazone
Phenytoin
Thiazides

include hypothermia, fluid and electrolyte loss, and infection. The main drugs implicated are sulfonamides, chloroquine, penicillin, phenytoin and isoniazid.

Fixed drug eruption

A fixed drug eruption is due to exogenous drugs or chemicals are the sole cause. It consists of erythematous round or oval lesions of a reddish, dusky purple or brown colour, sometimes featuring blisters, either bullae or vesicles. Initially, one lesion appears, although others may follow. The patient may complain of itching or burning in the affected area, but systemic involvement is usually absent. The eruption can appear within a day to a few weeks of ingesting the causative drug and can occur on any part of the skin or mucous membranes. The hands, feet, tongue, penis or perianal areas are most frequently affected. The site of the eruption is fixed, i.e. whenever the individual takes the causative drug the eruption occurs within hours at exactly the same site. Healing occurs over 7–10 days after the causative drug is stopped, although residual hyperpigmentation may be slow to resolve.[2,16,17] The pathogenesis of fixed drug eruption is not well understood. Familial cases have been reported and genetic susceptibility may have a role. There are many known causes, including food additives and pharmaceutical excipients. Sulfonamides, tetracyclines and NSAIDs are frequently implicated. Because phenolphthalein has been removed from most laxatives, it is much less often

Table 5.4 Some common causes of fixed drug eruption

ACE inhibitors
Allopurinol
Antimicrobials: co-trimoxazole, sulfonamides, tetracyclines, cephalosporins, penicillin, clindamycin, trimethoprim, metronidazole
Barbiturates
Benzodiazepines
Calcium channel blockers: amlodipine, diltiazem
Carbamazepine
Dextromethorphan
Diltiazem
Fluconazole
Lamotrigine
NSAIDs, including aspirin
Paclitaxel
Paracetamol
Phenolphthalein
Proton pump inhibitors: omeprazole, lansoprazole
Quinine
Salicylates
Terbinafine

ACE, angiotensin-converting enzyme.

the culprit than in past years. Where a fixed drug eruption is suspected, oral challenge to confirm the diagnosis is accepted and safe practice. Topical corticosteroids may help reduce the intensity of the reaction. Table 5.4 lists the most common drug causes.

Urticaria and angio-oedema

Drug-induced urticaria is the second most common form of cutaneous drug reaction after exanthematous reactions. Urticaria is seen in association with anaphylaxis, angio-oedema or serum sickness. The clinical appearance of drug-induced urticaria is indistinguishable from that from other causes, but is often more severe and may be accompanied by hypotension, breathing difficulties, shock, and even death. Urticaria lesions, sometimes known as nettle rash or hives, present as raised, itchy, red blotches or weals that are pale in the centre and red around the outside. Drug-induced urticaria may occur after the first exposure to a drug or after many previously well-tolerated exposures. The onset is more rapid than with other drug eruptions; lesions usually develop

within 36 hours of initial drug exposure. Individual lesions rarely persist for more than 24 hours. On rechallenge, lesions may develop within minutes. Urticaria is characterised as acute when it lasts 6 weeks or less and chronic when it persists beyond this. Drugs are the cause of a minority of cases of chronic urticaria, and in this situation it may be difficult to establish the cause.[18] Acute anaphylaxis and anaphylactoid reactions typically present with angio-oedema, urticaria, dyspnoea and hypotension.

Serum sickness begins 6–14 days after the initial exposure to foreign protein and has distinctive skin findings. Erythema first occurs on the sides of the fingers, toes and hands, before a more widespread morbilliform eruption occurs in about two-thirds of patients. About half the cases of serum sickness have systemic symptoms such as fever, arthralgia and arthritis.

Angio-oedema is a vascular reaction resulting in increased permeability and fluid leakage, leading to oedema of the deep dermis, subcutaneous tissue or submucosal areas. It is rarer than urticaria. The tongue, lips, eyelids or genitalia are generally affected, and the oedema may be either unilateral or symmetrical. Angio-oedema of the upper respiratory tract can result in serious acute respiratory distress, airway obstruction and death.

The mechanisms involved in this spectrum of urticarial reactions are believed to be immunological, mediated by IgE; mediated by circulating immune complexes (serum sickness); and non-immunological. The latter group may involve complement activation, release of cutaneous mast cell mediators, or altered chemical pathways such as arachidonic acid metabolism.[2,18,19] Table 5.5 shows some drugs that may cause urticarial reactions, with their associated mechanisms.

It is essential to take a detailed medication history when a patient presents with urticaria, remembering that pharmaceutical excipients may be a trigger. It can be especially difficult to identify the causative drug in patients taking several medicines, all started at about the same time. The problem for which the patient is being treated, such as infection, may be the cause or may exacerbate a pre-existing urticaria. Specialist skin testing (e.g. radioallergenosorbent test (RAST), skin testing, leukocyte histamine release, tryptase measurement) may help identify the cause. Positive rechallenge is required to confirm that urticaria is caused by a particular drug, but most physicians remain wary of the potential risks and is rarely justified.

Management of urticarial reactions involves stopping the causative agent and treatment with an oral antihistamine. Where there is a systemic

Table 5.5 Some drugs that may cause urticaria/angioedema

Mechanisms of drug-induced urticaria	
Mechanism	*Example drugs*
Drugs acting through IgE receptors to the drug on mast cells triggering degranulation	Antibiotics (penicillins, cephalosporins, sulfonamides, tetracyclines), antiepileptics
Drugs that cause mast cell degranulation	Codeine, opioids, tubocurarine, atropine, hydralazine, pentamidine, quinine, radiocontrast media, vancomycin, dextran
Drugs that pharmacologically promote or exacerbate urticaria	Aspirin, NSAIDs, ACE inhibitors, monoclonal antibodies
Immune complex formation precipitation and activation of complement	Penicillin, sulfonamides, thiouracils, cholecystographic dyes, aminosalicylic acid
Excipients in the medication that provoke allergic or pseudoallergic reactions	Benzoic acid, butylated hydroxytoluene, sulfites, aspartame, colourings, tartrazine, preservatives

Ig, immunoglobulin.
Adapted from ref. 18.

involvement, hypotension, respiratory problems, or serum sickness, a short course of oral corticosteroids may be necessary.[2,18] Where urticaria or angio-oedema are a component of anaphylaxis or an anaphylactoid reaction, resuscitation guidelines should be followed.[20] When these reactions occur they should always be reported to the appropriate regulatory authority.

Angiotensin-converting enzyme (ACE) inhibitors are one of the most common causes of angio-oedema. The estimated incidence is 0.1–1% in Caucasians, but may be higher in people of African-American origin.[21,22] In most cases the reaction occurs in the first week of treatment, often within hours of the initial dose. However, in some cases it has developed after prolonged therapy of up to several years, and it may recur intermittently while the drug is continued.[22–24] It has been shown that continuing use of ACE inhibitors after the first episode of angio-oedema results in a markedly increased rate of recurrence, with serious morbidity. ACE inhibitors should therefore be withdrawn immediately in any patient who presents with angio-oedema, and they are contraindicated in patients with a history of idiopathic angio-oedema.

The mechanism of ACE-inhibitor-induced angio-oedema is thought to involve increased levels of bradykinin. For this reason it has been

presumed that the use of angiotensin-II receptor antagonists, which theoretically do not affect bradykinin, should not present a risk for patients who had this complication while taking ACE inhibitors. However, angiotensin-II receptor antagonists have recently been implicated as a cause of angio-oedema,[25–27] and their safety for use in this situation is now debated. Cicardi *et al*. carried out a retrospective analysis of 64 patients who had experienced angio-oedema while taking an ACE inhibitor.[22] An angiotensin-II receptor antagonist seemed to sustain angio-oedema in only two of 26 patients subsequently switched to this drug class. An angiotensin-II antagonist may be tolerated in patients with ACE-inhibitor-induced angio-oedema, but caution is needed as angio-oedema can have serious consequences.

Aspirin and other NSAIDs are another common cause of urticarial reactions, with an estimated prevalence of 0.1–0.3%.[28] Facial angio-oedema is the most frequent adverse skin reaction associated with NSAIDs. These reactions seem to be more common in children and young adults, and patients with a history of chronic urticaria. Some, but not all, patients show a mixed clinical pattern of cutaneous and respiratory symptoms (e.g. rhinitis, breathlessness). Some patients react to NSAIDs belonging to different chemical classes ('cross-reactors'), whereas others experience problems with agents in only one particular NSAID chemical group ('single reactors'), suggesting that the underlying mechanisms may be respectively pseudoallergy and IgE.

Acne

Some drugs can cause or exacerbate acne. The term acneiform is applied to drug eruptions that resemble acne vulgaris. The lesions are papulopustular but comedones are usually absent.[29] Corticotropin (ACTH), corticosteroids, androgens (in females), oral contraceptives, haloperidol, isoniazid, phenytoin and lithium are among the most frequently implicated drugs.

Psoriasis and psoriasiform eruptions

Psoriasiform eruptions are similar to idiopathic psoriasis and typically consist of erythematous plaques surmounted by large dry silvery scales. A number of drugs can induce psoriasis in patients with no previous history, and some can worsen pre-existing psoriasis, although many reports are anecdotal and causality is unknown. One definite trigger is

lithium, which can unveil psoriasis in susceptible patients or aggravate existing psoriasis.[30] The time course between initiation of the causative agent and exacerbation or formation of the eruption varies between drugs, from less than 1 month to more than 3 months.[2]

Several investigators have confirmed that interferon alfa may either induce or worsen psoriasis.[31,32] The lesions were shown to improve on drug withdrawal and to recur on rechallenge. In patients with pre-existing psoriasis symptoms usually developed within the first month of interferon treatment, but in those with no previous history they developed after at least 2 months' treatment. Other interferons have also been implicated.[33,34] Terbinafine can also cause or exacerbate psoriasis.[35–37] The eruption tended to develop within 2 months after starting treatment and generally resolved on discontinuation of the drug.

The effect of chloroquine and hydroxychloroquine on psoriasis is variable: in some studies most patients treated noted no change in their condition,[38] whereas in others symptoms worsened in a large proportion of patients.[39] It is clear that psoriasis may worsen in some patients, and this may make choice of therapy difficult in some situations, such as malaria prophylaxis in a patient with psoriasis. Care should be taken with the use of hydroxychloroquine in patients with psoriatic arthropathy.

Over the past 20 years, skin eruptions have been described with numerous beta-blockers. Practolol was withdrawn worldwide following a serious syndrome termed the oculomucocutaneous syndrome, featuring a psoriasiform rash, xerophthalmia due to lachrymal gland fibrosis, otitis media, sclerosing peritonitis and a lupus-like syndrome.[40] The pathogenesis of this problem remains unknown, but it appears to have been unique to practolol. Psoriasiform eruptions have since been reported with several beta-blockers,[30] including ophthalmic preparations (e.g. timolol).[41] Cross-reactivity within the class has also been noted.

Beta-blockers may also transform psoriasis into pustular or erythrodermatous psoriasis. The time to onset of the reaction can vary from days to up to a year after initiation of therapy. The underlying mechanism is unknown, but it is notable that $beta_2$ receptors are present in the epidermis.

Drug-associated or -exacerbated psoriasis is typically resistant to treatment indicated for idiopathic psoriasis. The causative agent should ideally be stopped or the dose reduced. Most cases begin to improve within days without the need for specific treatment, and lesions have usually cleared within weeks. Topical treatments such as corticosteroids or calcipotriol may accelerate resolution.

Table 5.6 Drugs that may cause psoriasiform eruptions or exacerbate psoriasis

ACE inhibitors	Interferons
Beta-blockers	Lithium
Chloroquine and hydroxychloroquine	NSAIDs
Digoxin	Penicillamine
Gold	Terbinafine
Granulocyte colony-stimulating factor (G-CSF)	Tetracyclines
	TNF-alpha antagonists

TNF, tumour necrosis factor.

Purpura

Purpura describes small cutaneous extravasations of blood. It is an occasional feature of drug-induced skin eruptions, and in some cases it is the main characteristic. The main causes are thrombocytopenia or platelet dysfunction (drug-induced thrombocytopenia and platelet dysfunction are discussed in Chapter 12). However, a similar picture can be caused by damage to small blood vessels, either by immunological mechanisms or by changes in vascular permeability. Tests of haemostasis, including platelet function, are usually within normal limits. Drugs associated with non-thrombocytopenic purpura include aspirin, quinine, sulfonamides, atropine and penicillin.

Vasculitis

The term vasculitis refers to inflammation of the blood vessels. The vasculitides comprise a diverse group of conditions that may be manifest mainly as a systemic or cutaneous disorder; both types may be due to drug therapy.[42] Several drugs can induce both systemic vasculitis with cutaneous manifestations and cutaneous vasculitis without other organ involvement. About 10% of cases of acute cutaneous vasculitis are believed to be drug induced. The precise mechanism is unknown; however, it appears to be a type III hypersensitivity reaction with immune complex deposition in postcapillary blood vessels. Cutaneous vasculitis commonly presents with raised purpuric (purple) lesions on the legs, ranging in size from a pinpoint to several centimetres. Characteristically the margins are irregular or stellate. Other lesions include erythematous macules, haemorrhagic blisters and ulceration. Occasionally the buttocks, upper extremities, or even the trunk may be involved. Systemic symptoms, such as malaise, arthralgia and fever, are less common.

The most common type of cutaneous vasculitis is leukocytoclastic. Skin biopsy may be required for accurate diagnosis. The histopathological picture is characterised by necrosis of cutaneous blood vessel walls, neutrophil infiltration and haemorrhage.[2] Henoch–Schönlein purpura is a type of vasculitis which frequently involves the skin, joints, gastrointestinal system, kidneys, heart and central nervous system (CNS). It may be associated with aspirin, gold, penicillins or quinidine. Other types of vasculitis that may be drug induced include polyarteritis nodosa-like vasculitis, pustular hypersensitivity vasculitis and pigmented purpuric dermatoses.

Vasculitic lesions typically develop within several weeks of the initiation of the causative drug. The skin lesions may persist for up to 4 weeks or longer, and in some cases become yellow-brown upon healing. It is often difficult to identify the cause of cutaneous vasculitis; infection, malignancy and connective tissue disease need to be excluded. Drug therapy should be stopped at the first suspicion and the condition usually subsides thereafter.[43] Systemic corticosteroids and immunosuppressants may be of some benefit in severe cases.

Propylthiouracil is associated with a hypersensitivity syndrome that typically manifests as a vasculitis involving one or more organ systems.[44] In some cases the clinical features may be limited almost entirely to the skin, although joint involvement has frequently been noted. The time to onset of the reaction varies between 1 week and several years. Most affected patients recover quickly when the drug is withdrawn, but some require prolonged treatment with high-dose corticosteroids and immunosuppressants. Some drugs frequently implicated in cutaneous vasculitis are shown in Table 5.7.

Table 5.7 Some drugs that may cause cutaneous vasculitic reactions

Allopurinol	Hydralazine
Aspirin	Interferons
Beta-lactam antibiotics	Methotrexate
Carbamazepine	Minocycline
Carbimazole	NSAIDs
Co-trimoxazole	Penicillamine
Diltiazem	Propylthiouracil
Erythromycin	Retinoids
Furosemide	Sulfasalazine
Gold	Sulfonamides
Haemopoietic growth factors (G-CSF and GM-CSF)	Thiazides
	Thrombolytic agents

GM, granulocyte-macrophage.

Erythema multiforme, Stevens–Johnson syndrome and toxic epidermal necrolysis

Erythema multiforme (EM), Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are considered by many to represent variants within a continuous spectrum of disease.

EM can result from several underlying causes. Most cases are due to herpes virus infection, but up to 20% are drug-induced. As the name implies, it can present in a variety of patterns. Patients typically present with fever and a flu-like syndrome before developing the skin eruption. The classic pattern affects the hands, feet and limbs more than the trunk. There may be blisters, papular lesions or erythematous areas. A characteristic lesion is one of concentric rings, variously described as target, iris or bull's-eye shaped. Involvement of the mucosa is common, so the mouth, eyes and genitalia may be affected, when the condition is usually called SJS.

Infections are a more common cause of EM than drugs, and many cases have been wrongly blamed on drugs. EM may be due to vaccination, a variety of topical medications, and some environmental substances (e.g. nickel).[1,45] When the condition is suspected all medicines, especially those introduced within the past month, should be discontinued as there is a risk of progression to SJS or TEN. Table 5.8 lists some drugs that are commonly implicated in EM and SJS.

SJS comprises fever, malaise, myalgia, arthralgia, and extensive erythema multiforme of the trunk and face. It is frequently drug induced. There may be skin blistering and mucosal erosion covering up to 10% of the body surface area. This syndrome is distinct from TEN, but there is a degree of overlap as severe forms of SJS can evolve into TEN and several drugs can produce both entities.[46–48] The estimated

Table 5.8 Some drugs that may cause erythema multiforme or Stevens–Johnson syndrome

Barbiturates	Macrolides
Beta-lactam antibiotics	Mefloquine
Carbamazepine	NSAIDs
Chlorpropamide	Phenothiazines
Co-trimoxazole	Phenytoin
Gold	Rifampicin
Histamine H_2-antagonists	Sulfonamides
Lamotrigine	Tetracyclines
Leflunomide	Thiazides

incidence of SJS ranges between 1.2 and 6 per million population per year. In about 50% of cases the cause is not known. The fatality rate is believed to be about 5%.

A large number of drugs have been implicated as a cause of SJS. Penicillins, tetracyclines, sulfonamides and NSAIDs are among the most common. Patients with HIV infection seem to be at increased risk of developing SJS with co-trimoxazole.[49] Drugs that may be responsible for the reaction should be stopped immediately. Bachot and Roujeau[48] examined the impact of the date of drug withdrawal in a large series of patients with SJS or TEN, and noted that the mortality rate was lower in patients whose drug therapy was stopped early than in those who continued to use suspect drugs after the onset of blisters. Management involves systemic corticosteroids, fluid replacement and antibiotics, if required. Drug rechallenge is never justified.

Toxic epidermal necrolysis

Toxic epidermal necrolysis (TEN), or Lyell's syndrome, is a medical emergency. The disorder is characterised by widespread full-thickness epidermal necrosis with involvement of more than 30% of the body surface area. Commonly, there is severe involvement of the mucous membranes (oropharynx, eyes and genitalia). The estimated incidence ranges from 0.4 to 1.2 per million population per year.[46] It has a high associated mortality approaching 40%. The main cause in adults is drugs (Table 5.9). Patients with HIV infection, systemic lupus erythematosus and bone marrow transplant recipients seem to be predisposed to this disorder.[48,49] Elderly patients and those with extensive TEN have a worse prognosis. Drug-induced TEN is rare in children, in whom the diagnosis must be distinguished from staphylococcal 'scalded skin syndrome'.[46,50]

TEN presents with a prodromal period of nausea, vomiting, conjunctivitis, pharyngitis, sore throat, chest pain, myalgia and arthralgia.

Table 5.9 Some drugs that may cause toxic epidermal necrolysis

Allopurinol	Nitrofurantoin
Antituberculous drugs	NSAIDs (especially oxicam derivatives)
Barbiturates	Penicillins
Carbamazepine	Phenytoin
Gold	Salicylates
Griseofulvin	Sulfonamides
Lamotrigine	Tetracyclines
Leflunomide	

These symptoms may last up to 14 days. The acute phase consists of persistent fever and a burning or painful skin rash. The rash generally begins on the face or upper trunk and is characterised by poorly defined erythematous or dark-coloured macules, irregular target-like bullae, or diffuse ill-defined erythema. The affected skin may develop flaccid bullae or may detach irregularly, sometimes in large sheets. The lesions generally progress and extend in waves over a 3–4-day period, but can progress rapidly in a few hours. The conjunctivae are commonly affected 1–3 days before the appearance of skin lesions. Buccal, nasopharyngeal and pulmonary tract desquamation and erosion may be present. The oesophageal and perianal mucosae are affected less often. The consequences of such a massive loss of epidermis include dehydration, increased energy expenditure, and local or systemic infection such as septicaemia. In severe cases, other organ systems can be involved: hepatocellular damage, pneumonia, nephritis and myocardial damage may occur.

The mechanisms responsible for TEN are unknown, although a hypersensitivity–immunological basis is suspected.[6,48] Identification of the causative drug is often difficult. In general, most drugs causing TEN have been given in the previous 1–3 weeks. Drugs started less than 7 days or more than 2 months before the onset of the reaction are unlikely to be responsible. Phenytoin-induced TEN can occur at any time between 2 and 8 weeks after initiation of therapy, and may progress despite discontinuation of the drug.

There has been debate about where this serious condition should be managed. Most experts now agree that management in a specialist burns unit is preferred. Treatment involves the careful protection of exposed dermis and eroded mucosal surfaces, managing fluid and electrolyte balance, nutritional support, and close monitoring for evidence of infection. Fluid rehydration is essential because epidermal loss results in massive fluid shifts and dehydration. Antibiotic therapy should be given at the first sign of sepsis, rather than prophylactically. The place of systemic corticosteroids in the management of TEN is controversial. The best available data suggest that corticosteroids should be avoided in the most severe cases.[48] The benefits of short-term high doses of steroids prior to skin blistering have not been determined in prospective trials.[51] High doses of intravenous immunoglobulins have been used in small numbers of TEN patients, with apparent success,[48,52] but the potential benefits of this treatment require further evaluation. Immunosuppressive agents such as cyclophosphamide have also been given to some patients, with claimed benefits.

The antiepileptic lamotrigine causes serious skin reactions.[53] About 1:1000 adults treated develop these reactions, including SJS and TEN.

Children are at increased risk; the frequency of these problems may be as high as 1:300–1:100. Factors increasing the risk include the use of higher than recommended doses, rapid dose escalation, and concomitant use of valproate. Most of these problems have developed within 8 weeks of starting lamotrigine and resolved upon withdrawal, but deaths have occurred.[54,55]

Blistering drug eruptions

Idiopathic pemphigus and bullous pemphigoid are autoimmune disorders. Idiopathic pemphigus typically features superficial flaccid blisters, although sometimes erythema, crusting and scaling are the major clinical signs. Idiopathic bullous pemphigoid is characterised by large tense blisters developing on an erythematous base. The fluid within is often haemorrhagic. A number of drugs, most of which contain a thiol (or sulphydryl) group in their molecular structure, such as penicillamine or captopril, have been implicated in causing a disorder closely resembling these idiopathic conditions (Table 5.10).[56] Cicatricical pemphigoid is a rare variant in which mouth ulcers, eye problems and other complications may develop, with subsequent scarring. Linear IgA disease results from a deposition of IgA along the basement membrane zone. There are two somewhat different conditions, one affecting childhood and one adults. In the adult form the trunk is almost always affected but lesions can occur elsewhere.

Blistering drug eruptions consist of drug-induced pemphigus and pemphigoid, linear IgA bullous dermatosis and pseudoporphyria cutanea tarda.[2,6] The clinical presentation may comprise widely scattered large, firm bullae, classical but with fewer lesions, scarring plaques, an erythema multiforme-like picture or a pemphigus-like picture. About half of all cases

Table 5.10 Some causes of blistering drug eruptions

Type of eruption	*Causative drugs*
Pemphigus	Captopril, cephalosporins, penicillin, penicillamine, piroxicam, gold/sodium aurothiomalate
Bullous pemphigoid	Furosemide, ACE inhibitors (captopril, enalapril), penicillin, penicillamine, chloroquine, sulfasalazine
IgA bullous dermatosis	Captopril, ceftriaxone, co-trimoxazole, furosemide, G-CSF, interleukin-2, lithium, NSAIDs, penicillin, rifampicin, vancomycin
Pseudoporphyria cutanea tarda	NSAIDs, tetracycline, thiazides, furosemide

have oral involvement. In general, affected patients are younger than those with idiopathic disease. The mechanism is unknown; the presence of autoantibodies similar to those occurring in idiopathic pemphigus has been demonstrated.

The entire clinical spectrum of pemphigus has been reported in association with penicillamine. As many as 7% of patients taking it for more than 6 months develop a blistering eruption. This is thought to be a cutaneous manifestation of the autoimmunogenic properties of the drug. The condition usually improves when penicillamine is stopped, but may persist for many years.

Treatment for all forms of drug-induced blistering eruptions starts with discontinuation of the causative agent. This leads to resolution or improvement in most cases. Many patients benefit from oral corticosteroids until signs of active disease remit, often many weeks later. Immunosuppressants are required rarely. In a minority of patients the lesions persist, or new lesions develop after stopping the causative drug. These patients should be given conventional treatment for idiopathic pemphigus.

Photosensitivity

Photosensitivity denotes a reaction occurring when a photosensitising agent in or on the skin reacts to normally harmless doses of ultraviolet or visible light. It may be due to topical or systemic drugs (Table 5.11). Up to 8% of cutaneous drug reactions are photosensitivity eruptions.

Table 5.11 Some drugs associated with photosensitivity reactions

Frequent	Less frequent
Amiodarone	Antidepressants (tricylic, MAOIs)
NSAIDs	Antifungals
Phenothiazines (particularly chlorpromazine)	Antimalarials
Retinoids	Benzodiazepines
Sulfonamides	Beta-blockers
Tetracyclines (particularly demeclocycline)	Carbamazepine
Thiazides	Griseofulvin
	Oral contraceptives
	Quinine
	Quinolones
	Retinoids
	St John's Wort
	Sulphonylureas

MAOI's, monoamine oxidase inhibitors.

Drug-induced photosensitivity is classified as either phototoxic or photoallergic.[57] Some drugs may induce photosensitivity by precipitating porphyria (e.g. hepatic damage from oral contraceptives) or lupus erythematosus (e.g. hydralazine). Patients who report photosensitivity should be questioned about the medications they are taking and the products they are applying to the skin. Sunscreens, fragrances, and occasionally soaps may cause photoallergic reactions. Phototoxic and photoallergic reactions occur in sun-exposed areas of skin, including the face, neck, hands and forearms. A widespread eruption suggests exposure to a systemic photosensitising agent, whereas a localised eruption indicates a reaction to a locally applied topical photosensitiser.

Phototoxic reactions are common and can be produced in most individuals given a high-enough dose of drug and sufficient light exposure. The eruption is usually evident within 5–20 hours of exposure, and resembles exaggerated sunburn with erythema, oedema, blistering, weeping and desquamation. The rash is confined to areas exposed to light. Hyperpigmentation may remain after other features have subsided. Patients taking potent photosensitising agents on a long-term basis should be warned of the problem and counselled on the need to avoid direct sunlight, to wear protective clothing and to use sunblocks.[57,58] In most cases of phototoxic drug eruption it is not necessary to stop the medication provided protection from the sun is possible. Several antibiotic classes are associated with photosensitive reactions, including the sulfonamides, tetracyclines and quinolones.[59]

Amiodarone is associated with a 30–50% incidence of photosensitivity. Symptoms develop within 2 hours of sun exposure, as a burning sensation followed by erythema. A small number of affected patients develop slate-grey pigmentation on light-exposed areas. Light sensitivity may persist for up to 4 months after the drug is stopped. Cutaneous pigmentation slowly fades after amiodarone is stopped, but may persist for months to years. The problem is related to both the dosage and the duration of drug therapy. Skin cells and cells of other organs in affected patients have been found to contain myelin-like lysosomal structures and membrane-bound granules. This generalised derangement of lysosomal storage may be the basis for other adverse effects of amiodarone, such as interstitial alveolitis, acute hepatitis and disturbed thyroid function.[60,61]

Chlorpromazine may cause a phototoxic response when given in high doses. The reaction is characterised by a burning, painful erythema within minutes of exposure to sunlight, either directly or through windowpanes. Erythema may persist for more than 24 hours. Occasionally, a golden-brown or slate-grey pigmentation, predominantly of exposed

sites, may be seen. Photoallergy is less common than phototoxicity and may occur after exposure to chlorpromazine powder.[57]

Photoallergic drug reactions occur when ultraviolet energy causes the drug to bind as a hapten to protein on epidermal cells, creating an antigen that sensitises nearby lymphocytes.[6] It occurs in predisposed individuals who have been previously sensitised. After cessation of the drug, the reaction develops after re-exposure. These are delayed-type hypersensitivity reactions and their onset is often delayed by as long as 24–72 hours after exposure to the drug and light. Unlike phototoxic reactions, the reaction may spread beyond irradiated areas. The reaction usually manifests as a pruritic eczematous eruption. Erythema and vesiculation are present in the acute phase. The incidence of photoallergic reactions is less than that of phototoxic reactions. Most systemic drugs causing photoallergy also cause phototoxicity. These reactions may occur as a result of local photocontact dermatitis to a topical photoallergen, or of systemic drug therapy. Medications suspected of causing photoallergic drug reactions should be discontinued, as even minimal amounts of further sun exposure can lead to reactions of increasing severity.

Lichenoid drug eruptions

Lichenoid drug eruptions (LDE) are so called because of their resemblance to idiopathic lichen planus. The first drugs reported to cause lichenoid skin reactions were arsenicals used in the treatment of syphilis. Several causative drugs are now known (Table 5.12), although LDE are quite rare in comparison with other drug-induced skin reactions. The lesions can be described as small, shiny, purplish polygonal papules, sometimes with a network of white lines known as Wickham's striae. They are usually itchy, but can be asymptomatic. The surrounding skin

Table 5.12 Some drugs that may cause lichenoid eruptions

ACE inhibitors	Interferon alfa
Antihistamines	Lithium
Antimalarials	Methyldopa
Beta-blockers	NSAIDs
Captopril	Penicillamine
Carbamazepine	Phenothiazines
Furosemide	Phenytoin
Gold	Proton pump inhibitors
Hydroxycarbamide	Sulphonylureas

is completely normal. LDE can rarely affect the buccal mucosa; a characteristic white lace pattern may be present.[62] Idiopathic lichen planus has a predilection for the flexor aspects of the forearms and legs, whereas a lichenoid drug eruption typically has a more symmetric involvement of the trunk and extremities.[2,6]

LDE tend to be extensive and may be linked with, or develop into, an exfoliative dermatitis. LDE can also result from contact dermatitis in photographic workers who handle certain *p*-phenylenediamines.[63] The clinical course of LDE has been investigated in many studies. The mechanism is thought to have an immunological basis. The time to onset of the reaction ranges from weeks to months after initiation of therapy. In most patients the symptoms cleared spontaneously within weeks to months of drug withdrawal. Postinflammatory hyperpigmentation can be significant and prolonged. In prolonged or severe cases, topical or systemic corticosteroids may be used.[63]

Pigmentary disorders

Many skin diseases are followed by changes in skin colour. In particular, after lichenoid eruptions and fixed drug eruptions there may be residual pigmentation. Drug-induced alteration in skin colour may result from increased (or more rarely decreased) melanin synthesis, increased lipofuscin synthesis, or cutaneous deposition of drug-related material (Table 5.13). Sometimes the exact nature of the pigment is unknown. The pigmentation may be widespread or localized, and pigment deposits occasionally occur in internal organs.

A brown patchy pigmentation on light-exposed areas may be a result of prolonged administration of phenytoin. It occurs in about 10% of patients, and women are more likely to be affected. The pigmentation is similar to chloasma, affecting mainly the face, neck and arms.

Pigmentary changes develop in about 25% of patients receiving antimalarials for more than 3 or 4 months. The shins and pretibial area are

Table 5.13 Some drugs that may cause pigmentation

Amiodarone (slate grey)	Imatinib
Chloroquine (blue-grey or brown)	Mepacrine (yellow)
Chlorpromazine (blue-grey)	Minocycline
Cytotoxic agents	Oral contraceptives (brown)
Gold (blue-grey)	Phenytoin (brown)
Hydroxychloroquine	

most commonly affected. Irregular patches from grey to blue-black in colour are seen. Patients who develop this pigmentation should undergo an eye examination, as corneal depositions and retinal damage frequently coexist. Antimalarials should preferably be discontinued in affected patients, as the retinal damage is irreversible.

Hyperpigmentation has been described after long-term use of minocycline and imipramine,[64] and more recently with the use of imatinib.[65–67]

Alopecia

Many drugs have been reported to cause hair loss (Table 5.14). The human scalp has about 100 000 hairs, 100 of which are shed daily. Human hair follicles undergo three cyclical stages: the actively growing phase of anagen, which lasts about 3 years and features 80–90% of the scalp's follicles; the brief involutionary phase of catagen; and the resting phase of telogen, which lasts about 3 months. The telogen phase culminates in the shedding of the hair shaft and at the same time new growth in the hair follicle begins.[68–70] Hair follicles produce two types of hair according to the area of the body. Vellus hair is soft and colourless, covering the body surface apart from palms and soles. Terminal hair is the large, coarse, pigmented hair that occurs on the scalp, eyebrows, axillae etc.

Drugs that induce hair loss may be classified according to the phase of the hair follicle cycle that is affected. In anagen effluvium, drugs induce an abrupt cessation of active anagen growth and the hairs are shed within days or weeks, with tapered and broken roots. Anagen hair loss is an expected pharmacological effect of cytotoxic chemotherapy and is often dose related. The hair loss is almost always reversible, but a delay of several weeks is common before regrowth begins. Alopecia is associated with alkylating agents such as cyclophosphamide, cytotoxic antibiotics such as

Table 5.14 Some drugs that may cause alopecia

Amfetamines	Interferons
Anticoagulants (warfarin, heparin, heparinoids)	Leflunomide
Antidepressants	Lithium
Antithyroid drugs	Oral contraceptives
Beta-blockers	Phenytoin
Carbamazepine	Retinoids
Cimetidine	Tamoxifen
Cytotoxic agents	Valproate
Hypolipidaemics	

bleomycin, vinca alkaloids, and platinum compounds. Scalp hypothermia may be useful to partially prevent hair loss in patients undergoing chemotherapy.

Telogen hair loss may be a consequence of drug therapy or events such as severe illness, and it can be difficult to establish the cause. It features a conversion in the hair root from the anagen phase to the telogen phase. Drug-induced telogen effluvium usually becomes evident 2–4 months after the treatment is started. Alopecia may or may not be noticeable, depending on the proportion of follicles involved. Hair loss is usually confined to the scalp, although the eyebrows, axillary and pubic regions may be affected. Spontaneous regrowth of hair at the follicle usually occurs within 2–5 months after the causative drug is discontinued. It can be very difficult to establish whether or not a particular drug is the cause of the hair loss. Alopecia is a well recognised sign of hypothyroidism and can occur when the disorder is drug induced (see Chapter 9).

Idiopathic androgenic alopecia (male pattern baldness) presents in several ways but often as a bitemporal recession of the hairline. In women, a diffuse thinning over the top of the scalp with preservation of the anterior hairline occurs. Drugs with androgenic activity may cause this problem, such as danazol, metyrapone and anabolic steroids. It can also occur with the oestrogen receptor antagonist tamoxifen.

Hair gain

There are two patterns of unwanted increase in hair growth, both of which may be associated with drug administration. Hirsutism is an excessive growth of coarse hair with masculine characteristics in a female. This is a consequence of androgenic stimulation of hormone-sensitive hair follicles. Drugs commonly responsible include testosterone, danazol, corticotropin, anabolic steroids and glucocorticoids. Patients with drug-induced hirsutism may also present with other dermatological signs of virilisation, such as acne.

Hypertrichosis is the growth of terminal and/or vellus hair on areas of the body where the hair is usually short, such as the forehead and cheeks. Table 5.15 shows some drugs that have been associated with the development of hypertrichosis. The problem is usually dose related and is reversible after drug withdrawal. Ciclosporin may produce hypertrichosis in 50% of transplant recipients, with the excess growth being most marked on the face and upper back. The problem is less frequent in conditions where lower doses of ciclosporin are used. Minoxidil causes

Table 5.15 Some drugs that may cause hypertrichosis

Androgens	Nifedipine
Ciclosporin	Penicillamine
Diazoxide	Phenytoin
Methoxsalen	Verapamil
Minoxidil	

Table 5.16 Some drugs that may cause nail disorders

Captopril	Lithium
Chloramphenicol	Methoxsalen
Chlorpromazine	Penicillamine
Cytotoxic agents	Phenytoin
Fluoroquinolones	Retinoids
Gold	Tetracyclines
	Thiazides

some degree of hypertrichosis in nearly all patients; this effect has led to its therapeutic use as a topical treatment for male pattern baldness.

Nail disorders

A large number of drugs of different classes can be responsible for the development of nail changes.[71,72] Such changes usually involve several or all of the nails, and appear within a few weeks of drug administration. Nail problems can be asymptomatic or associated with pain and impaired digital function. They are usually reversible on drug discontinuation. Nail abnormalities include Beau's lines (horizontal notches in the nail plate), brittle nails, onycholysis (separation of the nail plate from the nail bed), onychomadesis (separation of the nail plate from the matrix area, with progression to shedding) and paronychia (erythematous and tender nail folds). The nail can be considered to be homologous to hair and the same drugs frequently affect both tissues.[68] The pathogenesis of drug-induced nail abnormalities is not well understood, but most cases are thought to involve a toxic effect of the drug on the nail epithelia. Other potential factors may be drug deposition in the nail plate, leading to nail discoloration and impaired digital perfusion, causing necrosis of the nail apparatus or damage to the nailbed blood vessels. Some drugs that may cause nail disorders are shown in Table 5.16.

CASE STUDY 5.1

A 62-year-old man presented at the Accident and Emergency department with unilateral swelling of the face, lips, jaw line and cheek. About 24 hours ago he had noticed some swelling of his cheek, and since then it had gradually progressed and there was now massive swelling of his lips and face. He described having experienced several previous episodes of localised swelling of the face over the last 6–12 months. Medical history included hypertension and depression.

Current drug therapy:

- Enalapril 10 mg daily
- Bendroflumethiazide 2.5 mg daily
- Citalopram 20 mg daily

He had been taking all of these medicines for at least 5 years and had not taken any others recently.

What condition do the symptoms suggest?

The symptoms suggest angio-oedema, which is characterised by well demarcated non-pitting oedema commonly involving the face, lips, tongue, pharynx and neck. Occasionally the hands, feet, genitalia and mucous membranes of the gastrointestinal tract may be involved. In some instances it may cause respiratory distress due to laryngeal obstruction.

Which of the patient's medicines is most likely to be responsible?

Angio-oedema is a known adverse effect of ACE inhibitors, with an overall incidence of 0.1–0.5%.[23–25] Most patients develop the problem within the first week of treatment, but recent case reports indicate that delayed-onset angio-oedema, occurring after many years of treatment, is more common than was previously thought.[22] It has been suggested that the incidence may be as high as 1% for patients taking ACE inhibitors for more than 10 years. The precise mechanism for the reaction is unclear; increased bradykinin availability has been postulated, but other factors may be involved.[74] Predisposing factors for the development of angio-oedema include being of African origin, having a previous history of angio-oedema or complement C1 esterase inhibitor deficiency, and possibly poor compliance.

How should the problem be managed?

The management of acute angio-oedema depends on its severity at presentation. Any drug therapy suspected to be the cause should be discontinued immediately. Patients should be carefully examined for any evidence of respiratory compromise, such as stridor, dyspnoea, tongue swelling or

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CASE STUDY 5.1 (continued)

dysphagia. Patients with respiratory symptoms should receive subcutaneous or intramuscular adrenaline (epinephrine) and the airway must be maintained. Antihistamines and corticosteroids should be given until upper airway swelling has resolved. The patient's blood pressure should be monitored, and once the acute problem has settled a drug from another class of antihypertensive should be prescribed. Angiotensin-II receptor antagonists appear to be much less likely to cause angio-oedema, although the problem has been reported and a minority of patients may develop the problem with drugs from either class.[22] All serious suspected reactions should be reported to the Committee for Safety of Medicines (CSM) on a yellow card, even if well recognised.

CASE STUDY 5.2

Ms B, a 34-year-old woman, presented to her GP with a painful pruritic rash on her arms, legs and neck. The rash had begun within a day or so of sun exposure and was not completely confined to sun-exposed areas. The affected skin was erythematous, with some blistering vesicles. Ms B had no recent use of any new skincare products or cosmetics. There was no significant medical history. Her only prescribed medication was the combined oral contraceptive pill, which she had been taking for the past 10 years. Ms B also reported taking ibuprofen when required for painful periods; she had been taking it over the last 48 hours.

What type of drug eruption do the symptoms suggest?

The symptoms suggest drug-induced photosensitivity. With phototoxic reactions the eruption is usually evident within 5–20 hours of exposure. It resembles exaggerated sunburn with erythema, oedema, blistering, weeping and desquamation. The rash is confined to areas exposed to light. Photoallergic reactions occur in individuals who have been previously sensitised. The reaction develops after re-exposure to the causative drug. The onset is often delayed by as long as 24–72 hours after exposure to the drug and light. There is a latent period during which sensitisation occurs, and the reaction generally develops within 24 hours of re-exposure. The skin beyond irradiated areas may be

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CASE STUDY 5.2 (continued)

involved. This reaction usually manifests as a pruritic eczematous eruption, with erythema and vesiculation in the acute phase. Photoallergic reactions are less common than phototoxic reactions (see Table 5.11 for a list of drugs causing these reactions).

How should the patient be managed?

The features suggest a photoallergic reaction, so the suspect drug should be discontinued as even minimal amounts of further sun exposure can lead to reactions of increasing severity. In phototoxic drug eruptions it is not always necessary to stop the medication, provided protection from the sun is possible.

NSAIDs are a known cause of photosensitivity reactions. Oral contraceptives have also rarely been linked with photosensitivity,[73] but in this case ibuprofen seems a more likely cause. Photosensitive eruptions vary in severity. Mild cases may be managed with antihistamines and topical steroids. In severe cases hospital admission may be required. The GP advised Ms B to use paracetamol instead of ibuprofen as an analgesic in the meantime, and to continue her oral contraceptive. She prescribed a short course of cetirizine and hydrocortisone 1% cream. The patient was advised to use high-factor sunscreens regularly when outdoors.

One month later Ms B was referred to the dermatology clinic in the local hospital. She described a continued worsening skin rash despite somewhat irregular sunscreen use. She underwent patch and phototesting and completed a detailed questionnaire on photosensitisers. The questionnaire revealed that Ms B had been taking St John's Wort intermittently over the last 6 months for premenstrual mood swings.

Could St John's Wort be implicated as a cause of photosensitivity?

Photosensitivity has been associated with herbal medicines rarely; St John's Wort is the most commonly implicated herb.[75–77] Ms B had not mentioned its use to the GP, as she believed 'natural' products to be completely safe. Phototesting indicated that Ms B was markedly photosensitive in the UVA and UVB range. She was advised to stop taking St John's Wort. At follow-up 4 months later she reported no symptom recurrence. This case illustrates the importance of a complete medication history for the prompt identification and management of ADRs. The patient was unaware that complementary therapies could have significant side effects. Diagnosis was further complicated by concurrent use of two other medicines that can cause this type of skin eruption.

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