Drug eruptions

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Introduction

The last four decades have seen an enormous increase in the use of potent and toxic drugs as therapy. The considerable advances that these drugs have provided in the control and prevention of disease are matched by their potential to produce unwanted side effects many of which are reflected in the skin.

These side effects cannot in the main be predicted. Tests in animals may not reliably be extrapolated to the human and only occasionally can the occurrence of side effects be gauged from the structural formula of a new drug. With some fifty new drugs developed each year the practitioner is challenged simply to keep pace with their therapeutic indications. The results of one survey suggested that 30% of prescriptions from general practitioners was based on data supplied by drug companies. In 1985 it is also increasingly common to find that patients, when faced with a chronic disease have sought several medical opinions or have taken refuge in remedies which rely more on advertising than their therapeutic effectiveness. The available information suggests then that drug reactions are likely to be common.

In a recent study (Black & Somers, 1984), drug-related illness accounted for some 6% of hospital admissions in a year. It has been estimated that the average inpatient in a British hospital receives five drugs whilst one in an American hospital receives nine. Since a large majority of allergic reactions affect the skin the incidence of drug-induced cutaneous eruptions probably reflects the risk of allergic drug reactions in general. Reactions to drugs in over twenty thousand medical inpatients were studied in a large collaborative study (Arndt & Jick, 1976). Skin reactions occurred in a little over 2%. Despite the lack of data on non-hospitalized patients it is clear that even if only 2% of patients receiving drugs experience a 'rash' it is a number that we can all ill afford.

Mechanisms of adverse drug reactions

An adverse drug reaction is commonly defined as any response to a drug that is unintended and occurs at doses used in the prophylaxis or therapy of disease. Adverse reactions may occur as a result of inappropriate metabolism, idiosyncrasy or hypersensitivity to a drug. Impaired metabolism may result from altered oxidation or acetylation of a drug as may be seen in slow-acetylators in isoniazid-induced acne. An idiosyncratic reaction is an inbuilt abnormal response to a drug such as may occur when barbiturates or sulphonamides are given to a patient with porphyria. Hypersensitivity or allergy to a drug is mediated by an antigen-antibody reaction. Previous exposure and sensitization to the drug is a prerequisite though it is possible for a drug to induce antibody formation without clinical symptoms of hypersensitivity.

Hypersensitivity reactions are normally classified into four types (Gell & Coombs, 1963) – Type 1 (immediate or anaphylactic), Type 2 (cytotoxic or autoallergic), Type 3 (immune complex disease) and Type 4 (cell-mediated or delayed). The vast majority of drug reactions are due to hypersensitivity and this review will be restricted to a brief discussion of these allergic responses and a description of some of the common skin reactions provoked by drugs.

Type 1 reaction

This is mediated by IgE or reagin. IgE antibodies are produced in response to a drug or drug-hapten complex and attach themselves preferentially to the mast cell. On exposure to antigen there is mediator release from the mast cell which then results in the well-described reactions of urticaria, angio-oedema, asthma and, in severe cases, anaphylaxis.

Type 2 reaction

This may present with thrombocytopenia, leucopenia or haemolytic anaemia. In this reaction the antigen (drug) combines with a platelet or red cell, for example, and stimulates the formation of antibodies to the drug-cell combination. Sedormid purpura, quinine
purpura, many of the haemolytic anaemias, including that due to high dose penicillin therapy (Petz & Fudenberg, 1966) and methyldopa, are examples of this type of reaction. Some 10 to 20% of patients receiving methyldopa develop a positive Coombs’ test but only 0.5 to 1.0% develop a haemolytic anaemia. Approximately 70% of reported drug-induced immune haemolytic anaemias are a result of methyldopa. Leucopenia of immunological origin often with the presence of anti-leucocyte agglutinins is not infrequently a reaction of drugs.

Type 3 reaction

The initial exposure to the drug sensitizes and results in antibody, usually IgM or IgG, production. After an interval antigen-antibody complexes form and are deposited in the peripheral circulation. Complement is activated and causes accumulation of neutrophilic leucocytes which release lysosomal enzyme that destroys tissues. The commonly recognized systemic reaction in this category is the serum sickness syndrome. Fever, arthralgia and lymphadenopathy are typical features and classically arise from hypersensitivity to foreign serum. A similar clinical picture may result 1 to 3 weeks after treatment with penicillin, para-aminosalicylic acid or sulphonamides. Vasculitis, when a feature of the Type 3 reaction, is often attributed to sulphonamides but may also be caused by phenytoin, thiouracils, chlorpromazine, aspirin, gold and penicillin.

Type 4 reaction

This T-cell mediated or delayed hypersensitivity type of reaction is the basis of an allergic dermatitis often due to a topical medication. In a large European study (Bandmann et al., 1972), a third of the patients with an allergic contact dermatitis showed a hypersensitivity to a topical medicament. Sensitization is more likely to occur if the medication is applied to damaged skin. The importance of this ‘contact’ allergy is that it prohibits the systemic use of the same or related drug. If the offending drug is mistakenly taken it produces a widespread dermatitis. Amongst the contact sensitizers ethylenediamine hydrochloride used as a stabilizer in some creams is of particular importance. It cross-reacts with drugs used systemically such as aminophylline which consists of two-thirds theophylline and one-third ethylenediamine. Some antihistamines which are derived from ethylenediamine may also cause a generalized eruption if given to a sensitized patient (Fisher, 1976). Another recognized sensitizer is benzoate found in anti-pruritic preparations, in local applications for the treatment of haemorrhoids and in some sunburn remedies. Benzoate is a derivative of para-aminobenzoic acid (PABA) and therefore may cross-react with other PABA compounds such as procaine and dubucaine. Topical antihistamine, freely available as an over-the-counter preparation, is a common sensitizer as is neomycin especially when applied to chronic stasis dermatitis or otitis externa (Leyden & Kligman, 1979).

Types of cutaneous reactions

Skin reactions to drugs are diverse. In a series of 464 cases during 1966–1970, Kuokkanen (1972) found that exanthematus eruptions were the most common and accounted for 46% of reactions. Urticaria occurred in 23% of cases, fixed drug eruption in 10%, erythema multiforme in some 5% and other reactions in less than 5% each. In another more recent study (Kauppinen & Stubb, 1984) exanthemas again formed the largest group, 42% of 446 inpatients, fixed eruptions occurred in 21%, urticaria-angioedema in 12.5% and erythema multiforme with Stevens-Johnson syndrome accounted for approximately 6%. The remainder comprised eczema, toxic epidermal necrolysis, photosensitivity reactions, purpura and the systemic lupus erythematosus (SLE) syndrome.

Exanthematous eruption

This type of reaction can be caused by almost any drug. Itch may or may not be associated and differentiation from a viral exanthem may at times be difficult. The greatest incidence occurs with the penicillins and the eruption commonly consists of maculo-papular erythematous lesions. The risk of developing penicillin hypersensitivity is increased in patients with a previous history of other drug allergy and in those of whom the drug is given parenterally. In one study (Shapiro et al., 1969) a rash was reported in 4.5% of 622 patients treated with penicillins other than ampicillin, in 9.5% of 422 patients treated with ampicillin and in 1.8% of 2941 patients not receiving either of these drugs. Although ampicillin may provoke urticaria, it commonly causes a morbilliform eruption (Figure 1) which lasts a few days. An increased incidence of ampicillin rash occurs in infectious mononucleosis, cytomegalovirus mononucleosis, lymphatic leukaemia and in viral respiratory infections (Almeyda & Levantine, 1972). In these conditions the rash may also be somewhat prolonged.

Other drugs commonly associated with an exanthematous eruption include barbiturates, sulphonamides and allied anti-diabetic and diuretic drugs, phenytoin, erythromycin, allopurinol and gold salts. Gold salts were first used in France in the 1920s and 1930s though their efficacy as an anti-rheumatic drug was confirmed very much later (Fraser, 1945). Two forms of these drugs are in common use, the aqueous
based sodium aurothiomalate and the oil based aurothioglucose. Both drugs are administered intramuscularly. Overall, approximately 30% of patients started on chrysotherapy may, at least temporarily, have to discontinue the drug because of side effects, the most common being a rash or mucous membrane lesions. The most common eruption is erythematous, maculo-papular and pruritic, but a lichen-planus like eruption or a pityriasis rosea-like rash also occurs (Penneys et al., 1974). After the reaction has settled gold therapy can generally be restarted without incident (Klinefelter, 1975).

Allopurinol, an analogue of hypoxanthine, is an inhibitor of xanthine oxidase and is used widely in the prophylaxis of gout. Its major side effect is an erythematous maculopapular eruption though occasionally urticaria and toxic epidermal necrolysis have been seen. A drug rash has been noted in some 2% of patients taking allopurinal alone (Boston Collaborative Drug Surveillance Program, 1972) but the incidence rose to 22.4% in patients treated simultaneously with both allopurinol and ampicillin.

Table I Hypersensitivity drug reactions

<table>
<thead>
<tr>
<th>Type</th>
<th>Reaction</th>
<th>Drug commonly responsible</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Urticaria:</td>
<td>Penicillin</td>
</tr>
<tr>
<td></td>
<td>Angio-oedema:</td>
<td>Aspirin</td>
</tr>
<tr>
<td></td>
<td>Asthma:</td>
<td>Foreign sera</td>
</tr>
<tr>
<td></td>
<td>Anaphylaxis:</td>
<td>Penicillin</td>
</tr>
<tr>
<td>2</td>
<td>Thrombocytopenic purpura:</td>
<td>Quinine</td>
</tr>
<tr>
<td></td>
<td>Granulocytopenia:</td>
<td>Gold</td>
</tr>
<tr>
<td></td>
<td>Haemolytic anaemia:</td>
<td>Methyldopa</td>
</tr>
<tr>
<td>3</td>
<td>Vasculitis:</td>
<td>Sulphonamides</td>
</tr>
<tr>
<td></td>
<td>Serum sickness:</td>
<td>Penicillin</td>
</tr>
<tr>
<td></td>
<td>L.E. syndrome:</td>
<td>Hydralazine, Procainamide</td>
</tr>
<tr>
<td>4</td>
<td>Contact dermatitis:</td>
<td>Ethylenediamine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neomycin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Topical antihistamine</td>
</tr>
</tbody>
</table>
Urticaria and angioedema

Urticaria or ‘hives’ presents as well-defined, erythematous, raised often oedematous patches in the skin. The lesions are usually multiple, of variable size and invariably pruritic. Individual wheals seldom last more than 24 to 48 hours which is a useful diagnostic sign. Episodes lasting less than 6 weeks are arbitrarily classified as acute and those longer than 6 weeks as chronic. Angioedema is characterized by plaques of subcutaneous oedema which may be painful and tender. Urticaria results from degranulation of mast cells in the dermis, releasing histamine and other mediators. Penicillin and its derivatives are the most common causes of a Type I reaction in which urticaria may be a prominent feature (Figure 2, Table I). Cephalosporins, sulphonamides, blood products and vaccines prepared in eggs may also induce an urticaria as part of the Type I hypersensitivity reaction. A variety of drugs may induce histamine release by a direct action on mast cells. Morphine sulphate, curare and polymyxin antibiotics belong to this group. Urticaria is often a feature of the serum sickness syndrome, and, finally, aspirin and non-steroidal anti-inflammatory agents may induce urticaria (Ros et al., 1976). It is postulated that these drugs inhibit prostaglandin production and the lack of the inhibitory action of prostaglandins allows the development of urticaria.

In a 17 year prospective study of the clinical characteristics of patients with a history of allergy to aspirin (Speer et al., 1981), the most common manifestation was urticaria-angioedema. In these patients 90% were also sensitive to inhalants (76%), foods (74%) and other drugs (43%). The ten most common drugs which may induce urticaria as reported to the Committee on Safety of Medicines in the United Kingdom between the years 1964 and 1983 (Griffin, 1983) are shown in Table II.

Table II The top ten causes of drug-induced urticaria reported to the Committee on Safety of Medicines 1964–1983 (Griffin, 1983)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Year of Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cotrimoxazole</td>
<td>1981</td>
</tr>
<tr>
<td>Fenbufen</td>
<td>1984</td>
</tr>
<tr>
<td>Benoxaprofen*</td>
<td>1981</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>1984</td>
</tr>
<tr>
<td>Fenclon efenac</td>
<td>1984</td>
</tr>
<tr>
<td>Feprazone</td>
<td>1981</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>1981</td>
</tr>
<tr>
<td>Alclofenac*</td>
<td>1981</td>
</tr>
<tr>
<td>Nalidixic acid</td>
<td>1981</td>
</tr>
<tr>
<td>Amoxycillin</td>
<td>1981</td>
</tr>
</tbody>
</table>

* Drug now discontinued.

1. 1976) Antihistamines do not prevent a fixed drug eruption. In general a single drug is responsible but some patients may exhibit a fixed drug eruption to several drugs. In a recent review of the literature (Korkij & Soltani, 1984) 68 drugs had been reported as responsible for a fixed drug eruption. Common offenders include quinine, sulphonamides, phenolphthalein, barbiturates, oxyphenbutazone and chlor Diazepoxide. Phenolphthalein is considered a safe and reliable drug and hence found in proprietary purgatives, and because it is tasteless it is included in those sold in the form of chewing gum or chocolate. The mechanism which determines the localization

Figure 3 Balano-posthitis caused by fixed drug eruption showing lesions.
of the skin lesions remains unexplained. Patch testing on unaffected skin with the drug responsible for the fixed eruption has invariably produced negative results whilst occasionally a positive response has been obtained when the patch test has been applied to previously affected but 'healed' skin (Welsh, 1961). A blood-borne mediator has been identified as a possible cause in a phenolphthalein-induced fixed eruption (Wyatt et al., 1972) but this fails to explain why the lesions are so localized.

**Erythema multiforme**

The diagnostic lesion is the iris or target lesion (Figure 4). As the name multiforme implies it may present with several different types of lesions. These may consist of urticated papules or, as in the severe form of the disease, bullae, which become widespread and are associated with ulceration of the oral and genital mucosa—the Stevens-Johnson syndrome.

Erythema multiforme is considered to be a hypersensitivity reaction commonly to a drug or to an underlying virus or bacterial infection. The commonest associations are with preceding herpes simplex or mycoplasma infection. Streptococcal infection, infectious mononucleosis, tuberculosis, sarcoidosis, X-ray therapy of malignant disease and sometimes malignancy itself are other recognized causes. The most common drug causes of erythema multiforme are sulphonamides, phenytoin, barbiturates, phenylbutazone, sulphonyleureas, penicillin and salicylates.

In a recent review of the literature 40 drugs had been implicated as the cause of erythema multiforme (Huff et al., 1983). Sulphonamides were the most frequent offenders. Sulphonamide-associated erythema multiforme usually appears a week or two after therapy but may occur within hours in patients who have previously been sensitized to the drug. Stevens-Johnson syndrome may also be caused by the long acting sulphonamides (Carroll et al., 1966), penicillins, dipherhydantoin and chlorpropamide (Bianchine et al., 1968).

**Photosensitivity**

Photosensitivity is an all-encompassing term to describe untoward reactions to non-ionizing radiation. There are two main types – phototoxicity and photoallergy. A phototoxic reaction relies on a high concentration of a photosensitizing agent in the skin and occurs when a sufficient quantity of light of appropriate wavelength reaches the skin. Everyone is capable of exhibiting a phototoxic reaction which presents as erythema, urticaria and oedema within 24 hours of light exposure. The eruption is confined to light exposed areas commonly the face, V area of neck, dorsum of the hands and the feet. Acute erythema is usually followed by hyperpigmentation. A phototoxic reaction may occur on first administration and subsides quickly on withdrawal of the drug. Drugs recognized as causes include the tetracycline group especially 'demethylchlortetracycline', nalidixic acid, chlorothiazide, sulphonamides and griseofulvin.

A photoallergic reaction is less common and may occur with small quantities of a drug. Photoallergy may be of the 'immediate' type and then commonly presents as solar urticaria or produces an eczema as a Type 4 reaction (Horio, 1984). The latter variety is the more frequently encountered. The eruption, unlike the phototoxic reaction, may spread to areas which have not been light exposed. Normally there is a delay of 48 hours before the onset of the reaction. Although drugs administered systemically will induce photoallergy it is important to recognize that a photoallergic dermatitis may be caused by a topically applied photosensitizer. In practice it may be difficult to differentiate between a phototoxic and a photoallergic reaction in an individual patient especially as similar drugs produce both types of reaction. Those drugs which may cause photoallergy include chlorpromazine, chlorothiazide, sulphonamides and griseofulvin.

**LE syndrome**

A syndrome clinically indistinguishable from systemic lupus erythematosus may be provoked by a variety of drugs. Those commonly identified include hydralazine, procainamide, isoniazid and phenytoin.
The development of SLE with these drugs appears to be dose related and with hydralazine a dose greater than 200 mg/d (300 mg in rapid acetylators) is more likely to induce the syndrome.

The syndrome may present with a variety of skin signs which include erythema with the familiar 'butterfly' rash, urticaria, purpura, photodermatitis, alopecia, livedo reticularis, cutaneous vasculitis, hyperpigmentation and nail fold telangiectasia. Arthralgia and pleurisy also occur but renal and central nervous system involvement is uncommon. Tests for antinuclear factor are invariably positive and LE cells are commonly found. Antibodies to single stranded-DNA may be found but those against double stranded DNA are rare. A genetic predisposition to the syndrome has been claimed because the HLA antigen DRW-4 is commonly identified in patients. Indeed the combination of HLA-DRW-4, female sex, slow acetylator status and a minimum dose of 200 mg/d of hydralazine almost inevitably led to the syndrome in one study (Batchelor et al., 1980). Other drugs known to provoke the syndrome are griseofulvin, methyl-dopa, chlorpromazine, para-aminosalicylic acid and thioracil.

**Lichen planus-like drug eruption**

Several drugs produce an eruption identical with or virtually indistinguishable from lichen planus (Figure 5). Lesions in the mouth are more frequent in 'true' lichen planus but the distribution of the eruption over the body is similar in the two varieties. In addition the lesions in both types heal with pigmentation, and histology, in most cases, cannot separate a drug-induced lichen planus from that which arises de novo. Gold and organic arsenicals were amongst the first to be recognized as drugs which produced a lichenoid rash. Arsenic is now considered outdated as a therapeutic measure though gold has gained in popularity in recent years for the treatment of rheumatoid arthritis. Mepacrine was found to induce a lichenoid eruption as long ago as the Second World War when troops who took the drug as an antimalarial agent developed the typical rash. Chloroquine will also cause a lichenoid eruption and thiazide diuretics, chlorothiazide and hydrochlorothiazide (Harber et al., 1959) are known to cause a photosensitive lichenoid eruption. Amphenazole, a respiratory stimulant, may cause bone marrow depression with long term use but lichenoid eruptions may also be induced. Methyldopa includes in its potential side effects a lichenoid rash.

**Drug-induced alopecia**

Hair growth is normally divided into three stages: telogen when the hair is resting, anagen when it is...
actively growing and catagen when it is involuting. In
the adult, approximately 85% of the scalp hair is in
anagen, 14% in telogen and 1% in catagen. With hair
loss associated with the contraceptive pill, the telogen
hairs are shed – a phenomenon known as telogen
effluvium. Acute disease or emotional stress may
prove a similar hair loss. With cyclophosphamide
therapy some anagen follicles enter catagen
prematurely and inhibition of mitosis results in a
constriction of the hair shaft. These hairs may be shed
4–6 days after the first effective dose. Anti-cancer
drugs commonly cause alopecia of the scalp though
with long term use of chemotherapeutic agents there
may also be loss of axillary and pubic hair. Severe
loss is common with cyclophosphamide, the
nitrosoureas (e.g. lomustine) and doxorubicin. The
hair returns on stopping the drug though occasionally
it is of a different colour and texture than previously
(Falkson & Schulz, 1981). Heparin, the coumarins and
indandiones all cause a telogen effluvium 2 to 3
months after starting anticoagulant therapy. Anti-
thyroid drugs, thiouraëls and carbimazole, may also
induce alopecia. Loss of scalp hair occurred in five
women who were given carbimazole in doses varying
between 15 and 60 mg/d for 4 to 40 weeks. All
improved when carbimazole was discontinued or the
dose reduced (Papadopoulos & Harden, 1966).

Drug-induced hyperpigmentation

The antimalarials cause pigmentary changes in some
25% of patients receiving these drugs for more than 3
to 4 months (Levantine & Almeya 1973). Mepacrine
produces a diffuse yellowish discolouration of the
skin. It occurs in most patients who receive the drug
and fades a few weeks or several months after therapy
is discontinued. Chloroquine may whiten hair and at
the same time stain the skin a bluish-grey colour.
Prolonged high doses of chlorpromazine and related
phenothiazines produce hyperpigmentation, par-
ticularly in sun-exposed areas of skin (Satanove,
1965). The pigmentation is cumulative and fades only
a little in winter. The skin colour changes range from
tan in the early stages to slate-grey later and finally to
purple. Minocycline, a tetracycline derivative, used in
the treatment of acne vulgaris, may cause patchy or
diffuse pigmentation normally described as blue-black
in colour (McGrae & Zelickson, 1980; Simons &
Morales, 1980).

Chloasma is a well recognized side effect of oral
contraceptives. In one study some 3 of 10 patients
receiving the drug developed the pigmentation (Res-
nek, 1967). Discontinuation of the oral contraceptive
may cause partial remission in pigment though in
many the chloasma remains unchanged.

Hyperpigmentation is also a well recognized com-
plication of several anti-cancer drugs. Those common-
ly reported include bleomycin, busulphan, cyclophos-
phamide, systemic fluorouracil, hydroxyurea and
mithramycin. The hyperpigmentation associated with
these drugs appears to be unrelated to increased
ACTH or melanocyte stimulating hormone activity.
Bleomycin induced pigmentation occurs in approxi-
mately 30% of patients receiving the drug and may be
diffuse, patchy or linear. The patchy pigmentation is
often prominent on pressure areas—the elbows, knees
and buttocks (Blum et al., 1973). Long term therapy
with busulphan can produce a diffuse pigmentation
akin to Addison’s disease (Harrold, 1966). Cyclophos-
phamide hyperpigmentation may be widespread
(Harrison & Wood, 1972) or localized to the palms
soles or nails (Shah et al., 1978). Mithramycin
produces hyperpigmentation in 35% of patients on the
drug whilst long term treatment with hydroxyurea
induces both alopecia and pigmentation (Kennedy et
al., 1975).

Where are we after 60 years?

Some sixty years ago Henry Semon in his article on
Drug Eruptions in this Journal (Semon, 1926) de-
scribed the problem of halogen acne, the lesions which
arsenic may induce, the use of mercury ointment as
treatment of pediculosis pubis and the development of
idiosyncrasy to aspirin and quinine. In 1985 only the
latter two drugs survive as therapeutic agents. The
diagnosis of a drug eruption is no easier today than it
was six decades ago. In many ways it is more difficult
with the profusion of drugs and plethora of recognized
side effects. Penicillin allergy can now be reliably
confirmed by ‘scratch’ and ‘prick’ skin tests and
intradermal techniques using benzylpenicilloyl
polylysine conjugate and a mixture of minor determin-
ants of penicillin (Chandra et al., 1980). Patch testing
is valuable in the diagnosis of a contact dermatitis but
can give misleading results when used to diagnose
reactions not of the cell mediated-delayed hypersen-
sitivity type. Laboratory tests otherwise have not
provided a fail-safe method of isolating a single drug
from many as the cause of a specific drug reaction.

In the main the best the modern clinician can do is to
suspect a drug and reproduce the rash by reintroduc-
ing the drug, the so called provocation test. In practice
this is not always possible nor desirable. The physician
is often forced to react to the eruption as an amateur
sleuth who has been invited to decide the odds on a
particular suspect drug as the cause of the cutaneous
offence. Clearly there is urgent need for research into
the vexed problem of drug eruptions which occasion-
ally cause death, undoubtedly increase the length of
inpatient stay for a considerable number of patients
and are a source of physical and psychological discom-
fort for many.
References


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