Review of Drug-Induced Skin Reactions

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INTRODUCTION

The beneficial effects of drugs are coupled with the unavoidable risk of untoward effects. Every drug can produce untoward consequences, even when used according to recommended methods of administration. Adverse drug reactions can involve every organ and system of the body and are frequently mistaken for signs of underlying disease. Thirty per cent of reported adverse drug reactions involve the skin.[1-3] The skin reaction may mimic a spontaneously occurring skin disorder and is therefore included in the differential diagnosis of most skin diseases. Alternatively, the drug may produce quite specific changes. A drug-induced skin reaction can develop after the first dose, or after a period of sensitisation. Pigmentation, nail changes or effects on hair may take some months to become apparent. Skin reactions range from mild rashes to severe, life-threatening reactions including angioedema, Stevens-Johnson syndrome, vasculitis and toxic epidermal necrolysis. The relative occurrence of drug-induced skin reactions has been reported as: 46% maculopapular, 23% urticarial, 10% fixed eruptions, 5% erythema multiforme, 4% exfoliative dermatitis, 3% photosensitivity reaction, and 9% other.[4-7] For an appropriate diagnosis to be made, it is important to carefully examine the eruption surface qualities, in addition to the location and distribution. Knowledge about drug-induced adverse effects in skin helps physicians and pharmacists provide rational, safe and optimum drug use.[5,6]

MECHANISMS OF DRUG-INDUCED SKIN REACTIONS

Generally, drug molecules enter the skin by passive diffusion from the circulation, which is influenced by factors such as the physicochemical properties of the drug.[8] Adverse effects in the skin are induced by immunologic, non-immunologic and unknown mechanisms.[6,7] Most adverse skin drug reactions occur by non-immunologic mechanisms. Immunologic reactions require activation of host immunologic pathways and are designated as drug allergies. Drug reactions occurring through non-immunologic mechanisms may be due to activation of effector pathways, overdose, cumulative toxicity, side effects, ecologic disturbance, interactions between drugs, metabolic alterations, exacerbation of pre-existing dermatologic conditions, or inherited protein or enzyme deficiencies.[6,7] It must be noted that the mechanism of many drug reactions is unknown.

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Immunologic Drug Reactions

Multiple factors determine the capacity of a drug to elicit an immune response, including the molecular characteristics of the drug and host factors. Route of administration, degree of drug exposure, individual variability in absorption and metabolism, and frequency of high-dose and interrupted courses of therapy are important risk factors for the development of drug allergy.[8-10]

Allergic drug reactions are most commonly IgE- or immune-complex-dependent. The antibodies responsible for immune-complex-dependent drug reactions are largely of the IgG or IgM class.

Serum sickness is an example of immune-complex-dependent reactions that are usually seen with penicillins, sulphonamides, thiouracils, cholecystographic dyes, phenytoin, aminosalicylic acid, streptomycin, heparin, and antilymphocyte globulin.

Non-Immunologic Drug Reactions

Drugs can induce reactions by direct release of mediators from mast cells and basophils (e.g. opiates, polymyxin B, radiocontrast media, and dextrans) or they may activate complement in the absence of antibody (e.g. radiocontrast media). Drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) may alter pathways of arachidonic acid metabolism. Phototoxic reactions result from absorption of sufficient radiation in reactive tissue by the drug or its metabolite. Some drugs can exacerbate pre-existing diseases. Examples include: lithium (psoriasis, dermatosis), beta-blockers (lichenoid drug eruptions, allergic reactions, lupus erythematosis, psoriasis), anticonvulsants (toxic epidermal necrolysis), cimetidine (dermatitis) and vasodilators (allergic reactions, lupus erythematosis).

Genetic defects in the elimination of toxic reactive drug metabolites may result in drug reactions; for example, hypersensitivity syndrome associated with the use of sulphonamides and anticonvulsants.

Alterations in patients' immunologic status resulting from bone marrow transplantation and HIV infection may increase the incidence of cutaneous reactions (e.g. dapsone, trimethoprim, amoxicillin-clavulanate).[7-10]

CHARACTERISTICS OF DRUG REACTIONS

Exanthematous Eruptions

Exanthematous drug rashes appear early in therapy—previously sensitised patients develop a rash at 1 to 3 days, and others most commonly between 7 to 13 days. The drug rash is generally symmetrical and of sudden onset, and may be accompanied by lymphadenopathy. In contrast, any fever tends to be mild, an enanthem absent, and eosinophilia more likely. Exanthematous eruption is common with penicillins, sulphonamides, gold, phenytoin, carbamazepine, captopril, nitrofurantoin, chlorpromazine, phenytoin, frusemide, hydroxychloroquine, naproxen, diltiazem and allopurinol.[7-11]

Urticaria and Angioedema

These are vascular reactions of the skin—urticaria involves the upper dermis and is a pruritic swelling of the skin, often presenting as wheals, while angioedema is a non-pruritic swelling of the skin, which involves subdermal tissues. Urticaria and angioedema may be associated with anaphylaxis. The great majority of cases of urticaria/angioedema are idiopathic and are not drug related.[7,9] Chronic urticaria may have many different causes or may be idiopathic. Acute urticaria, known as nettle rash or hives, is a common drug reaction, usually occurring within 36 hours of drug exposure. Individual lesions rarely persist for more than 24 hours. Angioedema has a lower incidence than urticaria. The tongue, lips, eyelids or genitalia are generally affected and the oedema may be either unilateral or symmetrical.

Angioedema is a potential problem with all angiotensin converting-enzyme (ACE) inhibitors. In most cases, the reaction occurs in the first week after starting therapy, often within hours of the initial dose. However, in some cases it has developed after prolonged therapy of up to several years.[7] Other drugs, such as NSAIDs, radiographic dyes, penicillins, opiates, amphetamines, hydralazine, quinine and blood products may induce urticarial reactions and angioedema.

Acneiform Eruptions

Four major factors play a role in the aetiology of acne—extent of sebum excretion, follicular hyperkeratosis, hormonal effect and the bacteriology of the gland. Drugs that affect any of these factors may induce acne. Drugs implicated include androgens, oral contraceptives, corticosteroids, isoniazid, lithium, and medicines containing iodides or bromides.

Photosensitivity

Photosensitivity reactions may be phototoxic or photoallergic in nature. In both phototoxicity and photoallergy, the light energy is believed to cause a transient excitation of the toxicant molecule which, on returning to the lower energy state, generates a reactive, free radical intermediate. In phototoxicity, these organic radicals act directly on the cells to cause lesions, whereas in photoallergy they bind to body proteins. These modified proteins then stimulate the immune system to produce antibodies.

Phototoxic reactions are dose-dependent, occur in a high proportion of those exposed, may occur on first exposure and have a short latency, while the opposite applies in photoallergic reactions. Clinically, phototoxic reactions resemble sunburn with epidermal necrosis, dermoepidermal separation and a sparse superficial lymphohistiocytic dermal infiltrate.[8,10,11]

Photoallergic reactions show a more varied morphology, which may be eczematous or papular and less localised. Photoallergic reactions occur in predisposed individuals who have been previously sensitised. There is a latent period during which sensitisation occurs and the reaction generally develops within 24 hours of re-exposure. Unlike phototoxic reactions, the reaction may spread beyond irradiated areas. Most systemic drugs causing photoallergy, also cause phototoxicity. These reactions may occur as a result of local photocontact dermatitis to a topical photoallergen or as a result of systemic drug therapy.

Amiodarone, tetracyclines, sulphonamides, griseofulvin, ciprofloxacin, NSAIDs, thiazides, nalidixic acid, frusemide, and etretinates are common causes of phototoxic reactions. Phenothiazines, quinine and quinidine are common causes of photoallergic reactions.[7,10]

Psoriasiform Eruptions

Drugs may produce psoriasiform eruptions or exacerbate existing psoriasis. Macroscopically, the eruption consists of patchy erythema and scaling, worst over the knees and elbows, with more hyperkeratosis of palms and soles than is usual in idiopathic 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 β_2 receptors are found in the epidermis. Psoriasis induced by beta-blockers is reported to be resistant to antipsoriatic therapy until the beta-blocker has been stopped. Other drugs like lithium, chloroquine, NSAIDs and interferon alpha may cause or exacerbate psoriasis.

Vasculitis

Cutaneous necrotising vasculitis often presents as palpable purpuric lesions that may be generalised or limited, with urticarial lesions, ulcers, and haemorrhagic blisters. Drugs are thought to cause about ten per cent of acute cutaneous vasculitis.[7] The mechanism is believed to be immune-complex-mediated. Vasculitic reactions may occur 7–21 days after beginning therapy with some drugs. The vasculitis can also affect vessels in the kidney, liver, and gastrointestinal tract, in which case it may be life-threatening. The lesions of cutaneous vasculitis mainly involve the lower legs.[7] Drug-induced vasculitis is difficult to diagnose. Other causes to eliminate include Henoch-Schonlein purpura in young patients, cryoglobulinaemia, polyarteritis nodosa, infection, and collagen vascular disease. The drugs implicated include propylthiouracil, allopurinol, thiazides, penicillins, sulphonamides, NSAIDs, radiographic contrast media, retinoids, oral contraceptives and phenytoin.[7,9,10,11]

Fixed Drug Eruptions

Fixed drug eruption is the only cutaneous reaction for which drugs are the sole cause.[7,10] Fixed drug reactions are characterised by one or more sharply demarcated, erythematous lesions in which hyperpigmentation results after resolution of the acute inflammation. Lesions often involve the face, hands, feet, genitalia and oral mucosa and produce a burning sensation. The eruption generally appears within 24 hours of drug ingestion and can occur on any part of the skin or mucous membranes. Healing occurs over seven to ten days after the causative drug is stopped, although there may be residual hyperpigmentation. Phenolphthalein, sulphonamides, tetracycline, phenylbutazone, carbamazepine and barbiturates may cause this reaction.[10]

Skin Malignancy

Drugs may facilitate the development of both pre-malignant and malignant skin lesions. Immunosuppressives, hydroxyurea, phenytoin, carbamazepine, allopurinol, amiloride, diltiazem, clomipramine and cyclosporin are among the most common drugs that can cause skin malignancy.[9,11]

Erythroderma

Widely distributed erythema, known as erythroderma, may be caused by eczema, psoriasis, leukaemia, or lymphoma, as well as by drugs. Sulphonamides, gold, isoniazid, streptomycin, phenytoin and carbamazepine are noted causes of erythroderma.[7,9,10]

Lichenoid Drug Eruptions

These eruptions are clinically and morphologically similar to idiopathic lichen planus but they differ from the idiopathic form in having features of psoriasis, eczema, bullous pemphigoid, or cutaneous lymphoma. The lesions can be described as small, shiny, polygonal papules, sometimes with characteristic white lines known as Wickham's striae. They are usually itchy but they can be asymptomatic. The surrounding skin is completely normal. Lichenoid drug eruptions rarely affect the buccal mucosa—a characteristic white lace pattern may be present. Lichenoid drug eruptions tend to be extensive and may be linked with, or develop into, exfoliative dermatitis. The drugs mainly implicated are the thiazides, frusemide, chloroquine, quinine, streptomycin, ethambutol, gold, penicillamine, carbamazepine, phenytoin, methyldopa, beta-blockers, captopril, and enalapril.[7,9,10]

Bullous Dermatoses

A number of drugs may be associated with the development of pemphigus. Drug-induced pemphigus differs from the idiopathic form in that it may occur in younger patients, there may be relative absence of eosinophils on routine histology, and tissue-bound and circulating antibasement membrane zone IgG antibodies may be absent. The drug-induced disorder has a broad spectrum of clinical presentation, comprising widely scattered large firm bullae, classical but fewer lesions, scarring plaques, an erythema multiforme-like picture and a pemphigus-like picture. The drug-induced variant can feature clinical characteristics of both pemphigus and of being pemphigoid. The mechanism is unknown—both immune and toxic mechanisms have been proposed. Penicillamine, captopril, piroxicam, penicillins, rifampicin, cephalexin, frusemide, and sulphonamides may precipitate bullous dermatoses.[7,9,11]

Erythema Multiforme

As the name implies, erythema multiforme can present with a variety of patterns. It is an acute, self-limiting inflammatory disorder of skin and mucous membranes and is characterised by distinctive lesions of the iris or other target organs. The classic pattern affects the hands and feet more than the trunk. It tends to be symmetrical and acral, especially on the hands. In its mild form it is sometimes termed erythema multiforme minor to distinguish it from the major form (Stevens-Johnson syndrome). The latter is a severe, blistering skin reaction, which affects the mucous membranes of the oropharynx, eyes, and genitalia. It is often associated with sore throat and malaise. About 10% of cases of erythema multiforme minor are caused by drugs, which cause 50% of erythema multiforme major. Infections are a more common cause of erythema multiforme than drugs and many cases have been wrongly blamed on drugs.[8,10] Erythema multiforme may be due to vaccination, a variety of topical medications, and some environmental substances (e.g. nickel). The estimated incidence of Stevens-Johnson syndrome ranges between 1.2 and 6 cases per million population per year. In about 50% of cases the cause is not known. The fatality rate is believed to be about five per cent.[7,10] The main drugs implicated in Stevens-Johnson syndrome are: sulphonamides, penicillins, NSAIDs, carbamazepine, phenytoin, cephalosporins, rifampicin, allopurinol, and cyclophosphamide, although almost 200 other drugs have been implicated.[7]

Toxic Epidermal Necrolysis

This is a more severe form of Stevens-Johnson syndrome where considerable amounts of the epidermis may be shed. This is the most serious cutaneous drug reaction and may be fatal.[8,9] The histological picture is much the same as in erythema multiforme, but with a sparser dermal inflammatory infiltrate. Eighty per cent of cases of toxic epidermal necrolysis are caused by drugs.[2,4,7] The estimated incidence ranges from 0.4 to 1.2 per million population per year. It has a high associated mortality of about 30%. The condition usually becomes apparent 1 to 3 weeks after starting drug treatment. A higher incidence has been reported in patients with systemic lupus erythematosus, HIV infection and in bone marrow transplant recipients. Elderly patients and those with extensive toxic epidermal necrolysis have a worse prognosis. Drug-induced toxic epidermal necrolysis is rare in children, in whom the diagnosis must be distinguished from staphylococcal scalded skin syndrome. In general, most drugs causing toxic epidermal necrolysis have been given in the previous one to three weeks. A drug is unlikely to be the cause if it was first given in the preceding 24 hours or if it has been taken for more than three weeks. Generally the same drugs that cause erythema multiforme are implicated in this reaction. The reaction is most often associated with sulphonamides, aminopenicillins, anticonvulsants, the 'oxicam' NSAIDs and allopurinol.[7]

Pigmentation Changes

A variety of pigmentary changes in the skin can be caused by drugs. Abnormal pigmentation is mainly produced by disposition of drugs in the skin, stimulation of melanogenesis, or by a combination of these two factors. Phenothiazines, antimalarial drugs, minocycline, silver, gold, bismuth, mercury, cytotoxic drugs, zidovudine (accumulation in the nails), clofazimine, methysergide, nicotinic acid, oral contraceptives, adrenocorticotropin and amiodarone have been reported to influence pigmentation.[10]

Nail Changes

Drug-induced nail changes include onychomadesis, nail fragility, onycholysis, paronychia, pigmentation, and vascular changes. The effect is usually transient and disappears with drug withdrawal. Etretinates, tetracyclines, chloramphenicol, chlorpromazine, thiazides, chemotherapeutic and cytotoxic drugs, and chloroquine may cause adverse nail effects.[5,10]

LOCAL EXPOSURE TO TOXIC AGENTS

Medicinal compounds, food constituents, environmental agents and a host of other sources can cause cutaneous toxicity. Effects may be apparent immediately or may develop after days, weeks or years. The most common reactions to agents that contact the skin are inflammatory reactions to irritants, allergens and photosensitisers. The

reactions include irritant dermatitis, chemical burns, cumulative dermatitis, allergic contact dermatitis, light-induced cutaneous toxicity, cutaneous carcinogenesis, acne-like eruptions, and chloracne.[8,11]

ANTINEOPLASTIC THERAPY

Adverse effects to antineoplastic agents are common, especially in rapidly proliferating tissues such as mucous membranes, skin, hair and nails. The incidence of these reactions is variable. Some reactions such as stomatitis and alopecia are clearly dose-dependent; others such as hyperpigmentation occur unpredictably.[11] Evaluating an oncology patient with a cutaneous reaction can be difficult. The patients usually have complex medical problems; they are often taking many different medications, and their immune systems are usually altered by their disease and/or therapy. It may be helpful to chart the sequence of events (rash, fever, and white blood cell count) and the medication administered. Important information can be obtained from histologic examination of skin biopsy specimens, especially when infection is considered in the differential diagnosis.

ROLE OF LABORATORY TESTS

Routine laboratory tests show no specific change in common skin reactions.[11] In more serious reactions, laboratory data include eosinophil count >1000, lymphocytosis with atypical lymphocytes, and abnormal liver function test results. Intradermal skin testing (e.g. penicillin) can identify sensitivity resulting from drug specific IgE bound to mast cells. Its alternative is the radioallergosorbent test (RAST), measuring serum IgE against particular antigens. Delayed skin reactions, lymphocyte proliferation and lymphokine release stimulation tests detect drug-specific cellular immunity but have limited value. In patients with sensitivity to phenytoin and sulphonamides, an *in vitro* lymphocyte cytotoxicity assay shows increased cytotoxicity of lymphocytes incubated with a drug metabolite generating system, but this is only of research value.

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