

## ACUTE CUTANEOUS ADVERSE DRUG REACTIONS

Cutaneous adverse drug reactions (CADR) are a common form of adverse drug reaction, affecting up to 3% of hospital patients. Almost any drug can cause a CADR and the effects can range from mild to life-threatening. When investigating a possible CADR it is important to include in the history all current/recent drugs, topical, over the counter (OTC), alternative medicines, vaccines and contrast media. It is important to evaluate the likely causality using a formal algorithm such as the Naranjo algorithm (see page 7 of the 'Pink Book'). All suspected CADRs should be reported to the Centre for Adverse Reactions Monitoring (CARM).

### MECHANISMS AND CLASSIFICATION

There is growing evidence that the majority of CADRs have an immunological (allergic) basis. There is also emerging evidence of genetic predispositions to many of these CADR in relation to certain drugs for e.g. HLA B\*5801 allele and allopurinol induced Stevens-Johnson syndrome. One useful way of classifying CADRs is by dividing them into acute and chronic CADR. Acute CADR such as urticaria and angioedema are mostly specific drug-induced syndromes that require prompt diagnosis and treatment. Chronic CADR usually mimic dermatological diseases such as drug-induced pemphigus and acneiform eruptions. In this bulletin, acute CADRs are discussed.

### EXANTHEMATOUS REACTION

Exanthematous reaction (also called maculopapular rash) is the most common CADR, accounting for 75% of all drug rashes. The lesions consist of erythematous macules or papules which begin on the trunk and progress to become confluent, covering large patches of skin. It is accompanied by pruritis and low grade fever. Onset is almost always within 4 to 14 days of introducing a new drug but occurs sooner on rechallenge. The reaction is thought to occur via Type 4 (cell-mediated) hypersensitivity, and chemically related drugs may cause cross reactions. For most drugs the incidence of exanthematous reaction is around 1%, however allopurinol, antiepileptic drugs, sulfonamides, penicillins and cephalosporins cause reactions in >3% of patients. The rash resolves within days of stopping the drug. Antihistamines, steroids and topical anti-pruritics help with symptomatic relief.

### URTICARIA AND ANGIOEDEMA

Urticaria (hives) involves the superficial dermis and is characterised by intensely pruritic, circumscribed and oedematous lesions with central pallor. Individual lesions enlarge, coalesce and disappear over a few hours. Angioedema involves the deeper dermis and subcutaneous tissues and usually occurs on the face, lips, tongue and larynx as a pale pink swelling. Urticaria and angioedema can be complicated by life-threatening anaphylaxis with airway compromise and circulatory failure. These conditions occur via Type 1 (IgE mediated) hypersensitivity.

Onset is within minutes to 36 hours of taking the drug. Penicillins, cephalosporins and sulfonamides are classic examples. Management of urticaria involves stopping the drug, and use of antihistamines. Severe angioedema and anaphylaxis are medical emergencies and require adrenaline and corticosteroids. Non-IgE mediated reactions are called *anaphylactoid* reactions. These occur via various non-immune mechanisms. Some implicated drugs are intravenous contrast media, ACE-inhibitors and NSAIDs.

### STEVENS-JOHNSON SYNDROME

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but the most severe CADR with a mortality of 30%. If suspected, the drug must be stopped immediately. The lesions are irregular, dusky-red or purpuric macules that progressively coalesce and become necrotic. They appear first on the upper trunk, proximal extremities and face then rapidly spread to the rest of the body. They are usually preceded by mucocutaneous erosions. The condition is called SJS when it affects <10% of body surface area (BSA) and TEN if >30% of BSA is involved. SJS/TEN begin within 4 weeks of starting a drug. Systemic manifestations include fever, leucopenia, deranged liver function tests, intestinal and pulmonary complications. The mechanism is thought to be a cell-mediated cytotoxic reaction against epidermal cells, leading to their widespread apoptosis. Sulphonamides, antiepileptics, NSAIDs, allopurinol and nevirapine are associated with a higher risk of developing SJS/TEN. Treatment is symptomatic with emphasis on fluid/electrolyte balance and nutritional support.

### PHOTOSENSITIVITY

Photosensitive eruptions are divided into two types – phototoxic and photoallergic. Phototoxic reactions are more common and are caused by absorption of ultraviolet light (usually UVA) by the drug, which releases energy and damages cells. The reaction looks like exaggerated sunburn. Commonly implicated drugs include NSAIDs, quinolones, tetracyclines, amiodarone and phenothiazines. Photoallergic reactions are due to a lymphocyte mediated reaction triggered by UVA. The eruption is characterised by widespread dermatitis in sun exposed areas. Phenothiazines, sulfonamides, and NSAIDs can produce photoallergic reactions.

### HYPERSENSITIVITY SYNDROME

Hypersensitivity syndrome is characterised by erythematous follicular papules and pustules, and fever. Onset is usually 2-6 weeks after a drug is started. Associated features are arthralgia, lymphadenopathy, liver, renal and/or hematologic abnormalities. Hypersensitivity syndrome most likely occurs via Type 4 (cell-mediated) hypersensitivity. Phenytoin, carbamazepine, phenobarbitone and sulfonamides are commonly implicated drugs. Management consists of stopping the drug, and use of oral corticosteroids if severe.

ACUTE CADRs	SOME IMPLICATED DRUGS	ACUTE CADRs	SOME IMPLICATED DRUGS
<b>Exanthematous reactions</b>	allopurinol, antiepileptic drugs, sulfonamides, penicillins, cephalosporins	<b>Hypersensitivity syndrome</b>	phenytoin, carbamazepine, minocycline, phenobarbitone, sulfonamides, allopurinol
<b>Urticaria/Angioedema</b>	penicillins, cephalosporins, sulfonamides, local anaesthetic agents	<b>Fixed Drug eruption</b>	tetracyclines, barbiturates, sulfonamides, NSAIDs, salicylates
<b>Anaphylactoid reactions</b>	contrast media, ACE-inhibitors, NSAIDs, aspirin	<b>Hypersensitivity Vasculitis</b>	allopurinol, NSAIDs, cimetidine, penicillins, cephalosporins, fluoroquinolones, sulfonamides
<b>SJS/TEN</b>	sulfonamides, antiepileptic drugs, NSAIDs, allopurinol, nevirapine	<b>Serum sickness-like reaction</b>	cefaclor, penicillins, propranolol, minocycline, trimethoprim-sulfamethoxazole
<b>Photosensitivity</b>	quinolones, tetracyclines, amiodarone, phenothiazines, sulfonamides, NSAIDs	<b>Anticoagulant induced skin necrosis</b>	warfarin, heparin