



Cutaneous adverse drug reactions are a common problem affecting ambulatory and hospitalized patients. Older patients may be predisposed to adverse drug reactions due to inappropriate medication prescription, age-associated changes in pharmacokinetics and pharmacodynamics, altered homeostatic mechanisms, multiple medical pathologies, and use of drugs with a narrow therapeutic margin. In this second of two articles, the management of cutaneous adverse drug reactions is reviewed.

Key words: adverse drug reaction, skin, cutaneous, rash, drug eruption, treatment, management.

Cutaneous Adverse Drug Reactions in Older Adults

Part II: Management

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Management of Cutaneous Adverse Drug Reactions

The comprehensive risk management of adverse drug reactions (ADR) involves strategies prior to even commencing a new therapy. These include avoiding the prescription of inappropriate medication as far as possible, noting previous adverse reactions and taking account of existing risk factors (e.g., renal impairment necessitating allopurinol dosage reduction). This article focuses on management of a patient after the diagnosis of a cutaneous ADR has been made (Table 1 and Figure 1).¹

Step 1: Withdraw the suspected drug(s)

Once a diagnosis of cutaneous ADR has been made, the suspected drug(s) should be discontinued as soon as possible. This may be sufficient to resolve mild drug-induced exanthematous or urticarial eruptions. It has been shown that prompt withdrawal of causative drugs may decrease mortality in Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).²

Step 2: Investigate for systemic involvement

Investigations for systemic involvement should be undertaken if the patient is unwell or has other clinical signs such as fever, lymphadenopathy or hepatomegaly. These include blood count, serum biochemistry, liver function tests, urinalysis and urine/blood cultures. Abnormalities may indicate a

severe ADR such as drug hypersensitivity syndrome (DHS). Hypothyroidism can be a late complication of DHS and thyroid function tests should be evaluated a few months after the adverse reaction.³

Clinical observation for signs of progression to SJS or TEN should be undertaken. These signs include mucous membrane involvement and progressive blistering of the skin.

Step 3: Commence general supportive treatment

There may be a lower threshold for admission to hospital in older patients, particularly if they have one of the more serious cutaneous ADRs such as DHS, acute generalized exanthematous pustulosis (AGEP), SJS or TEN. Erythrodermic patients (exhibiting a rash involving body surface area >90%) may also require admission as they can potentially lose excessive fluid and heat through inflamed skin. Particular attention to fluid and electrolyte balance, nutrition, infection control and analgesia is important in these groups of patients with more severe cutaneous ADR. Management of TEN patients, who have widespread epidermal detachment, may be most appropriate in a burns unit or other intensive care environment. Patients with TEN require urgent and regular ophthalmological assessment to prevent the ocular complications that are the major morbidity of patients who survive.

Step 4: Apply specific topical therapy

Emollients and topical corticosteroids, with or without the addition of cooling agents (e.g., menthol or camphor), may help to ease the pruritus often associated with exanthematous and urticarial drug eruptions. Frequent applications of emollient are necessary to reduce heat and fluid loss through the skin in erythrodermic patients.

Step 5: Begin specific systemic therapy

Systemic therapy for cutaneous ADR includes the use of antihistamines, corticosteroids, other immunosuppressants and intravenous immunoglobulin (IVIG). Systemic agents (other than antihistamines) are unnecessary in simple exanthematous and urticarial eruptions, where withdrawal of the implicated drug and symptomatic treatments are usually sufficient.

Antihistamines are helpful for pruritic eruptions and for urticarial eruptions. They are of little benefit in more serious cutaneous ADR. A useful combination is to prescribe non-sedating antihistamines (e.g., cetirizine, fexofenadine, loratadine) during the day and sedating antihistamines (e.g., hydroxyzine, diphenhydramine) at night. However, it is important to remember that elderly patients may be particularly susceptible to the sedative effects of all antihistamines.

The use of corticosteroids for cutaneous ADR is controversial. In DHS, oral prednisone (1mg/kg/day) is usually given with resultant rapid improvement of cutaneous and systemic features. Corticosteroid dosage should then be tapered slowly (over weeks to months) to prevent a relapse of the syndrome. In TEN, there is no strong evidence for the benefit of corticosteroids and some evidence of a possible detrimental effect. Therefore, the routine use of corticosteroids in the treatment of TEN is not advocated.⁴

Immunosuppressant drugs such as cyclosporine and cyclophosphamide have been reported to be effective in the

treatment of TEN, but only in case reports and uncontrolled studies. These drugs require further investigation before they can be recommended.⁵

The use of IVIG for TEN has been of interest since a study reported its efficacy. IVIG is thought to work by blocking TEN-related apoptosis.⁶ Further studies have also shown beneficial effect and there is increasing use of IVIG for TEN despite the lack of prospective, randomized, placebo-controlled trials.⁷

Step 6: Conduct further investigations

After patients have recovered from cutaneous ADRs, several questions may remain outstanding. Which drug caused the adverse reaction? Can this drug ever be taken in the future? Which other drugs will need to be avoided? Which drugs can I safely take in the future? Although it can be difficult to answer these questions with certainty, further investigations may clarify these issues.

Skin testing encompasses prick testing, intradermal testing and patch testing. Skin prick testing involves pricking the skin through an allergen solution. Intradermal testing involves injecting a small amount of allergen intradermally, raising a bleb in the skin. Skin prick tests and intradermal tests are of particular use in assessing allergy to penicillin and other b-lactam antibiotics, local anaesthetics and general anaesthetic agents.

Patch testing involves application of a potential allergen to the skin (usually on a patient’s back) for 48 hours. The patch is then removed and the area assessed at that time and a further 48 hours later. Patch testing may be useful in cutaneous ADR in which T-cell mediated mechanisms are implicated. Patch testing is more sensitive if performed in a site previously affected by FDE. Certain drugs such as b-lactam antibiotics and carbamazepine may produce higher rates of positive patch tests.⁸ Patch testing does not seem to be useful in SJS and TEN patients.⁹ There are several possible explanations for false-negative tests patch tests that may result. These include insufficient penetration of drug through the

Table 1: Managing a Patient During and After an ADR

Withdraw the suspected drug(s)
Investigate for systemic involvement
Commence general supportive treatment
Apply specific topical therapy
Begin specific systemic therapy
Conduct further investigations / desensitization
Advise patients and family physician
Inform regulatory authorities

skin and inadequate knowledge, in most ADRs, of whether the relevant antigen is the native drug or a drug metabolite.

It should be noted that many factors may influence skin testing results. These include methodology used (e.g., drug type, vehicle type, drug concentration) and the time interval between ADR and skin testing. Few validated protocols exist and various potential pitfalls of skin testing are discussed in other reviews.¹⁰

Oral challenge with the suspected drug, also known as drug provocation testing, is considered by some authors to be the “gold standard” test to confirm causation. Others question the value and safety of the test, particularly in patients who have suffered a severe ADR. An individual risk-benefit evaluation must be made prior to drug provocation testing and a recent review article provides useful guidelines.¹¹

Table 2: Precipitants of Myocardial Ischemia

Myocardial Oxygen Supply
– Acute coronary syndrome
– Anaemia
– Hypotension
Myocardial Oxygen Demands
– Arrhythmia e.g., atrial fibrillation
– Hyperthyroidism
– Uncontrolled hypertension
– Uncontrolled heart failure

Cutaneous Adverse Drug Reactions

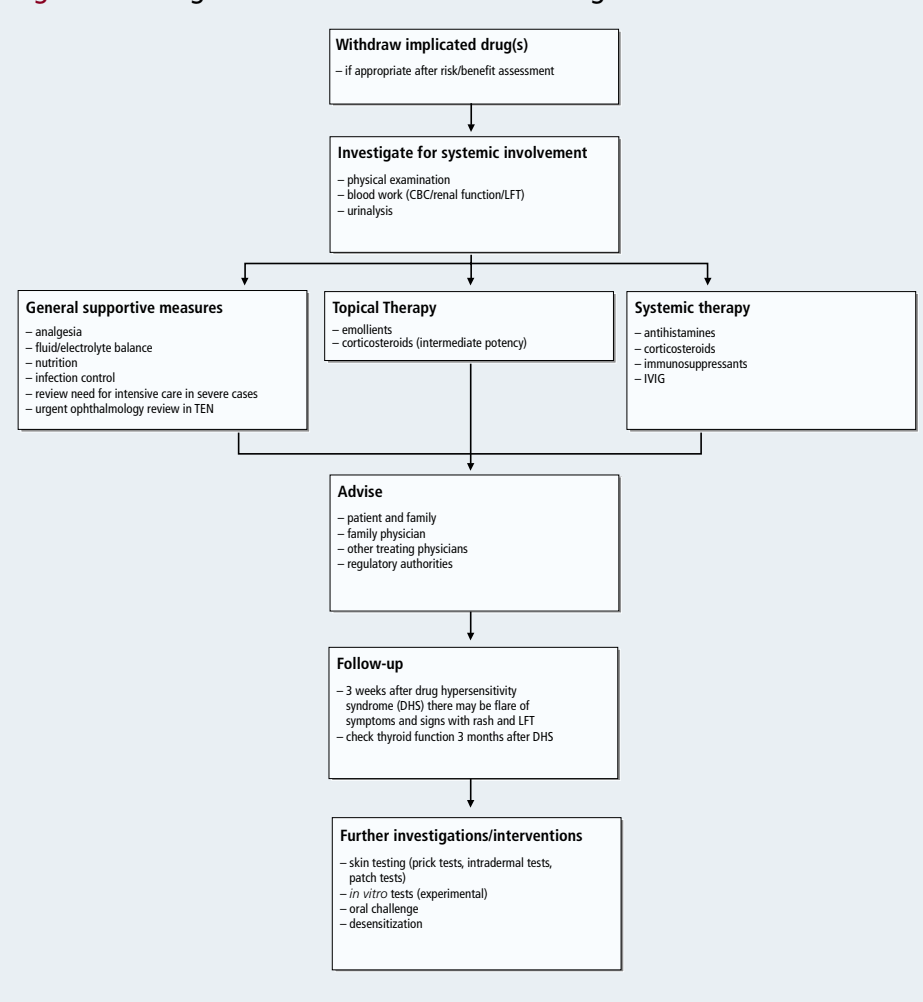
Table 3: Clinical features suggestive of high risk of an adverse outcome in patient with chest pain

History	ECG
<ul style="list-style-type: none"> – Ongoing chest pain – Rest pain lasting more than 10-15 minutes – New chest pain with minimal activity 	<ul style="list-style-type: none"> – ST segment elevation – ST segment depression – T inversion > 2mm – Left bundle branch block
Symptoms associated with chest pain	Stress ECG
<ul style="list-style-type: none"> – Dyspnea – Loss of consciousness 	<ul style="list-style-type: none"> – Low exercise capacity – ST depression at low load – > 2mm ST depression – ST depression lasting > 5 mins in recovery
Examination	
<ul style="list-style-type: none"> – Systolic BP < 90 mmHg – Signs of heart failure 	

Desensitization, whereby a drug is reintroduced at a small dose and then gradually increased, has been undertaken in an attempt to induce tolerance to

that drug. This procedure has been described with penicillins, trimethoprim/sulfamethoxazole and allopurinol.¹²⁻¹⁴

Figure 1: Management of Cutaneous Adverse Drug Reactions



In vitro tests include lymphocyte toxicity assays, lymphocyte transformation (proliferation) assays, drug-induced interferon-g release test, macrophage migration inhibition tests and generation of drug-specific T-cell clones.¹⁵⁻¹⁹ These tests provide interesting insights into possible mechanisms involved in cutaneous ADR. At present, these tests are largely research tools and are not widely available in clinical practice.

The various tests described in the preceding paragraphs are best performed by specialists with specific interest and expertise in the area of ADR. If this type of service is not available locally, then the aim of the treating physician should be to identify and avoid the most likely causative drug and inform the patient of what classes of drugs can be safely taken in the future.

Step 7: Advise patients and family physician

On the basis of history, examination and further investigations, patients should be informed of drugs to avoid and of any potentially cross-reacting drugs.

Cross-reactivity is often an area of concern for patients and physicians. There is a cross-reaction rate of approximately 2% between penicillins and cephalosporins.²⁰ Patients with hypersensitivity reactions to one of the aromatic anticonvulsants, such as phenytoin, phenobarbital and carbamazepine, have a 75% chance of cross-reacting to the other drugs in this class.¹⁶ There may also be an increased risk of hypersensitivity to these aromatic anticonvulsants in first degree relatives. Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) cause problems due to cyclooxygenase (COX) inhibition and resultant leukotriene production. Oral drug challenge can be used to evaluate NSAIDs that can be tolerated; otherwise, COX-II inhibitors can be prescribed. It is unclear whether patients with ADR to sulfonamide antibiotics have an increased risk of reactions to non-aromatic amines such as sulfonureas, thiazide diuretics, furosemide and celecoxib. One study suggested that there

was no rationale for avoiding celecoxib in patients with allergy to sulfonamide antibiotics.²¹ Another recent study reported an association between hypersensitivity to sulfonamide antimicrobials and a subsequent allergic reaction to sulfonamide non-antibiotics, but this appears to be due to a predisposition to allergic reactions rather than to cross-reactivity with sulfonamide-based drugs.²²

Relevant information about a patient's ADR and other drugs to be avoided should be conveyed to the patient's family physician and other treating physicians. ADRs should be clearly documented in family practice records and in hospital charts. Patients should be encouraged to wear a MedicalAlert bracelet (www.medicalert.ca).

Step 8: Inform regulatory authorities

Reporting of suspected ADRs is an important part of post-marketing surveillance of drug safety. Unusual reactions or reactions to newly licensed drugs should be reported to regulatory authorities and to drug manufacturers. In Canada, information about reporting ADRs and contact details of pharmaceutical manufacturers can be found in the Compendium of Pharmaceuticals and Specialties (CPS) published annually by the Canadian Pharmacists Association. Another useful resource for further information on reporting ADRs is the Therapeutic Products Directorate on the Health Canada Website (www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt).

Conclusion

Cutaneous ADRs are a common problem in the older adult population and can cause significant morbidity and mortality. Most reactions are mild and resolve with symptomatic treatment and discontinuation of the causative drug. More severe reactions such as DHS, SJS and TEN may require inpatient management with specific systemic treatment. Appropriate advice should be given to the patient, family members and other treating physicians in order to avoid future

adverse reactions. Regulatory authorities and drug manufacturers should be informed of ADRs, particularly unusual reactions or reactions to newly licensed preparations. ◆

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