Summary

- Although cutaneous drug reactions can range from benign to potentially life threatening, they are often reported simply as a “rash.”
- Being specific in the adverse event (AE) description will aid in the safety assessment of the drug.
- Here, HSA provides a review of the most common cutaneous drug reactions and a supplemental checklist that could be submitted with the standard AE reporting form for cutaneous drug reactions.

Cutaneous drug reactions represent one of the most common adverse events (AEs) reported in drug therapy. The overall incidence rate of such events is between 2–3% in hospitalised patients.1 In many cases, these reactions are reported simply as a “rash” to the Health Sciences Authority. For example, in 2011, out of 23,724 local reports captured in the national AE database, 61.3% of AE reports were related to cutaneous reactions. Of these, 49.4% contain “rash” as the only AE description and close to 40% of such reports were assessed as serious by the reporting physician. However, rash as an AE is too general a term to allow for further evaluation. Being specific in the AE description will aid in the safety assessment of the drug and increase inter-observer accuracy, which is important for communications among healthcare professionals.

The clinical presentation of cutaneous drug reactions is highly variable, ranging from benign reactions such as exanthematous or maculopapular eruption, photosensitivity, and urticaria, to severe and potentially life-threatening reactions such as drug induced hypersensitivity syndrome (DHS), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN).2 The morphology, progression and drugs most frequently associated with each of these reactions are given below.

Common Cutaneous Drug Reactions

1 Maculopapular/exanthematous drug eruption

This is the most common cutaneous adverse drug reaction and is also known as a morbilliform or maculopapular eruption. Erythematous macules may become papular and confluent. Lesions on the legs and feet may appear purpuric. The clinician should be alerted to the possibility of toxic epidermal necrolysis if the skin is tender or dusky-looking, and if there are mucous membrane erosions. Drug hypersensitivity syndrome should be considered if there is associated oedema, pustules, lymphadenopathy, hepatitis and peripheral eosinophilia. Many drugs have been implicated to cause drug exanthems and these include beta-lactams, quinolones, sulfamethoxazole and diuretics. The rash typically begins 5-14 days after the start of a new medication and occasionally occurs a few days after the drug has been discontinued.
2 Photosensitive drug eruption (phototoxic or photoallergic)

Erythema with or without blistering occurs in sun-exposed sites when light interacts with the drug. Drugs commonly associated with cutaneous phototoxic reactions include griseofulvin, tetracyclines, NSAIDS and fluoroquinolones; those associated with photoallergic reactions include thiazide diuretics, sulfonamides, sulfonylureas and phenothiazines. Onset maybe delayed by as long as 24-72 hours.

3 Urticaria

Lesions may appear within minutes to days following drug administration, and individual lesions usually last less than 24 hours. Examples of commonly implicated drugs include beta-lactams, non-steroidal anti-inflammatory drugs (NSAIDs), anaesthetics and contrast media.

4 Fixed drug eruption (FDE)

Common sites of occurrence include the lips, genitalia, hands and feet. Lesions resolve with post-inflammatory hyperpigmentation and recur at the same site with re-administration of the causative drug. Lesions may be single, or less commonly, few or multiple (generalized FDE). They appear 1 to 2 weeks after initial exposure to the drug, and within 24 to 48 hours with subsequent exposures. Drugs frequently associated with FDE include NSAIDS, sulfonamides and tetracyclines.

5 Drug-induced vasculitis

Drug-induced small vessel vasculitis is usually confined to the skin, but systemic involvement should also be excluded. Causative drugs include penicillins, sulfonamides, NSAIDS and thiazides. Onset is usually within 1 to 3 weeks of taking the drug.
6 Drug hypersensitivity syndrome (DHS)

DHS, also known as drug rash with eosinophilia and systemic symptoms (DRESS), develops 2 to 6 weeks following commencement of the causative drug. Common culprit drugs include anti-convulsants (phenytoin, carbamazepine and phenobarbital), sulfonamides, dapsone and allopurinol. Clinical features include fever, rash, lymphadenopathy and arthritis. The cutaneous eruption is often a morbilliform exanthematous and oedematous rash, with occasional pustules, vesicles and purpura. Hepatitis may be severe and peripheral eosinophilia is usually prominent. The rash and hepatitis may persist for weeks to months after drug withdrawal. Mortality from DHS is usually due to fulminant hepatitis, hence the importance of recognising this syndrome.

Systemic corticosteroids are usually recommended in the treatment of DHS. It is important to note that the duration of oral steroid treatment for DHS should be continued for a longer period as compared to the typical 2-week duration of treatment for other types of drug reactions. Oral steroids may be continued for up to 3 months or more and withdrawal must be very gradual to prevent relapse and rebound of the reaction.

Erythematous oedematous plaques

7 Stevens-Johnson syndrome (SJS) and Toxic epidermal necrolysis (TEN)

SJS and TEN are life-threatening severe cutaneous adverse drug reactions. Patients with epidermal detachment involving less than 10% of body surface area (BSA) are classified as SJS, those with >30% BSA involvement as TEN and those with 10 to 30% BSA involvement as SJS-TEN overlap. Examples of implicated drugs include allopurinol, anti-convulsants, sulfonamides and NSAIDs. SJS and TEN usually begin within 4 weeks of commencement of the implicated drug, but may occasionally be delayed up to 8 weeks. Mucous membranes are involved, and ocular sequelae may be serious, leading to corneal scarring and visual impairment. The clinician should be alerted to possible early TEN in any patient presenting a painful drug exanthem.

Dusky and purpuric macules with vesiculation

Erosions on the lips and perioral skin

TEN: Confluent epidermal detachment

8 Acute generalised exanthematous pustulosis (AGEP)

AGEP is a benign condition with spontaneous resolution with desquamation within 2-3 weeks. It is characterised by numerous small sterile pustules erupting over erythematous plaques. The eruption may begin within 3-5 days in intertriginous areas and mucous membranes may be involved. Additional features include fever, leukocytosis and eosinophilia. Common causative drugs include beta-lactam antibiotics, macrolides and calcium channel blockers. The main clinical differential diagnosis is acute pustular psoriasis.

Superficial pustules coalescing to form small lakes of pus on an exanthematous background
Managing and reporting a suspected adverse event caused by a drug/vaccine

It is important to recognise cutaneous drug reactions as early as possible. All drugs introduced within 4-12 weeks before the onset of the adverse reaction should be considered. The management of the condition will differ depending on the clinical diagnosis. Regardless of the specific condition, however, prompt withdrawal of the suspected drug is key to averting a serious drug reaction.

To file an AE report on cutaneous drug reactions, fill up either the blue Vaccine Adverse Event (VAE) reporting form (for vaccines) or the yellow Adverse Drug Reaction reporting form (for other health products) and submit them to:

Vigilance Branch/Health Products Regulation Group
Health Sciences Authority
Phone: (65) 6866 3538
Fax: (65) 6478 9069
OR Email to HSA_productsafety@hsa.gov.sg
OR Online Reporting at http://www.hsa.gov.sg/ae_online

Other than the essential information in an AE report, the following information would be very useful when filing out an adverse event report involving the skin. This checklist can be attached to the AE reporting form.

Checklist to include when filing an AE report involving the skin

Did the patient exhibit any of the following symptoms?

Please tick as many as appropriate:

<table>
<thead>
<tr>
<th>1. Morphology of rash</th>
<th>3. Involvement of other organs (please state):</th>
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<tbody>
<tr>
<td>macules and papules</td>
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<tr>
<td>pustules</td>
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<td>urticaria</td>
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<td>purpura</td>
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<td>vesicles or bullae</td>
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<td>erosions</td>
<td></td>
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<tr>
<td>mucosal erosions</td>
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<tr>
<td>others (please state)</td>
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<tr>
<th>2. Areas of involvement</th>
<th>4. Diagnosis (if available):</th>
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<tbody>
<tr>
<td>localised</td>
<td></td>
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<tr>
<td>generalised</td>
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<td>others (please state)</td>
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<th>5. Preceding/concurrent URTI symptoms:</th>
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6. Concurrent illness or infection:

In addition, cutaneous skin reactions may be associated with other systemic reactions such as fever and hepatitis. Please include such information if available.

It is important to report other medications (including TCM and herbal medication) besides the suspected drug(s).

Acknowledgement

The above diagnostic guide was developed by the Health Sciences Authority in consultation with Dr Audrey Tan, Consultant, National Skin Centre and with inputs from A/Prof Tay Yong Kwang, Chief and Senior Consultant, Dept of Dermatology, Changi General Hospital.

References

   Drug-induced skin reactions Anne Lee and John Thomson http://www.pharmpress.com/files/docs/ADRe2Ch05.pdf