SPECIAL ARTICLE

AN APPROACH TO THE EVALUATION AND DOCUMENTATION OF ADVERSE DRUG REACTION

C L Goh

ABSTRACT

This paper reviews an approach to the evaluation and documentation of suspected adverse drug reaction(ADR). I propose an algorithm for the evaluation of suspected ADR. I recommend that the adverse drug reaction scoring system(ASS) or the adverse drug reactions probability scale(APS) be used when evaluating suspected ADR. In these two scoring systems, points are allotted according to response to a series of questions on events relating to the clinical manifestations of the suspected ADR. Depending on the total points scored the probability of the suspected ADR are classified as definite, probable, possible and unlikely. When a patient's suspected ADR is classified as definite, then no further investigation is necessary. The patient should be considered sensitive to the drug. In a case where the suspected ADR is classified as probable or possible then further investigations should be considered to confirm the diagnosis. If the nature of ADR is life threatening only in-vitro test should be done. If the nature of ADR is not life threatening, in-vivo and oral provocative test dosing may be considered. It should be considered if the suspected drug in question cannot be substituted and when it is very frequently prescribed.

Key Words: drug allergy, provocative test dosing, drug eruption, drug reaction

SING MED J. 1989; No 30: 285 - 289

INTRODUCTION

The subject of adverse drug reaction is bewilderingly complex. Not only are there difficulties in definition but also the characteristics of drug reaction are by no means simple. There is no consistently pathognomonic symptomology and pathology. It is difficult to differentiate an immunologically mediated (allergic type) reaction from an non-immunologically mediated reaction. There is at present no single test which can reliably and invariably detect which drug reactions are allergic. In-vitro and in-vivo tests are beset with false positive and false negative response. At times, it may be important to establish the presence of allergy to a drug when it is potentially life-saving. All suspected drug allergy should be evaluated carefully. In this paper I review some reports on approaches to the evaluation of suspected adverse drug reaction. I propose an algorithm to evaluate patients with suspected adverse drug reaction.

EVALUATION

The investigation and identification of an adverse drug reaction still depends largely on circumstantial evidence and the clinical skills of the attending physician. A knowledge of the clinical criteria and the varied manifestations ascribed to drug allergy, and syndromes commonly associated with certain drugs, is of great value in evaluating suspected adverse drug reactions. Unfortunately, none of the clinical manifestations is unique or specific for drug reaction.

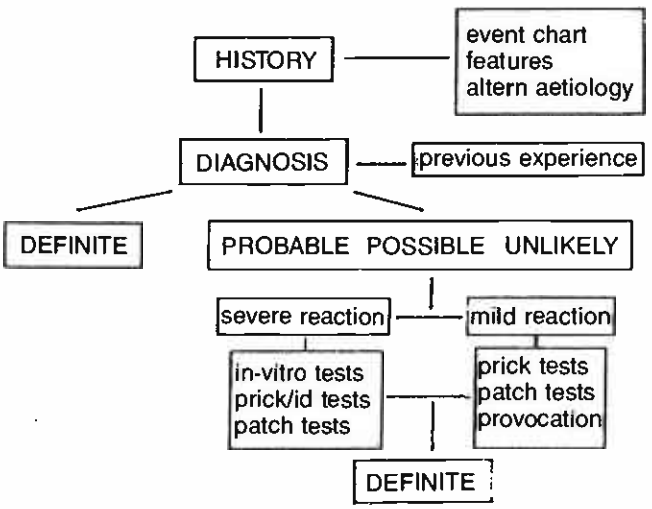
National Skin Centre
1 Mandalay Road
Singapore 1130

CL Goh, MBBS, M Med, MRCP (UK) AM.

Figure 1 shows a proposed algorithm in the investigation of a suspected adverse drug reaction. The following steps should be considered in evaluation.

1. History
2. In-vitro tests
3. In-vivo tests
4. Provocative test dosing

Figure 1
AN ALGORITHM FOR EVALUATION OF SUSPECTED DRUG REACTION
altern = alternative, id = intradermal



1. History.

History forms the most important basis for diagnosing adverse drug reaction. Table 1 and 2 are two summarized algorithms designed by Kramer et al (adverse drug reaction scoring system(ASS))(1) and Naranjo et al. (adverse drug reactions probability

Table 1
OUTLINE OF ASS SCORING STRATEGY (1)

Score:	+1	0	−1
Axis I	CM well accepted as ADR to suspected drug	CM is not well known or drug is new	CM previously unreported as ADR to well-known drug
Axis II	(a) No good alternative candidate (score +2); or	Candidate(s) exist, but no good ones	Good alternative candidate
	(b) Otherwise unexplained exacerbation or recurrence of underlying illness (score +1)		
Axis III	Timing as expected for ADR for this drug-CM pair	Timing equivocal or nonassessable	Timing inconsistent for ADR for this drug-CM pair (score −2)
Axis IV	Drug level or other data provide unequivocal evidence of overdose	Unobtained, unknown, or equivocal level or other evidence of overdose	Drug level strongly against overdose
Axis V	(a) CM improves suitably after dechallenge; or	(a) CM improved, but degree or rate are unexpected; or	(a) CM improves without dechallenge; or
	(b) Nature of CM prevents assessment of dechallenge	(b) CM is treated by auxillary maneuver	(b) Potentially reversible CM fails to improve after dechallenge
Axis VI	CM unequivocally recurs or exacerbates on rechallenge	(a) No rechallenge attempted; or (b) Response of CM obscured by auxilliary maneuver	CM fails to recur or exacerbate on rechallenge
Overall Assessment:	Definite — 6 to 7 Possible — 0 to 3	Probable — 4 to 5 Unlikely — Less than 0	ASS = Adverse drug reaction scoring system CM = clinical manifestation ADR = adverse drug reaction

Table 2
OUTLINE OF APS SCORING STRATEGY (2)

To assess the adverse drug reaction, please answer the following questionnaire and give the pertinent score

		Yes	No	Do not know	Score
1	Are there previous conclusive reports on this reaction?	+1	0	0	
2	Did the adverse event appear after the suspected drug was administered?	+2	−1	0	
3	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
4	Did the adverse reaction reappear when the drug was readministered?	+2	−1	0	
5	Are there alternative causes (other than the drug) that could on their own have caused the reaction?	−1	+2	0	
6	Did the reaction reappear when a placebo was given?	−1	+1	0	
7	Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8	Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	
9	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
10	Was the adverse event confirmed by any objective evidence?	+1	0	0	
				Total score	

Overall Assessment	Score
Definite	> 8
Probable	5 — 8
Possible	1 — 4
Unlikely	< 1

APS = Adverse drug reaction probability scale

scale(APS))(2) respectively. The details on the usage of the two systems should be referred to. Both systems have been reported to show reproducibility and validity(3,4). Both algorithms utilize a scoring system to assess the probability of an adverse drug reaction. Relevant questions are asked and scored. The scores are totalled and compared to a probability scale. In case of polypharmacy each suspected drug is scored individually. The algorithms do not help to differentiate allergic from non-allergic reaction but is useful to ascertain causal relationship between drug and reaction.

In history taking the following caveats apply:

a. Many patients regard "drug" to include addictive drugs such as heroin, opium, cannabis, etc. only. The physician should define the meaning of "drug" clearly to the patients. It should include all preparations (including non-prescription items) taken systemically or applied on the skin or mucous membrane to treat symptoms and to improve well-being.

b. If there is a negative drug history always ask direct questions. It is necessary to ask for a history of chronic disease such as hypertension, diabetes, heart disease, etc. as medications taken for these conditions are often not considered as drugs by the patients. One should also ask for common complaints such as headaches, dysmenorrhoea for which patients often self-medicate with non-prescription preparations.

c. Query the patient about drug ingestion repeatedly if the initial reply is negative. It is not uncommon that a patient suddenly recalls that he had taken some drugs prior to the reaction.

It may be useful to ask the patient to bring in all medications from home for identification.

Using the algorithm we should be able to classify the suspected adverse drug reaction as DEFINITE, PROBABLE, POSSIBLE AND UNLIKELY. One should then decide on whether to proceed on with in-vitro, in-vivo tests or provocative test dosing.

DEFINITE association

When a DEFINITE association is found no further investigations is necessary. Where allergy is suspected steps must be taken to ensure that the drug should never be administered to the patient again. In-vitro test may be performed to confirm the diagnosis.

PROBABLE or POSSIBLE or UNLIKELY association

When a PROBABLE or POSSIBLE or UNLIKELY association is found, in-vitro, in-vivo tests and provocative testing dosing may be considered. The decision to proceed with further investigations will depend on the type of adverse reaction experienced and the type of the suspected causative drug(s). The following is recommended:

i). Where the adverse reaction to the suspected drug was severe and life-threatening e.g. anaphylaxis, Stevens-Johnson syndrome, toxic epidermal necrolysis, acute hepatitis, acute haemolysis etc. in-vivo or provocative test dosing should not be performed. The only exception is when a suitable alternative drug is not available i.e. where benefit of the drug outweighs any risk. Under such situations, in-vivo and provocative test dosing (and desensitization) should only be performed just before the decision to administer the drug (within 48 to 72 hours). It should never be performed for academic purposes or to satisfy the patient's request for such testing.

ii). Where the adverse reaction is mild and not life-threatening, in-vivo or provocative test dosing may be considered. They may be performed when the suspected drug is very frequently prescribed e.g. common antibiotics (tetracycline, ampicillin, co-trimoxazole, erythromycin), analgesics (paracetamol, aspirin), and common non-prescription medicaments(paracetamol, aspirin). It is also sometimes indicated to ascertain the responsible drug in polypharmacy.

2. In-vitro test:

In-vitro tests have limited value for confirming drug allergy. A positive test will indicate an increased risk of positive reaction to in-vivo or provocative test dosing. A negative in-vitro test does not exclude allergy. Most drugs administered systemically are metabolized enzymatically in the body and it is the metabolites that are responsible for most allergic reactions. The nature of the active metabolites remains unknown for most drugs.

2a. IgE mediated reactions

The radioallergosorbant test (RAST) is the most well known. The usefulness of this test is limited by the lack of relevant drug metabolites for testing. The most commonly used RAST test for drug allergy is for penicillin allergy. The implication of a positive RAST test to penicillin metabolites is briefly discussed here.

The antigens capable of causing allergy in humans for penicillins consist of the major and minor antigenic determinants. Approximately 95% of parenteral penicillin combines with protein through the β-lactam ring to form the benzylpenicilloyl group (BPO) referred to as the major antigenic determinants. The remaining 5% of penicillin is metabolized by other pathways into various minor antigenic determinants. Some of these minor antigenic determinants are yet to be idenified. The minor antigenic determinants are usually responsible for the severe immediate hypersensitivity reaction. The major antigenic determinants for penicillin have been standardized and are commercially available for in-vitro and in-vivo use. Penicillin will induce an immune response in every person who receives the drug. Antibodies can be detected even in patients who deny ever having received the drug (probably sensitized from environmental sources). The mere presence of antipenicillin antibodies of any class does not necessarily denote clinical sensitivity upon penicillin administration(6). BPO specific IgE mediated immediate allergic reactions is rare. This is explained by the simultaneous production of BPO specific IgG which can act as a "blocking antibody". A positive BPO specific IgE although indicative of sensitization to penicillin is thus not diagnostic of clinical penicillins allergy. A positive antibody cautions the physician to the risk of clinical allergy to the drug and extreme care should be taken when an in-vivo or oral provocative test dosing is to be performed. A negative BPO specific IgE does not exclude penicillin allergy; allergy to the minor antigenic determinants has not been excluded.

2b. IgG and IgM mediated reactions

These tests are uaually used to detect drug-induced IgG and IgM antibodies. It is useful for some cases of drug induced thrombocytopenias, haemolytic anaemia, agranulocytosis and possibly some penicillin-induced exanthematous eruption.

2c. Cell mediated reactions

Lymphocyte blast transformation has been suggested as an in-vitro diagnostic test for delayed hypersensitivity reaction. The procedure is complex and takes time for results to be available. The results may not correlate with clinical reaction.

3. In-vivo tests:

In-vivo testing is of limited value in most cases of systemic drug allergy. A negative skin test does not exclude allergy. Risks include sensitizing patients and severe reaction during the procedure. When carefully performed and properly interpreted, in-vivo testing can be invaluable.

3a. Immediate scratch/prick/intradermal skin tests

These tests are used for the detection of IgE immediate hypersensitivity reaction only. Unfortunately the antigenic drug metabolites are usually not available for testing (except for penicillin). Prick test is reliable for high-molecular-weight compounds e.g. hormones, vaccines, antisera as these substances are antigenic themselves. A positive prick test is indicative of the presence of IgE antibodies against the antigen tested (after excluding non-immunological reactions). A positive prick test would be indicative of an increased risk of immediate hypersensitivity reaction to the drug. A negative prick test does not exclude allergy for reasons mentioned above.

Immediate prick testing for penicillin will be briefly discussed. The principle is similar to in-vitro detection of antipenicillin IgE antibodies. The major antigenic determinant (benzylpenicilloyl polylysine) is commercially available for prick testing. The minor antigenic determinants (MDM which contains penicilloates, penilloates and benzylpenicylloylamine) are still not commercially available. Benzyl penicillin G can be used instead but, although it is an important minor determinant, improved sensitivity results can be obtained from skin testing together with other minor determinants(MDM). In one study, skin testing with PPL alone gave positive results in 75% of patients with a history of penicillin allergy and 4% of patients with negative history(7). Among skin test positive patients 39% reacted to penicillin administration but less than 1% of skin test negative patients reacted. It should be noted that the incidence of positive skin test reaction in penicillin sensitive patients is inversely related to the time interval from skin test, falling from 90% reactivity to PPL at 3 months to 26% reactivity at a mean of 19 years afterwards(8). A positive prick test reaction indicates a high risk of immediate hypersensitivity reaction whereas a negative indicates a low risk of immediate hypersensitivity reaction when the drug is administered.

3b. Delayed skin tests

The test is little used as there is little correlation with the clinical picture generally.

3c. Patch tests and photopatch tests

These tests are invaluable in the diagnosis of delayed hypersensitivity reaction (cell mediated reaction) in contact allergy. It should be performed on all suspected cases of contact allergy to medicaments. Topical medicament is the commonest cause of allergic contact dermatitis in Singapore(9). Allergic contact dermatitis from topical medicament can present with severe generalized eruption mimicking adverse drug reaction from systemic administration(10,11).

The patch test might be useful to confirm drug allergies which present with maculo-papular eruption. It appears that a delayed hypersensitivity reaction is involved. Bruynzeel et al reported that 76% of their patients with evidence of delayed type hypersensitivity to penicillin gave positive patch test reaction to penicillin(12). Detection of such allergic reaction is important because such patients may react with an anaphylactic reaction on subsequent administration of the drug(13). Bruynzeel et al demonstrated that 5 of 23 patients with positive patch test to penicillin also showed immediate-type hypersensitivity reaction to prick test(12).

4. Provocative test dosing:

Provocative test dosing is done only if in-vitro and in-vivo tests (where available) are negative. The possibility of life-threatening anaphylaxis restricts the use of this procedure. The development of appropriate symptoms and signs on provocative test dosing is strong presumptive evidence that the patient is allergic to the drug. The procedure is indicated primarily under the following situations, viz:

a) the clinical manifestation was primarily cutaneous (non-life threatening).
b) the drug allergy is probable or possible.
c) the clinical manifestation may have been non-immunological e.g. vasovagal reaction.

The following precaution should be considered during provocative test dosing:

a) the benefit of the test outweighs the risk.
b) the relevant in-vitro and in-vivo tests are negative.
c) informed consent must be obtained from the patient.
d) it should be carried out by experienced physicians
e) personnel trained in resuscitation procedure and re suscitation medications and equipment should be on standby during the test.
f) the drug must be administered in sufficiently small doses initially and slowly increased unhurriedly.
g) when it is necessary to test several drugs, always begin with the drug least likely to have caused the allergy.

Documentation

Once drug allergy has been confirmed, proper and clear documentation of the allergy is imperative. Figure 2 outlines a recommended algorithm when a drug allergy has been confirmed:

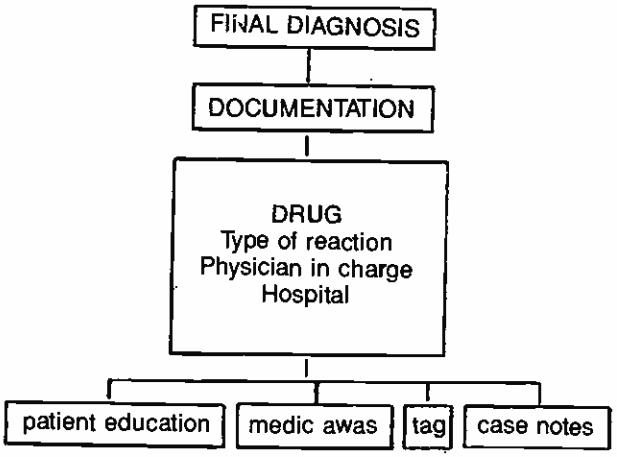


Figure 2

AN ALGORITHM FOR DOCUMENTATION AFTER CONFIRMATION OF AN ADVERSE DRUG REACTION

1. Documentation of the type of reaction. The type of reaction should be recorded. This information may become useful when the drug is inadvertently readministered again.
2. Patient education. The patient should be informed of the name of the drug. He should be informed of the likely sources of the drug(s). He should be instructed to remind his doctor of his allergy during every consultation.
3. Medic Awas registration/identification tags.
4. Special identification tags on medical records. All medical records, outpatient cards should be flagged. Warning signs on drug allergy should be displayed prominently on all patient's records.

Doctors treating patients with a history of drug allergy should be aware of drug cross-sensitivity. He should note that a drug may have many different generic names. He should note that several pharmaceutical preparations may contain multiple drugs.

REFERENCES

1. Kramer MS, Leventhal JM, Hutchinson TA, Feinstein AR. An Algorithm for the operational assessment of adverse drug reactions. Background, description, and instructions for use. JAMA 1979; 242: 623-33
2. Naranjo CA, Busto U, Sellers EM et al. A method for estimating the probability of adverse drug reaction. Clin Pharmacol Ther 1981; 30239-45
3. Hutchinson TA, Leventhal JM, Kramer MS, Karch FE, Lipman AG, Reinstein AR. An algorithm for the operational assessment of adverse drug reactions. Demonstration of reproducibility and validity. JAMA 1979; 242: 633-8
4. Busto CA, Naranjo CA, Sellers: Comparison of two recently published algorithms for assessing the probability of adverse drug reactions. Br J Clin Pharmac 1982; 13: 223-7
5. Levine BB: Immunologic mechanism of penicillin allergy. A heptagenic model system for the study of allergic diseases in man. N Engl J Med 1966; 275: 1115-25
6. DeSwarte RD. Drug Allergy. In Allergic Diseases, Diagnosis and Management. 3rd Edition, Ed Patterson R. Philadelphia, JB Lippincott Company, 1985. pg 502-661
7. Parker CW, Shapiro J, Kern M et al. Hypersensitivity to pencillanic acid in human beings with penicillin allergy. J Exp Med 1962; 115: 821-38
8. Budd MA, Parker BW, Norden CW. Evaluation of intra-dermal skin tests in penicillin hypersensitivity. JAMA 1964; 190: 203-5
9. Goh CL. Contact allergy to topical medicament in Singapore. Int J Dermatol 1989. 28:25-8
10. Goh CL. Contact sensitivity to proflavine. Int J Dermatol 1986; 25: 449-51
11. Goh CL. Urticarial and popular eruption in contact allergy. Int J Dermatol. 1989, 28:172-6
12. Bruynzeel DP, van der Flier MB, Scheper RJ, van Ketel WG, de Haan P. Penicillin allergy and the relevance of epicutaneous tests. Dermatologica 1985; 171: 429-34
13. Fellner MJ. Penicillin allergy 1976. A review of reactions, detection and current management. Int J Dermatol1976;15: 497-504