THE CEYLON MEDICAL JOURNAL

Established 1887

The Official Publication of the Sri Lanka Medical Association

Volume 52, No.2, June 2007

Quarterly ISSN 0009–0875

Continued overleaf

A clinicians' guide to adverse drug reactions

Pharmacovigilance is the "science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug related problems" [1]. The objective of this article is to promote better cooperation from health care professionals towards pharmacovigilance activities by defining and discussing terms used in the field of drug safety, particularly terms that are often misunderstood or misused, such as "drug", "adverse drug reaction" and "adverse event". We also discuss terms used to define seriousness, and its classification.

Let's start off with the definition of a "drug" or "medicine". The recent trend is to avoid the term "drug" and move towards "medicine" since abused substances also are loosely referred to as drugs. A medicine is a pharmaceutical product used in or on the human body for the prevention or diagnosis or treatment of disease, or for modification of physiological function [2]. Examples are: prevention of disease- vaccines; diagnosis of disease- radio-opaque contrast media used in radiology; treatment of disease- anti-bacterial agents; and modification of physiological function- thyroxine. Pharmacovigilance aims at monitoring problems related to any of these products.

There are many definitions for "adverse drug reaction" (ADR). But the terminology recommended by the WHO that has been in use for about 30 years, is preferred by most national ADR monitoring centres for uniformity. As defined by the WHO, it is a "response to a medicine which is noxious and unintended, and which occurs at doses normally used in man" [2]. Key concepts in this definition are, it is the response of a patient to a medicine in which individual factors may play a role, the phenomenon is noxious, it is unintended, and there is no overdose.

The term "side-effect", is commonly used in clinical settings and in the British National Formulary. The WHO clearly differentiates an ADR from a side-effect. Side-effect is "any unintended effect of a pharmaceutical product which is related to the pharmacological properties of the drug" [2]. Essential elements in this definition are, pharmacological nature of the effect (in contrast to the response of a patient as in an ADR), the effect is unintended, and is not necessarily noxious (in contrast to an ADR) (table 1). The usefulness of the definition to clinicians is that side-effects are expected problems, as they are part of the pharmacodynamics, and can be minimised by explaining to the patient, taking precautionary measures, or by lowering the dose.

An unexpected adverse reaction is "an adverse reaction, the nature or severity of which is not consistent with domestic labelling or market authorisation or expected from characteristics of the drug" [2]. Here the defining characteristic is that the effect is previously unknown, and most fall into the category of an ADR. Hence detecting unexpected adverse events during the post-marketing phase is a crucial responsibility of national

Published by

The Sri Lanka Medical Association
Wijerama House
6, Wijerama Mawatha
Colombo 7
Sri Lanka
Tel: +94 11 2693324
Fax: +94 11 2698802
Internet home page
http://www.slma.lk
e-mail: SLMA@eureka.lk

Printed by

Ananda Press
82/5, Sir Ratnajothi Saravanamuttu
Mawatha, Colombo 13
Sri Lanka
Tel: +94 11 2435975
Fax: +94 11 2385039
e-mail: anpress@sltnet.lk

This journal is indexed in BIOSIS, CAB International, EMBASE, and Index Medicus

pharmacovigilance centres. National centres alone cannot perform this task. They need the feedback from health care professionals who are the end-users of all the medicines registered in a country. For example increased cardiovascular mortality and morbidity which occurred with rofecoxib were unexpected ADRs, and recognising and reporting them by vigilant health care professionals in the USA led to clinical studies followed by withdrawal of rofecoxib from the market.

Table 1. **Examples for ADRs and side-effects (Using the WHO definitions)**

Example	*Is it an ADR?*	*Is it a side-effect?*
Penicillin induced anaphylaxis	Yes; it satisfies all the criteria of the definition	No; because it is not related to the pharmacological properties of the drug
Bleeding with anticoagulants	Yes; it satisfies all the criteria of the definition	Yes; it satisfies all the criteria of the definition
Drowsiness with antihistamines	No, it is not noxious	Yes; it satisfies all the criteria of the definition

In the clinical setting, health professionals should also appreciate the concept of "suspected adverse reaction," because lack of absolute confidence in the diagnosis of an ADR is a major contributor to under-reporting [3]. It follows that, even if one is not sure, it should be reported on suspicion as an "adverse event" or "adverse experience" which is defined as "any untoward medical occurrence that may present during treatment with a pharmaceutical product but which may or may not have a causal relationship with this treatment" [2]. The point here is the coincidence in time with only suspicion of a causal relationship.

An "adverse event" is classified as an ADR only after a causal relationship has been established. The relationship between the drug and the reaction needs a careful review of information. As an example, cardiovascular events associated with rofecoxib were reported as "adverse events" at first, until clinical studies established an association. The phrase "associated with" signifies that there is only a reasonable chance that the event may have been caused by the drug, unlike the phrases "caused by" and "due to" [4]. After causality assessment ADRs are classified as shown in tables 2 and 3.

Serious adverse events or reactions are defined by the WHO as "those that are life-threatening or fatal, cause or prolong hospital admission, cause persistent or significant disability/incapacity or concern misuse or dependence" [2]. The term a "serious adverse event" also includes cancer, congenital malformation, and any event that has not responded to medical treatment (table 4).

The clinical value of accurate documentation of ADRs is that it assists future determinations of whether the risks of prescribing a specific drug or drug class outweigh the potential benefits for an individual patient. To achieve this, nomenclature surrounding drug safety needs to be clear and unambiguous, so that health care professionals, patients, manufacturers, and regulators understand each other precisely.

We have here attempted to clarify nomenclature. A clear understanding of terms will help clinicians to recognise and treat drug-related harms, and lead to a substantial increase in reporting of suspected ADRs to the national pharmacovigilance unit.

Table 2. **Classification of ADRs** [5]

Type of reaction	*Mnemonics**	*Features*
A: Dose related	Augmented	Related to pharmacology (toxic effect or side-effect). eg. bradycardia with beta blockers, digoxin toxicity
B: Non-dose related	Bizarre	Unrelated to pharmacology (i) idiosyncratic eg. fractures with proton pump inhibitors (ii) immunological eg. penicillin rash
C: Dose and time related	Continuous or chronic	Related to cumulative drug use. eg. NSAID induced renal failure
D: Delayed effect	Delayed	Apparent only some time after use of drug eg. (i) endometrial carcinoma in women associated with the use of stilboesterol by their mothers during pregnancy, (ii) thalidomide taken by mothers in first trimester and phocomelia in the baby
E: Withdrawal	End of use	Related to discontinuation that is too abrupt eg. Addisonian crisis after steroid withdrawal

*The letters A, B, C, D and E help to remember the type of reaction.

Table 3. **Essential differences between Type A and Type B ADRs with examples**

Description	*Type A (augmented)*	*Type B(bizarre)*
Explanation	Can be explained by pharmacology of drug	Cannot be explained by pharmacology of drug
Predictability	Predictable	Unpredictable
Dose dependence	Dose dependent	Not dose dependent
Contribution	Related to drug factors	Related to patient factors
Prevalence	Common (about 75%)	Less common (about 25%)
Severity	Usually mild with low mortality	Can be severe with high mortality
Relationship to pharmacodynamics	Excess pharmacodynamic effect of the drug	Not part of drug's pharmacodynamics
Response to stopping the drug/reducing the dose	Usually reversible with stopping the drug/reducing the dose	Do not respond to stopping the drug / reducing the dose
Detection in pre-marketing clinical trials	Detectable in pre-marketing clinical trials and often already identified before marketing	Difficult to detect
Animal studies	Reproduced in animal studies	Cannot be reproduced
Examples	1. Bleeding with anticoagulants 2. Bronchospasm with beta blockers	1. Penicillin induced anaphylaxis 2. Primaquine induced haemolysis in patients deficient in G6PD

Table 4. **Some examples of serious ADRs**

ADR	*Example*
Results in death	Death caused by penicillin induced anaphylaxis
Life threatening	Pancytopenia associated with anti-cancer drugs
Persistent or significant disability/incapacity	Nicolau syndrome associated with intramuscular injection of nonsteroidal anti-inflammatory drugs and subsequent amputation of the affected limb
Requires inpatient hospitalisation	Hepatitis with anti-TB drugs
Prolongation of existing hospitalisation	Usually seen when new drugs are added while in hospital and ADRs occur due to drug interactions
Cancer	Bladder cancer with cyclophosphamide
Congenital malformation	Sodium valproate and neural tube defects
Events that have not responded to medical treatment	Hepatitis caused by some drugs (eg. marcolides) is prolonged.

Acknowledgements

We acknowledge the Collaborating Centre for International Drug Monitoring, Uppsala, World Health Organization for their guidance. We declare that we have no conflicts of interest in regard to this article.

References

1. World Health Organisation. The importance of pharmacovigilance. Safety monitoring of medicinal products. Geneva: World Health Organisation; 2002.
2. World Health Organisation. Collaborating Centre for International Drug Monitoring. Safety Monitoring of Medicinal Products, Guidelines for setting up and running a Pharmacovigilance Centre. Uppsala: World Health Organisation; 2000.
3. Belton KJ, Lewis SC, Payne S, Rawlins MD, Wood SM. Attitudinal survey of ADRs reporting by medical practitioners in the United Kingdom. *British Journal of Clinical Pharmacology* 1995; **39**: 223-6.
4. Stephens MDB. Introduction. In: Stephens MDB, Talbot JCC, Routledge PA, editors. Detection of New Adverse Drug Reactions. 4th ed. London: Macmillan Reference Ltd; 1998. p. 1-57.
5. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis and management. *Lancet* 2000; **356**: 1255-9.

S Sri Ranganathan[1] and **R Fernandopulle**[2]; [1]*Senior Lecturer and* [2]*Professor, Department of Pharmacology, and National Adverse Drug Reaction Monitoring Centre, Faculty of Medicine, Kynsey Road, Colombo 8.*

Correspondence: SSR, *e-mail: <sshalini14@hotmail.com>.*