

Pharmacovigilance: a brief glimpse

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Editorial

One of the changes decided on for the new format of our merged Journal is that the CPD questions will only be available on request. The request can be sent to Lucille Pick, c/o SA Family Practice/Geneeskunde, PO Box 2731 Rivonia 2128. Alternatively a fax can be sent to 011-807-6611 or an e-mail to saafp@netactive.co.za. The questions will then be forwarded to you. Please ensure that your return details are clear in whatever form you make your request.

This edition's CPD is in some ways a continuation of the December article¹ in which we considered the possible drug interactions of Salie's antiretroviral therapy with her carbamazepine. Such drug interactions are one of many components of the growing science of pharmacovigilance. In this edition we take a broader, more global look at this topic.

An extraordinarily useful resource in terms of international regulatory decisions and reports on the safety of medicines is used to provide examples in this article. Please note that the WHO is not in itself a regulatory body. Some of the safety issues raised will already have been addressed by the MCC, whereas others will not. You may choose to take note of decisions made elsewhere - and you could even find out if the manufacturers (or whoever has registered a medicine) have informed our regulatory authority of these changes. (A condition of registration is to provide the MCC with ongoing safety data both nationally and internationally.)

Finally, I would urge everyone to remain aware of the broader aspects of pharmacovigilance while at the same time being on the look out for adverse drug reactions which may occur in your patients and/or practice. And please don't forget to complete and submit the 'yellow' adverse drug reaction forms whenever you suspect an adverse reaction or event.

Roy Jobson

1. Jobson MR, Moodley K. Managing HIV and AIDS: From Betty's Bay to Barcelona. SA Fam Pract 2003; 26(1):16-20.

One of the ethical foundations of medical practice is the injunction: *primum non nocere* or 'first do no harm'. This is the basis of the ethical principle 'non-maleficence' in the principle-based approach to bioethics.¹

However, as all practitioners know, every substance (including plain unadulterated H₂O) can have unwanted or harmful effects - which are dependent on a variety of factors.

The standard definition of pharmacovigilance is the 'science and activities relating to the

- detection,
- assessment,
- understanding, and
- prevention

of adverse effects or any other drug-related problem.²

In South Africa this function has been undertaken by the National Adverse Drug Events Monitoring Centre (NADEMC) for many years. The NADEMC was set up as a partnership between the MCC and the WHO.

More recently the definition of pharmacovigilance has been expanded to include

- Herbals
- Traditional and complementary medicines
- Blood products
- Biologicals (e.g. insulin)
- Medical devices
- Vaccines²

Many other issues are also of relevance to the science of pharmacovigilance:

- Substandard medicines
- Medication errors
- Reports of lack of efficacy
- Use of medicines for indications that are not approved and for which there is inadequate scientific basis
- Case reports of acute and chronic poisoning
- Assessment of drug-related mortality
- Abuse and misuse of medicines
- Adverse interactions of medicines with chemicals, other medicines, and food²

Table 1: Pharmacovigilance terminology

Adverse Drug Event/ Adverse Drug Experience	Any untoward medical occurrence that may appear during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with the treatment.
Adverse Drug Reaction (ADR)	A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.
Benefit/harm	Benefit and harm are the positive and negative subjective qualitative experiences of individual patients. These are not usually assessed except in modern quality of life studies or in case reports. Benefit and harm at a societal level may also be considered, but then must include relative effectiveness and risk, the impact of all the outcomes on society and include cost analysis.
Counterfeit Medicine	A medicine that is deliberately and fraudulently mislabelled with respect to identity and/or content and/or source.
Drug Alerts	The action of notifying a wider audience than the initial information holder(s) of a suspected association between a drug and an adverse reaction. Note that the term is used in different contexts that can be confusing, for example, an alert may be from a manufacturer to a regulator, or from a regulator to the public.
Effectiveness/risk	The balance between the rate of effectiveness of a medicine versus the risk of harm is a quantitative assessment of the merit of a medicine used in routine clinical practice. Comparative information between therapies is most useful. This is more useful than the efficacy and hazard predictions from pre-marketing information that is limited and based on selected subjects.
Lack of efficacy	Unexpected failure of a drug to produce the intended effect as determined by previous scientific investigation.
Pharmaco-epidemiology	The study of the use and effects of drugs in large numbers of people.
Risk evaluation	Risk evaluation is the complex process of determining the significance or value of the identified hazards and estimated risks to those concerned with or affected by the process.
Risk management	The making of decisions concerning risks, or action to reduce the consequences or probability of occurrence.
Side effect	Any unintended effect of a pharmaceutical product occurring at a dose normally used in man, which is related to the pharmacological properties of the drug.
Signal	Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information.
Spontaneous reporting	System whereby case reports of adverse drug events are voluntarily submitted from health professionals and pharmaceutical manufacturers to the national regulatory authority.
Unexpected Adverse Drug Reaction	An adverse reaction, the nature or severity of which is not consistent with domestic labelling or market authorization, or expected from characteristics of the drug.
Serious Adverse Event (SAE)³	any event that: <ul style="list-style-type: none"> • is fatal • is life-threatening • is permanently/significantly disabling • requires or prolongs hospitalization • causes a congenital anomaly • requires intervention to prevent permanent impairment or damage

In order to make sense of pharmacovigilance it is helpful to have an understanding of some of the more technical terminology commonly used. See Table 1.^{2,3}

Question 1:

How does one recognise an adverse drug reaction?

Answer 1:

Since ADRs may act through the same physiological and pathological pathways as different diseases, they are difficult and sometimes impossible to distinguish. However, the following step-wise approach may be helpful in assessing possible drug-related ADRs:

1. Ensure that the medicine ordered is the medicine received and actually taken by the patient at the dose advised.
2. Verify that the onset of the suspected ADR was after the drug was taken, not before and discuss carefully the observation made by the patient.
3. Determine the time interval between the beginning of drug treatment and the onset of the event.
4. Evaluate the suspected ADR after discontinuing the drugs or reducing the dose and monitor the patient's status. If appropriate, restart the drug treatment and monitor recurrence of any adverse events.
5. Analyse the alternative causes (other than the drug) that could on their own have caused the reaction.
6. Use relevant up-to-date literature and personal experience as a health professional on drugs and their ADRs and verify if there are previous conclusive reports on this reaction. The National Adverse Drug Event Monitoring Centre and the different Medicines Information Centres are very important resources for obtaining information on ADR. The manufacturer of the drug can also be a resource to consult.
7. Report any suspected ADR to the person nominated for ADR reporting in the hospital or directly to the National ADR Centre.³

Note: If there is not a person nominated for ADR reporting in a hospital you are associated with, consider approaching the Pharmacy and Therapeutics

Table II: The Erice Declaration^{*}

The Erice Declaration – on Communicating Drug Safety Information

The following declaration was drawn up at the International Conference on Developing Effective Communications in Pharmacovigilance, Erice, Sicily, 24-27 September 1997. It was attended by health professionals, researchers, academics, media writers, representatives of the pharmaceutical industry, drug regulators, patients, lawyers, consumers and international health organisations.

Preamble:

Monitoring, evaluating and communicating drug safety is a public-health activity with profound implications that depend on the integrity and collective responsibility of all parties – consumers, health professionals, researchers, academia, media, pharmaceutical industry, drug regulators, governments and international organisations – working together. High scientific, ethical and professional standards and a moral code should govern this activity. The inherent uncertainty of the risks and benefits of drugs needs to be acknowledged and explained. Decisions and actions that are based on this uncertainty should be informed by scientific and clinical considerations and should take into account social realities and circumstances.

Flaws in drug safety communication at all levels of society can lead to mistrust, misinformation and misguided actions resulting in harm and the creation of a climate where drug safety data may be hidden, withheld, or ignored.

Fact should be distinguished from speculation and hypothesis, and actions taken should reflect the needs of those affected and the care they require. These actions call for systems and legislation, nationally and internationally, that ensure full and open exchange of information, and effective standards of evaluation. These standards will ensure that risks and benefits can be assessed, explained and acted upon openly and in a spirit that promotes general confidence and trust.

The following statements set forth the basic requirements for this to happen, and were agreed upon by all participants from 34 countries at Erice:

1. Drug safety information must serve the health of the public. Such information should be ethically and effectively communicated in terms of both content and method. Facts, hypotheses and conclusions should be distinguished, uncertainty acknowledged, and information provided in ways that meet both general and individual needs.
2. Education in the appropriate use of drugs, including interpretation of safety information, is essential for the public at large, as well as for patients and health-care providers. Such education requires special commitment and resources. Drug information directed to the public in whatever form should be balanced with respect to risks and benefits.
3. All the evidence needed to assess and understand risks and benefits must be openly available. Constraints on communication parties, which hinder their ability to meet this goal must be recognised and overcome.
4. Every country needs a system with independent expertise to ensure that safety information on all available drugs is adequately collected, impartially evaluated, and made accessible to all. Adequate nonpartisan financing must be available to support the system. Exchange of data and evaluations among countries must be encouraged and supported.
5. A strong basis for drug safety monitoring has been laid over a long period, although sometimes in response to disasters. Innovation in this field now needs to ensure that emergent problems are promptly recognised and efficiently dealt with, and that information and solutions are effectively communicated.

These ideals are achievable and the participants at the conference commit themselves accordingly. Details of what might be done to give effect to this declaration have been considered at the conference and form the substance of the conference report.

Erice, September 27 1997

^{*} <http://www.who-umc.org/comm.html> (accessed 13/02/2003)

Committee (PTC) of that hospital (if one exists) to nominate such a person.

Any suspected adverse drug reaction should be reported on the standard

'yellow' form: a copy of which was provided in the December 2002 edition of SA Family Practice. Further copies are available from the Department of Health.

Another increasingly important area of pharmacovigilance is that of drug safety information (or lack thereof) particularly in terms of media reports

Table III: Examples of regulatory authority decisions in terms of drug safety:

Name of drug	Regulatory authority	Decision
Acetyl salicylic acid	Medicines Control Agency UK (MCA)	Extend the warning not to use aspirin in under-12 year old child to under 16 year old children
Ergotamine tartrate and caffeine suppositories	Food and Drug Administration (FDA) USA	New information to be included in the prescribing information states that ergotamine use is contraindicated with potent CYP 3A4 inhibitors such as ritonavir, nelfinavir, indinavir, erythromycin, clarithromycin, troleandomycin, ketoconazole and itraconazole. The resultant increase in levels of ergotamine and caffeine can lead to life-threatening vasospasm with cerebral ischaemia and/or ischaemia of the extremities.
Gamelonic acid	MCA	The approval of this derivative of evening primrose oil was withdrawn. The Committee on Safety of Medicines (CSM) of the MCA has reviewed the relevant information on the products and has concluded that the data do not support the current standards of efficacy required for the authorization of these products as medicines for the treatment of eczema and mastalgia. (My emphasis) Derivatives of evening primrose oil will still be available in the UK as a dietary supplement. Note: This was not so much a safety issue as a 'lack of efficacy' issue – falling well within the expanded definition of pharmacovigilance.
Isotretinoin	FDA	Changes to the prescribing information and labelling to include aggressive and/or violent behaviour as possibly being caused by isotretinoin; to advise caution in prescribing isotretinoin in patients on systemic corticosteroids or phenytoin. Information about the relationship in paediatric patients with osteoporosis, osteomalacia, backache and arthralgias is also mandatory.
Mefloquine	FDA	The prescribing information was updated to include as contra-indications: active depression, a recent history of depression, generalized anxiety disorder, psychosis or schizophrenia or other major psychiatric disorders or a history of convulsions. In using mefloquine as prophylaxis, the appearance of acute anxiety, depression, restlessness or confusion should be considered as prodromal to a more serious event, and the drug should be discontinued and alternatives used.
Parecoxib	European Medicines Evaluation Agency (EMA)	A public statement (press release/drug alert) was issued to warn of the risk of serious hypersensitivity and skin reactions. The EMA statement is based on the fact that serious reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme and exfoliative dermatitis, as well as anaphylaxis angioedema have occurred with valdecoxib and that these reactions could also occur with parecoxib, the prodrug of valdecoxib. Some of the reactions have occurred in patients with a history of allergic type reactions to sulphonamides. Doctors are alerted that parecoxib is contra-indicated in patients with a history of sulphonamide hypersensitivity.
Piper methysticum (kava kava)	Singapore	Declared it a poison
	UK	All licences revoked: 'banning order'
	Australia	Voluntary recall
	Canada	Mandatory recall
	Germany, Ireland, USA Switzerland, Austria New Zealand	(Decisions reported in previous editions of the newsletter.)
	(MCC – not reported in WHO newsletter)	Press statement, Drug alert, and Circular published. Recommendations from Pharmacovigilance Committee of MCC awaited.
Urokinase	FDA	Approval for the re-introduction of urokinase for the treatment of pulmonary emboli. Further warnings have been added and a statement that it is approved solely for use in the lysis of massive pulmonary emboli and pulmonary emboli accompanied by unstable haemodynamics.

and advertising. The 1997 Erice Declaration addresses this issue (Table II). Although systems for communication about the safety of drugs (press releases to the general public, drug alerts to health professionals via journals and societies, circulars) are available in the South African context, it is clear that these are not taken as seriously as, for example, a possible fault in a motor car.

The recent press release from the MCC about the possible hepatotoxicity of kava kava did not receive high priority in the local media; although the drug alert was published by the major health journals (including SA Family Practice⁴). Of about six pharmacists subsequently informally questioned (by myself) – only one was aware of the information. Ironically, despite being ‘banned’ in several countries around the world, kava kava remains available (at the time of writing) as an over the counter substance – even being available in a large chain store!

Question 2:

The only information most doctors receive about problems with drugs is when the pharmaceutical industry sends out a ‘dear doctor’ letter. Are there other sources of drug safety information?

Answer 2:

Many sources of drug safety information are available. For most practitioners it is particularly useful to have the information summarised, and to this end the WHO Pharmaceuticals Newsletter is particularly valuable. This quarterly publication summarises drug safety decisions that regulatory authorities (such as the SA Medicines Control Council) have made; highlights safety issues that have become apparent; may focus on a ‘drug of current interest’; and may include a ‘feature’ related to pharmacovigilance.

Examples of regulatory authority decisions reported in Newsletter 4 of 2002 are listed in Table 3.⁵

Some of the drugs mentioned in the ‘Safety of Medicines’ section of the newsletter include:

- Clozapine and cardiac monitoring.
- The use of inhaled corticosteroids and adrenal suppression in children (including a reminder that fluticasone should be used at half the dose of budesonide or beclomethasone).
- Indapamide and hyponatraemia.
- Isotretinoin and teratogenicity re-emphasised.
- Levofloxacin and tendonopathy (including ruptured tendons).
- Quinine and thrombocytopenia

(and a reminder that quinine is no longer recommended for the treatment of nocturnal cramps by the FDA).

- Risperidone and strokes or stroke-like episodes in elderly dementia.
- Statins and reducing the risk of myopathy.

CONCLUSION

In order to determine the extent to which patients are ill (or sometimes die) from adverse drug reactions, Family Physicians should be encouraged to be constantly alert to and aware of the possibilities and/or the probabilities of ADRs. When these are suspected – even if no definite causal relationship is clear, they should be reported to the NADEMC on the ‘yellow’ adverse drug reaction form. □

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4. SA Family Practice 2003;26(1):29.
5. WHO Pharmaceuticals Newsletters. 2002(4). <http://www.who.int/medicines/library/pnewslet/4news2002.pdf> (accessed 13/02/2003)



The National Asthma Education Programme (NAEP) helping you understand asthma

NAEP is an initiative aimed at educating patients, their relatives and caregivers, doctors and nursing staff on asthma. The primary objective is the facilitation of early recognition and diagnosis of the condition which results in significantly improved clinical outcome and often prevents unnecessary deaths.

Patients who are diagnosed early and who understand what they can do to help themselves have a significantly improved outcome.

The National Asthma Education Programme was established by academics for this very reason. It is a non-profit organisation that relies on sponsorships and fundraising.

All NAEP endorsed information gives patients and those associated with them peace of mind in terms of:

- it being true and correct
- scientifically proven
- non-commercial

Core Communication Objectives

1. To raise the level of awareness of asthma amongst the medical profession, the patient and the general public.
2. To profile NAEP as a credible source of scientific

information.

3. To motivate asthmatics to pursue an early diagnosis.
4. To educate the public on the diagnostic procedures, appropriate treatment and expectations in terms of their medical treatment.
5. To decrease mortality and morbidity rates associated with misdiagnosis, inappropriate treatment, ineffective treatment and non-compliance.

The NAEP telephone line is operational daily between 8.30 a.m. and 1.30 p.m. Monday to Friday. We can be reached on Tel: (011) 643 2755 or Fax: (011) 680 1313.

E-mail: naepr@netactive.co.za, Website: www.asthma.co.za

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