Pharmacovigilance: the devastating consequences of not thinking about adverse drug reactions

The burden of adverse drug reactions (ADRs) on patient care has been found to be high globally and is particularly high in South Africa.

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A meta-analysis of 69 prospective and retrospective studies conducted in various regions of the world involving 419 000 patients found that approximately 6.7% of all hospitalisations were as a result of ADRs.[1] A recent observational study conducted in the medical wards of a secondary hospital in the Western Cape estimated that 6.3% of hospitalised patients were admitted as a direct result of an ADR, while a further 6.3% of patients developed a significant ADR while in hospital.[2] More than half of the ADRs that occurred in patients in the community were considered to be preventable with improved prescribing, administration, monitoring and adherence.[2] Patients with HIV/AIDS were found to have an increased risk of ADRs.[2] This is probably due to the effect of the disease on the immune system (which is responsible for many idiosyncratic drug reactions) as well as the safety profile of the complex drug regimens that patients with HIV/AIDS are often receiving.

Additionally, a report by the Institute of Medicine in the United States estimated that between 44 000 and 98 000 people in US hospitals die each year because of medical errors, with medication errors playing a significant role in many of these.[3] Similarly, Runciman reports that medication errors are a major contributor to medical errors in Australia, with 26% of 27 000 hospital-related incidents being medication-related, as were 36% of 2 000 anaesthesia-related incidents, and 50% of 2 500 general practice incidents.[4] Even these startling statistics probably don't provide a complete picture of the size and severity of the problem. These studies usually exclude ADRs caused by overdose, drug abuse, or therapeutic failures. Several studies have also found that the cost of managing ADRs places a significant burden on health care budgets.[5] Some countries reportedly spend up to 15 - 20% of their hospital budget dealing with drug complications.[6]

It seems clear from the available evidence that ADRs have become a major global public health problem that needs to be addressed at all levels of health care.

Epidemic diseases such as HIV/AIDS, TB and malnutrition are well known to increase the risk of certain ADRs in patients. Reliable, independent drug information sources are not widely available and illiteracy is widespread in our communities. Self-medication and misuse of over-the-counter medicines and traditional and complementary medicines are widespread, adding to the potential risk of ADRs and drug-drug interactions. These and other factors are likely to increase the burden of drug-related morbidity and mortality in our country.

It seems clear from the available evidence that ADRs have become a major global public health problem that needs to be addressed at all levels of health care. The lack of awareness and appreciation of the size and severity of the problem as well as the misclassification of ADRs as other diseases or the underlying condition are partially to blame for this silent epidemic. Furthermore, a large proportion of these ADRs can be prevented through more judicious medicine use.

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Awareness: The first step

Developing awareness of the potential risks of medicines, both direct and indirect, while also understanding the extent of their benefits, is critical to addressing the problem of drug-induced diseases. Failing to maintain a sense of constant vigilance when using medicines in patients can have devastating and even potentially fatal consequences, particularly given the local context as discussed above. This vigilance is required throughout the patient-practitioner relationship, i.e. when patients are being asked about their medical and medicine use history, when diagnosing a condition, prescribing, monitoring and reassessing management.

ADRs are often referred to as the 'great masquerader of disease' as they usually mimic other diseases. This makes it difficult to attribute an adverse event to a medicine being used by the patient. Patients presenting with new signs or symptoms not clearly explained by the underlying condition need to be investigated for potential ADRs as well as other causes.

Patients are often reluctant to reveal to clinicians the range of medicines that they are taking concurrently with prescription medicines. These include over-the-counter medicines, herbal preparations, multivitamins and tonics. Obtaining an accurate and complete drug history from patients requires a non-judgmental, understanding approach that allows patients to reveal the extent of their medicine use without fear of recrimination. Such an interaction is also an opportunity for clinicians to highlight to patients the importance of using medicines and herbal/traditional preparations with care.

Often neglected, is the ongoing and routine monitoring of patients for adverse effects. In some cases, this includes more than just asking patients about adverse effects, but rather conducting relevant tests to check for problems such as renal or hepatic compromise, cardiovascular effects, neurological problems and metabolic disturbances. The package insert often provides advice on the nature and frequency of such monitoring in the case of medicines with a known risk for specific serious ADRs, e.g. liver function monitoring with methotrexate.

Actively encouraging patients to immediately report any adverse effects or intolerance to the medication throughout the course of treatment ensures that adverse effects that may be affecting adherence or causing

harm are identified as soon as possible and managed efficiently.

Clinicians can make a major contribution towards making medicines safer for all patients (not just their own) by reporting their suspicions of ADRs to the National Adverse Drug Event Monitoring Centre (NADEMC). The reporting instructions are provided in Table I, with addresses for obtaining the reporting forms. These reports are entered into an international database that is routinely analysed for signals of new risks associated with the use of medicines. In addition, these reports could result in additional investigations into the use of the implicated medicine in South Africa, educational initiatives to improve the safe use of the medicine, appropriate package insert changes to include the new ADR or changes in the scheduling, manufacture or availability of the medicines in South Africa. Ultimately these actions are intended to make these medicines safer to use.

'The safest medicines are the ones you know best'

When a new medicine is released onto the market there is still a great deal that is unknown about the safety of the product. Tests in animals are insufficient to predict safety in humans. The patients that are studied in pre-marketing clinical trials are usually limited in number and are studied for a short period of time under very controlled conditions. Therefore only the more common ADRs are detected.

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Information about rare but serious ADRs, chronic toxicity, drug interactions and risks in special patient groups (e.g. children, the elderly, pregnant women) is often not available or incomplete at the time of marketing.

New medicines that are still under patent are often marketed aggressively in order for pharmaceutical manufacturers to recoup their drug development costs. In recent years there have been many so-called 'blockbuster' medicines that have been withdrawn from the market as a result of fatal or life-threatening adverse effects only a few years after their launch. Clinicians are often under pressure from patients, colleagues and pharmaceutical representatives to use these medicines preferentially in their practice despite lack of a long track record of safety. Unfortunately, in countries like South Africa, where reporting of ADRs by clinicians is low, our understanding of the safety profile of these medicines is often delayed, resulting in a large population of patients exposed to medicines which may have an uncertain safety profile.

Table I. Reporting procedures for adverse drug reactions

Who should report adverse drug reactions?

All health professionals are requested to report all suspected ADRs to drugs (including vaccines, X-ray contrast media, traditional and herbal remedies), especially when the reaction is unusual, potentially serious or clinically significant. It is vital to report an ADR to the Medicines Control Council's Pharmacovigilance programme, even if all the facts are not available or if the reporter is uncertain that the medicine is definitely responsible for causing the reaction.

How to report an ADR

The Adverse Drug Reaction/Product Quality Form is enclosed in this *CME*. More ADR forms can be obtained by contacting the NADEMC or National Pharmacovigilance Centre or the Office of the Registrar of Medicines.

Registrar of Medicines
Department of Health
Private Bag X828
0001 Pretoria

Pretoria:
Tel: 012 395 8176/7/8 or 012 395 8197
Fax: 012 395 8775

Cape Town:
Tel: 021 447 1618
Fax: 021 448 6181

What should be reported?

- All ADRs to newly marketed drugs or new drugs added to the Essential Drugs List
- All serious reactions and interactions
- ADRs which are not clearly stated in the package insert
- Unusual or interesting adverse drug reactions
- All adverse reactions or poisonings to traditional or herbal remedies
- Product quality problems such as:
  - suspected contamination
  - questionable stability
  - defective components
  - poor packaging or labelling
  - treatment failures

Therefore clinicians are advised to avoid the use of medicines unless absolutely necessary. When required, medicines that are most familiar should be used unless the new medicines offer a meaningful benefit to patients. Clinicians should avoid changing therapy from known medicines to unfamiliar ones without good reasons. If a decision is made to prescribe a new medicine, clinicians should refer to reliable, unbiased information about that medicine, its benefits, risks, potential for interactions and monitoring requirements before prescribing such a medicine, e.g. the package insert.

What is pharmacovigilance?

The World Health Organization defines pharmacovigilance as 'the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems.' Ultimately these activities are aimed at protecting patients and the public from drug-related harms.[7]

Ensuring that patients are protected from the harmful effects of medicines is a shared responsibility. Pharmaceutical manufacturers, drug regulators, health care professionals and patients all need to understand the potential risks of these medicines and their responsibility in minimising and managing those risks.

Current pharmacovigilance activities in South Africa

The Medicines Control Council (MCC) is the statutory body that has the responsibility to ensure the safety, efficacy and quality of all medicines used by the South African public. Therefore it is also the responsibility of the MCC to monitor the performance of these medicines once they are marketed. Essential medicines are particularly important as they are used by a large percentage of the population.

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The MCC's national pharmacovigilance programme is co-ordinated by the National Pharmacovigilance Centre (NPC) in Pretoria. One of the units functioning under the NPC is the National Adverse Drug Event Monitoring Centre (NADEMC) in Cape Town. This is the unit of the MCC responsible for managing the national ADR database (ADRI) which houses all spontaneous reports of ADRs submitted by local health professionals and pharmaceutical manufacturers. The information in the national ADR database is used to identify signals of new, previously unknown or poorly understood ADRs and to include these in the labelling and package insert of the product. In some situations, information derived from spontaneous reports can provide adequate evidence to facilitate the withdrawal of a potentially unsafe medicine from the market. The data from the ADRI database are routinely fed into an international database of these reports housed in Sweden at the Uppsala Monitoring Centre (the WHO Collaborating Centre for International Drug Monitoring).

The MCC's Pharmacovigilance Committee advises the Council on how to prevent or minimise the risk of these ADRs in South Africa. The MCC may communicate their findings and recommendations to the appropriate organisations or individuals such as health professionals, pharmaceutical manufacturers, the Essential Drugs Programme or other directorates within the Department of Health, other public health institutions, the media and the public.

Medicines that are newer may be reported to be 'safe' mainly as a result of lack of adequate experience and knowledge of the potential risks of the medicine in the population.

The pharmacovigilance arena is rapidly evolving in South Africa. The antiretroviral and tuberculosis programmes are recognising the importance of targeted monitoring of the safety of the medicines they use in patients and developing targeted pharmacovigilance systems to address the particular problems with the medicines they commonly use. The national immunisation programme also monitors the safety of the vaccine products they use in both the public and private sectors. What should ultimately be developed is a pharmacovigilance system which is firmly integrated into clinical care, is effective in identifying and addressing ADRs that pose the greatest threats to the South African population, while ensuring that health workers and patients are confident of the pharmacovigilance system and the medicines they use in patients.

Conclusion

ADRs have the potential to cause significant harm in patients. There is increasing awareness of the significant global and local impact of ADRs on patient care and public health. Local factors such as the high prevalence of HIV/AIDS, tuberculosis, health systems failures and illiteracy among patients contribute to the burden of drug-related morbidity and mortality in South Africa. Health care workers need to develop an appreciation of the potential benefits and dangers of the medicines they prescribe for their patients.

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There needs to be an understanding of the fact that the safety profile of any medicine continues to evolve throughout the lifespan of that medicine. Medicines that are newer may be reported to be 'safe' mainly as a result of lack of adequate experience and knowledge of the potential risks of the medicine in the population. The national infrastructure aimed at addressing medicines safety issues is growing and evolving to meet the growing need for this activity. While this is encouraging, clinicians need to exercise caution and vigilance when prescribing, administering and monitoring the use of medicines in their patients. Moreover, reporting of unusual problems and reactions encountered with the use of these medicines to the NADEMC contributes to making these medicines safer for patients, both in South Africa and globally.

References available at www.cmej.org.za

IN A NUTSHELL

- Adverse drug reactions (ADRs) are an important cause of morbidity and mortality in patients.
- Studies suggest that approximately 6% of all hospitalisations into medical wards are as a result of an ADR.
- The cost of ADRs to the health care system and to patients themselves can be very high.
- Medical doctors should maintain a constant sense of vigilance when interacting with patients to prevent or identify and promptly manage drug-related problems as they arise.
- Prescribers need to be prudent when prescribing, using medicines only when absolutely necessary and using medicines they know well.
- The safety profile of new medicines is not completely understood, particularly during the initial years of use.
- New medicines should be used only when the benefits clearly outweigh the uncertainty of risk, and where the new medicine is clearly superior to more familiar medicine choices.
- Clinicians are strongly encouraged to report suspected ADRs to the National Adverse Drug Event Monitoring Centre in order to assist in the identification of new risks of ADRs (signals).
- Pharmacovigilance activities in South Africa are expanding and evolving in order to meet the need for ensuring that medicines used on a wide scale (e.g. vaccines, antiretrovirals, etc.) are as safe as possible.
- Guidelines on reporting ADRs are provided in Table I.

ADVERSE DRUG REACTION AND PRODUCT QUALITY PROBLEM REPORT FORM

(Identities of reporter and patient will remain strictly confidential)

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

NATIONAL ADVERSE DRUG EVENT MONITORING CENTRE
NADEMC

The Registrar of Medicines
Private Bag X 828
Pretoria 0001

Fax: 021 448 6181
Tel : 021 447 1618

In collaboration with the WHO International Drug Monitoring Programme

PATIENT INFORMATION

Name (or initials): ..... **Patient Reference Number:** .....
Sex: M F **Age:** ..... **DOB:** ..... / ...../ ..... **Weight (kg):** ..... **Height (cm):** .....

ADVERSE REACTION / PRODUCT QUALITY PROBLEM (tick appropriate box)

Adverse reaction ☐ **and/or Product Quality problem** ☐

Date of onset of reaction: ...../...../.....
Time of onset of reaction: .....hour.....min

Description of reaction or problem (include relevant tests/lab data, including dates):

1. MEDICINES / VACCINES / DEVICES (include all concomitant medicines)

Trade Name & Batch No. (Asterisk Suspected Product)	Daily Dosage	Route	Date Started	Date Stopped	Reasons for use

ADVERSE REACTION OUTCOME (Check all that apply)

☐ death
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ life-threatening
☐ hospitalisation
☐ other.....
.....
.....
.....

Event reappeared on rechallenge: Y N Rechallenge not done

Reaction abated after stopping medicine: Y N

Recovered: Y N
Sequelae: Y N
Describe Sequelae:.....
.....
.....
.....

COMMENTS: (e.g. Relevant history, Allergies, Previous exposure, Baseline test results/lab data)

2. PRODUCT QUALITY PROBLEM

Trade Name	Batch No	Registration No	Dosage form & strength	Expiry Date	Size/Type of container

Product available for evaluation? Y N

REPORTING HEALTHCARE PROFESSIONAL:

NAME: ..... QUALIFICATIONS:.....

ADDRESS: .....

....
Signature Date

Postal Code: ..... TEL: (.....).....

This report does not constitute an admission that medical personnel or the product caused or contributed to the event.

ADVICE ABOUT VOLUNTARY REPORTING

Report adverse experiences with:
- medications (drugs, vaccines and biologicals)
- medical devices (including in-vitro diagnostics)
- complementary/alternative medicines (including traditional, herbal remedies, etc.)

Please report especially:
- adverse drug reactions to newly marketed products
- serious reactions and interactions with all products
- adverse drug reactions which are not clearly reflected in the package insert

Report product quality problems such as:
- suspected contamination
- questionable stability
- defective components
- poor packaging or labelling
- therapeutic failures

Report even if:
- you're not certain the product caused the event
- you don't have all the details

Important numbers:

Registered Medicines and Traditional and Herbal remedies:
- phone: 021 447 1618
- fax: 021 448 6181

Investigational Products and Product Quality Problems:
- phone: 012 312 0243
- fax: 012 312 3114

Adverse Events Following Immunisation:
- phone: 012 312 0032
- fax: 012 312 3110

Confidentiality: Identities of the reporter and patient will remain strictly confidential.

Your support of the Medicine Control Council's adverse drug reaction monitoring programme is much appreciated. Information supplied by you will contribute to the improvement of medicine safety and therapy in South Africa.

SINGLE SUTURE

Smell of death in 'air from car'

For the first time, the smell of human remains could be used as evidence in court.

If the evidence is accepted, Arpad Vass from Oak Ridge National Laboratory in Tennessee will testify in the trial of Casey Anthony, who is accused of murdering her 2-year-old daughter. Vass will say that an air sample contains key chemicals given off by a decomposing body.

Vass tested air taken from the trunk of Anthony's car and concluded that it contained five of eight 'signature' chemical compounds given off by a dead body. Prior to the case, Vass had collected air samples from human cadavers as they decomposed over four years, to build a database of the key chemicals they contain. Comparing the air samples from the car with this database suggests it contained traces of human remains, Vass claims.

New Scientist, 21 May 2011, p. 4.

SINGLE SUTURE

Help dementia by shuffling chairs

Shuffling the furniture in care homes can have a positive impact on the behaviour of residents with dementia.

That's according to Louise Ritchie at the University of Edinburgh, who visited 20 care homes in the UK and found that chairs were often pushed against the walls in lounge areas, giving the rooms 'no real purpose'.

Simply shifting the furniture in seven care homes so that chairs formed small groups or faced a window, led to a 16% increase in active behaviours, such as watching TV. It also led to a 5% rise in social interaction.

Ritchie presented her findings at the British Psychological Society's annual conference in Glasgow recently.

New Scientist, 14 May 2011, p.16.