SAFETY OF MEDICINES IN ZAMBIA

A guide to detecting and reporting adverse drug reactions

Why health workers need to take action?
Introduction
The purpose of this Guide is to help health workers to participate in the very important process of continuous surveillance of safety and efficacy of the pharmaceutical products which are used in their clinical practice. Continuous evaluation of their benefit and harm will help to achieve the ultimate goal to make safer and more effective treatment available to patients.

The objectives of the Guide are to raise awareness of the magnitude of the drug safety problem and to convince health workers that reporting of adverse reactions is their moral and professional obligation. The ultimate goal of the Guide is to reduce drug morbidity and drug mortality by early detection of drug safety problems in patients and improving selection and rational use of drugs by health workers.

The Zambia Pharmacovigilance Centre (ZPVC) would be grateful to receive any comments on experience gained from the practical use of the Guide which would help in developing it further. Please contact the ZPVC with your comments:

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Definitions

**Pharmacovigilance:** The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

The related terms below are from “Safety Monitoring of Medicinal Products”:

1. An **adverse drug reaction (ADR)** is ‘a response to a medicine which is noxious (harmful) and unintended, and which occurs at doses normally used in man’.
   In this description it is of importance that it concerns the response of a patient, in which individual factors may play an important role, and that the phenomenon is noxious (an unexpected therapeutic response, for example, may be a side effect but not an adverse reaction).

2. 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’.

3. A **drug** or **medicine** is ‘a pharmaceutical product, used in or on the human body for the prevention, diagnosis or treatment of disease, or for the modification of physiological function’.

4. A **side effect** is ‘any unintended effect of a pharmaceutical product occurring at doses normally used by a patient which is related to the pharmacological properties of the drug’.
   Essential elements in this definition are the pharmacological nature of the effect, that the phenomenon is unintended, and that there is no deliberate overdose.

5. An **adverse event** or **experience** is defined as ‘any untoward medical occurrence that may present during treatment with a medicine but which does not necessarily have a causal relationship with this treatment’.
   The basic point here is the coincidence in time without any suspicion of a causal relationship.

6. A **serious adverse event** is any event that:
   - 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

7. A **signal** refers to ‘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.
The magnitude of the problem

During the last decades it has been demonstrated by a number of studies that medicine morbidity and mortality is one of the major health problems which is beginning to be recognised by health professionals and the public. It has been estimated that such adverse drug reactions (ADRs) are the 4th to 6th largest cause for mortality in the USA. They result in the death of several thousands of patients each year, and many more suffer from ADRs. The percentage of hospital admissions due to adverse drug reactions in some countries is about or more than 10%.

Norway 11.5%
France 13.0%
UK 16.0%

In addition suitable services to treat ADRs impose a high financial burden on health care due to the hospital care of patients with drug related problems. Some countries spend up to 15-20% of their hospital budget dealing with drug complications. Beside ADRs, medicine-related problems include also – drug abuse, misuse, poisoning, therapeutic failure and medication errors.

There is very limited information available on ADRs in Zambia, however, the National Drug Policy acknowledges the irrational widespread drug use in the country, including, preference for injections, antibiotics and availability of several types of medicines in homes.

In this situation one may expect the likelihood of a higher incidence of ADRs than may be on record. This problem is also caused by lack of ADR reporting. The large number of substandard and counterfeit products circulating on the Zambian market, a lack of independent information and the irrational use of drugs compound the likelihood of a higher incidence of ADRs than actually known.

Why postmarketing surveillance and reporting ADR is needed

The information collected during the pre-marketing phase of drug development is inevitably incomplete with regard to possible ADRs. This is mainly because:

- Tests in animals are insufficient to predict human safety;
- Patients used in clinical trials are selected and limited in number, the conditions of use differ from those in clinical practice and the duration of trials is limited;
- By the time of licensing exposure of less than 5000 human subjects to a drug allows only the more common ADR to be detected;
- At least 30,000 people need to be treated with a drug to be sure that you do not miss at least one patient with an ADR which has an incidence of 1 in 10,000 exposed individuals;
- Information about rare but serious adverse reactions, chronic toxicity, use in special groups (such as children, the elderly or pregnant women) or drug interactions is often incomplete or not available;
Recently the country has seen the introduction of new drugs for the management of diseases such as Malaria, TB, HIV/AIDS, for which there is insufficient safety data. It is therefore imperative to monitor the safety of these new medicines.

Thus, post-marketing surveillance is important to permit detection of less common, but sometimes very serious ADRs.

Therefore health professionals in Zambia should report on ADRs as it can save lives of their patients and others.

**Why pharmacovigilance is needed in Zambia**

There are differences among countries (and even regions within countries) in the occurrence of ADRs and other drug-related problems. This may be due to differences in e.g.:

- diseases and prescribing practices;
- treatment seeking behaviour
- genetics, diet, traditions of the people;
- drug manufacturing processes used which influence pharmaceutical quality and composition;
- drug distribution and use including indications, dose and availability;
- the use of traditional and complementary drugs (e.g. herbal remedies) which may pose specific toxicological problems, when used alone or in combination with other drugs.

Data derived from within the country may have greater relevance and educational value and may assist our regulatory authorities to make evidence-based decisions. Information obtained in one country (e.g. the country of origin of the drug) may not be relevant to other parts of the world, where circumstances may differ. Therefore, drug monitoring is of tremendous value as a tool for detecting ADRs and specifically in relation to counterfeit and substandard quality products. ADR monitoring is to help ensure that patients obtain safe and efficacious products.

The results of ADR monitoring have also a very important educational value.

**How voluntary reporting on ADRs can prevent new medicine tragedies from developing**

It took many decades before the deleterious effects of aspirin on the gastro-intestinal tract became apparent and almost as long before it was recognised that the protracted abuse of phenacetin could produce renal papillary necrosis; 35 years elapsed before it became clear that amydopyrine could cause agranulocytosis; and several years before the association of phocomelia with thalidomide became obvious.
Withdrawals from the market as a result of spontaneous reporting

<table>
<thead>
<tr>
<th>Generic Name (Brand Name)</th>
<th>Reason for withdrawal</th>
<th>Year of marketing</th>
<th>Year of withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>bromfenac (Duract)</td>
<td>serious hepatotoxic effect</td>
<td>1997</td>
<td>1998</td>
</tr>
<tr>
<td>encainide (Enkaid ®)</td>
<td>excessive mortality</td>
<td>1987</td>
<td>1991</td>
</tr>
<tr>
<td>flosequinan (Manoplax ®)</td>
<td>excessive mortality</td>
<td>1992</td>
<td>1993</td>
</tr>
<tr>
<td>temafloxacin (Omniflox ®)</td>
<td>haemolytic anemia</td>
<td>1992</td>
<td>1992</td>
</tr>
<tr>
<td>benoxaprofen (Orafl ex ®)</td>
<td>liver necrosis</td>
<td>1982</td>
<td>1982</td>
</tr>
<tr>
<td>mibebradil (Posicor ®)</td>
<td>multiple drug interaction</td>
<td>1997</td>
<td>1998</td>
</tr>
<tr>
<td>terfenadine (Seldane ®)</td>
<td>fatal cardiac arrythmias</td>
<td>1985</td>
<td>1998</td>
</tr>
</tbody>
</table>

After the “thalidomide tragedy” many countries have established drug monitoring systems for early detection and prevention of possible drug-related morbidity and mortality. Their success depends on the cooperation of the medical profession in reporting suspected ADRs, especially to new drugs.

Some examples demonstrate how very astute, alert and observant Health workers have been helped to prevent the development of drug morbidity and drug mortality by reporting on suspected ADRs which resulted in the withdrawal of dangerous drugs from the market or in restriction of their use.

Why health workers are in the best position to detect and report on ADRs

The effectiveness of a national postmarketing surveillance programme is directly dependent on the active participation of health workers. Health workers are in the best position to report on suspected ADRs observed in their every day patient care. All healthcare providers should report ADRs as part of their professional responsibility, even if they are doubtful about the precise relationship with the given medication.

You can reduce the suffering and save thousands of patients lives by doing one thing:
Report suspected adverse drug reactions.

How to recognize ADRs
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.
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 worker on drugs and their ADRs and verify if there are previous conclusive reports on this reaction. The Zambia Pharmacovigilance Centre is a very important resource 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 the district pharmacovigilance or directly to the Zambia Pharmacovigilance Centre.

What should be reported?
- For “new” drugs - report all suspected reactions, including minor ones;
- For established or well-known drugs - report all serious or unexpected (unusual) suspected ADRs;
- Report if an increased frequency of a given reaction is observed;
- Report all suspected ADRs associated with drug-drug, drug-food or drug-food supplements interactions;
- Report ADRs in special fields of interest such as drug abuse and drug use in pregnancy and during lactation;
- Report when suspected ADRs are associated with drug withdrawals;
- Report ADRs occurring from overdose or medication error;
- Report when there is a lack of efficacy or when suspected pharmaceutical defects are observed.
All drug-related problems e.g. product quality problems, suspected counterfeit products.

Thus, report all suspected adverse reactions that you consider of clinical
importance as soon as possible!

How to report ADRs?
Case Report Forms (CRF) may be obtained from the District, Provincial and Zambia Pharmacovigilance Centre. A sample of the CRF is provided in Appendix 1. However, if report forms are not available, a copy can be made from the sample provided in Appendix 1; further, verbal reports from members of the public may be accepted by a health worker who will in turn transcribe the information on to a CRF.

The completed Case Report Form should be sent to the district or provincial pharmacovigilance coordinator or Direct to the ZPVC.

Addresses: Refer Appendix 2

References

Useful Websites
WHO
www.who.int/medicines/
Section: Quality Assurance and Safety: Medicines
WHO Collaborating Centre for International Drug Monitoring (Uppsala Monitoring Centre)
www.who-umc.org

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Appendix 1  CASE REPORT FORM
Appendix 2  CONTACT ADDRESSES
Appendix 3 MANAGEMENT OF COMMON ADRs