PRINCIPLES OF
PHARMACOVIGILANCE

Dr. S. B. BHISE

NIRALI PRAKASHAN
ADVANCEMENT OF KNOWLEDGE

PRINCIPLES OF

PHARMACOVIGILANCE

For

All those interested in Drug Safety

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Dr. S. B. Bhise

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Preface

Pharmacovigilance is an emerging area for employment in recent years. Background of drugs is an advantage for anybody who wants to make a career in pharmacovigilance. Hence, pharmacists are well-suited to exploit the opportunity. The job potential is both local as well as global. Opportunities are enormous; only one has to make commitment for the career.

Hence, first book in the series on Principles of Pharmacovigilance is presented here. It will be followed by another book on Regulatory Aspects of Pharmacovigilance. The future books will depend on demand of stakeholders.

I have tried the contents of the book more informative and inclusive; however for an everchanging field like Pharmacovigilance, updates are probably a daily affair. I have attempted to make the content inclusive; however comments are welcome.

I appeal to all budding pharmacists, teachers and newcomers in the field to go through the contents and communicate constructive criticism to develop the book in coming editions.

September 2016 **Dr. S. B. Bhise**

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Introduction to Adverse Drug Reactions

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In the standard textbooks of pharmacology it is mentioned that consuming a drug is equivalent to consuming a risk. It is only when the benefit(s) associated with drug(s) are more than the risk(s), that the consumption of a drug is justified. Thus, it is the benefit vs risk ratio of the drug which decides whether a drug is to be taken or not. The next question is how to measure risks and how to measure the benefits. Due to individualization of drugs to patients, it is the clinical judgment of the physician to identify what will benefit the patient. At the same time, risk associated with the drug(s) can be ascertained by observations related to pharmacovigilance. The studies related to pharmacovigilance indicate what are possible risks associated with the drug. Every drug can be associated with possible adverse reactions, intended or unintended. The only exception to this generality is the case of drug(s) which are given in case of deficiency of specific components like vitamins or minerals. It is the study of possible adverse reactions of drugs which constitutes the essential content of Pharmacovigilance. This takes us to the definition of Pharmacovigilance.

Pharmacovigilance is a science which deals with adverse reactions to drugs. Although this meaning of the term Pharmacovigilance offers broad understanding about it, technical definition of few related terms are in place. Some important terms are defined here. Glossary of all terms is included in the Appendix.

1.1 DEFINITIONS AND CLASSIFICATION OF ADVERSE DRUG REACTIONS

1.1.1 Definitions

- **Absolute Risk**
  Risk in a population of exposed persons is the probability of an event affecting members of a particular population (e.g. 1 in 1,000). Absolute risk can be measured over time (incidence) or at a given time (prevalence).
- **Adverse Event (AE)**
  Any untoward medical occurrence that may occur 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 medical product, which is noxious and unintended, and which occurs for doses normally used in Human beings for the prophylaxis, diagnosis, or therapy of disease, or for the modification of a physiological function.
- **Attributable Risk**
  Difference between the risk in an exposed population (absolute risk) and the risk in an unexposed population (reference risk) is called attributable risk. Attributable risk is the result of an absolute comparison between outcome frequency measurements, such as incidence.
- **Effectiveness Vs. Risk**
  The balance between the rates 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.
- **Pharmacovigilance**
  The science and activities related to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.
- **Relative Risk**
  Relative risk is defined as, 'ratio of the risk in an exposed population (absolute risk) and the risk in an unexposed population (reference risk)'. Relative risk is the result of a relative comparison between outcome frequency measurements, e.g. incidences.
- **Risk**
  The probability of harm being caused; the probability (chance, odds) of an occurrence.

1.1.2 Classification of ADRs

The adverse reactions to drugs can be are classified on the basis of effects as given below:

Type A Effects:

These are the effects which are due to (exaggerated) pharmacological effects. Type A effects tend to be fairly common, dose related (i.e. more frequent or severe with higher doses) and may often be avoided by using doses which are appropriate to the individual patient. Such effects can usually be reproduced and studied experimentally and are often already identified before marketing. e.g. dryness of mouth caused by Atropine.

Interactions between drugs, especially pharmacokinetic interactions, may often be classified as Type A effects, although they are restricted to a defined sub-population of patients (i.e. the users of the interacting drug).

Type B Effects:

These occur characteristically in only a minority of patients and display little or no dose relationship. They are generally rare and unpredictable, and may be serious and are notoriously difficult to study. Type B effects are either immunological or non-immunological and occur only in patients, with - often unknown - predisposing conditions. Immunological reactions may range from rashes, anaphylaxis, vasculitis, inflammatory organ injury, to highly specific autoimmune syndromes. Also non-immunological type B effects occur in a minority of predisposed, *intolerant* patients, because of an inborn error of metabolism or acquired deficiency in a certain enzyme, resulting in an abnormal metabolic pathway or accumulation of a toxic metabolite. e.g. chloramphenicol-induced aplastic anaemia and isoniazid-induced hepatitis.

Type C Effects:

These effects refer to situations where the use of a drug, often for unknown reasons, increases the frequency of a disease. Type C effects may be both serious and common (and include malignant tumours) and may have pronounced effects on public health. Type C effects may be coincidental and often concern long term effects; there is often no suggestive time relationship and the connection may be very difficult to prove.

The adverse effects can also be classified on the basis of related cause. It is separately dealt in the section 1.3 related to causality assessment.

1.2 DETECTION AND REPORTING

1.2.1 Detection of 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 received is the medicine ordered 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 Pharmacovigilance Centre and Drug 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.

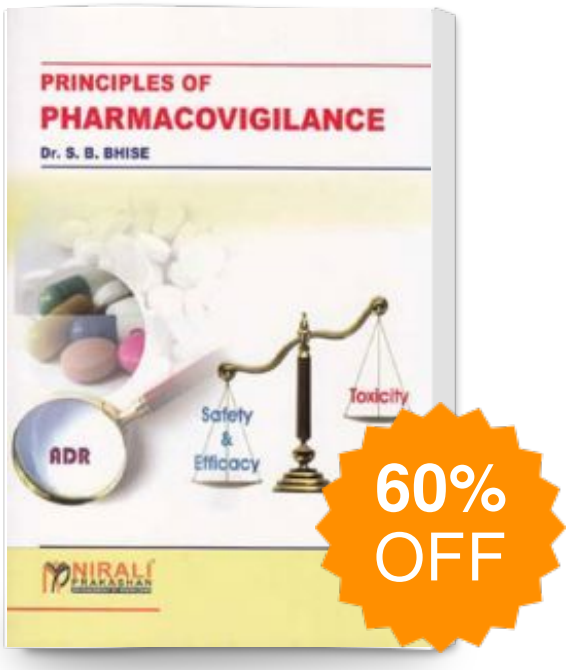
1.2.2 Reporting of ADRs

Within India, regulatory authorities have designed a format in which reports of adverse reactions are to be made. The form has been given in the appendix. There are specific instructions for filling up the form. Due to these instructions ambiguities in filling up the form are minimized. A similar form designed by USFDA is also available. The form by any regulatory authorities includes basic information about the patient, details about the suspected adverse reaction, details about all medications given to the patient, relevant laboratory data, and information about seriousness of the event is presented. Advice about what constitutes a serious adverse reaction, who can report, where the information is to be sent and what happens to the information is documented.

1.3 CAUSALITY ASSESSMENT

While reporting any adverse reaction, it is necessary to establish causal relation between the suspected drug and the observed effect. It is also possible that one of the disease process, interaction of the drug on disease process or even lack of effect of a drug exacerbating the disease process may be involved in the observed effect. In order to understand all such events, there is classification of adverse reactions based on causality. It is given below.

Principles Of Pharmacovigilance



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