Chapter First

Introduction
INTRODUCTION

The greatest of all drug disasters was the thalidomide tragedy of 1961–62. Thalidomide had been introduced, and welcomed, as a safe and effective hypnotic and anti-emetic. It rapidly became popular for the treatment of nausea and vomiting in early pregnancy. Tragically, the drug proved to be a potent human teratogen that caused major birth defects in an estimated 10,000 children in the countries in which it was widely used in pregnant women. This incidence made people aware about the importance of pharmacovigilance.1

Pharmacovigilance is the science and activities relating to detection, assessment, understanding and prevention of adverse effects or any other possible drug related problem2. There are guidelines and regulations available from Council for International Organizations of Medical Sciences (CIOMS), European Medical Agency (EMEA), US Food and Drug Administration (USFDA), Drug Controller General of India (DCGI) and others which focus on preclinical, premarketing and post marketing safety evaluations.

The need for pharmacovigilance arises from the fact that, not all adverse effects of the drugs get identified during clinical trials in the prelicensing stage and some safety hazards are only identified after wider use in the general population.2 There are differences among countries in the occurrence of ADRs (adverse drug reactions) and other drug related problems. This may be due to differences in:

- Diseases and prescribing practices
- Genetics, diet, traditions of the people
• Drug distribution and use including indications, dose and availability

• The use of traditional and complementary drugs which may pose specific toxicological problems, when used alone or in combination with other drugs

Pharmacovigilance has not picked up well in India and is in its infancy. India rates below 1% in reporting adverse event as against the world wide rate of 5%. This is due to ignorance of the subject and also lack of training of healthcare professionals in drug safety monitoring. India is heavily dependent on the data generated in other countries and advisory notes issued and regulatory actions taken by regulators elsewhere but information obtained in one country may not be relevant to other parts of world, where circumstances may differ. This makes it imperative to generate Indian data which would have greater relevance and educational value and may contribute to national regulatory decision making. Therefore pharmacovigilance is of tremendous value as a tool for detecting ADRs to help ensure that patient is getting safe and efficacious drugs.

The objectives of pharmacovigilance activities are: to collect data on medicines and suspected ADRs; to analyse the data; to keep track of the incidence and intensity of known ADRs; to examine data for signals of potential new harm; to devise policies to eliminate or mitigate risks from medicines; to ensure that such policies are implemented; and to assess the outcome of implementing them.
The elements of pharmacovigilance system are as follows:

1.1 Pharmacovigilance system

1.1.1: Methods for minimizing risks:

The first step of a pharmacovigilance system is to minimize the existing risks. This can be achieved by using various tools.

a. Training and supervision.

Standard treatment guidelines in the form of tables and charts for ease of use, mentioning contraindications, precautions, laboratory tests, specific guidelines for counseling about pregnancy testing and the use of contraception especially in relation to the menstrual cycle, could be used. All healthcare workers must be trained so that they can contribute to pharmacovigilance, risk minimization, risk assessment and documentation at programme initiation and at annual refresher courses. They could be certified after completion of training. Patients could be educated by village health workers using patient education material that highlights correct use of the drugs and provides information on the risks associated with use of the drugs.

b. Use of quality-assured medicine

Good quality medicines should be available to achieve desired therapeutic effects.

c. Safe care delivery:

(i) Use of pediatric formulation for children

Pediatric-strength capsules with a weight-banding chart to ensure correct dose calculation, and documentation of dose administration should be available.
(ii) Provision of dispensing information

Dispensing of a limited number of doses to ensure follow up and early detection of ADRs should be promoted.

(iii) Use of checklist in outpatients

Patient cards to document relevant parts of patient history e.g. menstrual history, pregnancy test results and contraceptive use in case of teratogenic drugs.

(iv) Provision of a patient-held treatment card.

An outpatient department (OPD) card with a checklist for identifying whether patients have relevant contraindications, including non-permissive laboratory test results, whether they have taken patient applicable precautions or received instruction for early detection and management of ADRs.

1.1.2: Pharmacovigilance methods for assessment of risk

a. Active surveillance:

(i) Cohort event monitoring;

Cohort event monitoring consists of prospective, observational studies in a cohort of patients for new clinical experiences (events) following exposure to the medicine. All adverse events, whether caused by a medicine (i.e. an ADR) or not, along with other relevant harms such as non-response, relapse, pregnancy, medication error and non-compliance with medication are recorded. The cohort of patients to be studied and the events to be monitored will vary from country to country depending on clinical trials already carried out in the country, healthcare facilities, capacity for pharmacovigilance and material resources.
(ii) Intensive monitoring of hospitalized patients

Patients with serious adverse reactions, non-response or relapse are referred to hospitals. All cases admitted to tertiary referral centres can be intensively monitored to record past history, ADRs and in-patient treatment.

(iii) Pregnancy registry

Pregnancy is recorded as an event as part of the cohort event monitoring study. Establishing a registry at the antenatal clinic and maternity unit with data collected regarding treatment will be useful to capture data on patients treated in the public health system as well as by private practitioners.

(iv) Deaths

As part of cohort event monitoring, all deaths will be recorded and their causes assessed by verbal autopsy. Where possible, the data will be cross-tabulated with data from governmental records of deaths. This will help capture data on patients treated in the public health system as well as by private practitioners.

b. Passive surveillance:

i) Spontaneous reporting

Spontaneous reporting is the most common method; it is easy to establish and the cheapest to run, but reporting rates are low. In districts where active surveillance cannot be done due to constraints of manpower and funds, passive surveillance can be done by spontaneous reporting using national ADR reporting forms if available, suitably modified if necessary.
ii) Focused reporting

This is a spontaneous reporting method with focus on certain drugs. For e.g. all spontaneous reports pertaining to adverse drug reactions of only pioglitazone or any anti-retroviral drug can be collected.

c. Assessing the preventability of adverse drug reactions.

Preventable drug-related harm can be assessed by studying:

- the occurrence of adverse events, and root-cause analysis of preventable drug-related harm, in the active and passive surveillance methods described above;
- surrogate markers such as pregnancy test results, compliance with contraception, early detection and instructions for failed contraception, other surrogate markers such as precautions taken for preventing ADRs (hydration to prevent nephrotoxicity) and timely referral to hospital for serious ADRs;
- the actions of health workers, e.g. prescribing a drug according to the recommendations of the guidelines (dose, duration, precautions), explaining to the patient about pregnancy testing and contraception;
- health workers’ knowledge and communication skills to inform about the risks, comprehension and compliance by patients; and
- retrospective analysis of case record forms, reports in health centres, hospitals, prospective active surveillance studies, cohort event monitoring
mentioned above and interviewing patients and health workers will all be useful in detecting preventable harm.

1.1.3: Analysis of pharmacovigilance data

Information from studies could be entered into a database using existing software such as Vigiflow and defining medicines and events according to dictionary terms in WHO-ART Adverse Reaction Terminology and WHO Drug Dictionary Enhanced (all from WHO Uppsala Monitoring Centre) as well as MedDRA, the Medical Dictionary for Regulatory Activities (from Maintenance and Support Services Organization, Chantilly, VA, USA). The pharmacovigilance officer could collate and analyse data. Subject experts and pharmacovigilance experts from the country and region could form an expert panel to review data and make recommendations. This would allow experience from studies performed for risk assessment and for testing risk minimization tools to be used to incorporate pharmacovigilance into public health programme practices. The aim will be to use the results of risk minimization and risk assessment studies and ongoing pharmacovigilance activity to improve the programme practices, to modify guidelines and to bring about regulatory changes if required.
1.2 Need for pharmacovigilance of Antiretroviral and antidiabetic therapy:

Antiretroviral therapy (ART) is the method of fighting HIV virus with drugs. It does not kill the virus but only suppresses it by slowing down growth and reproduction of the virus\(^5\). It has proven to be highly effective in the treatment of HIV/AIDS infection in industrialized countries. Antiretroviral treatment for HIV infected patients was first introduced in 1986 and zidovudine, a nucleoside reverse transcriptase inhibitor was the first drug used for the treatment\(^6\). It was observed that single drug therapy was short lived and thus later combination of 2-3 drugs was used as it gives sustained benefit. Current ART regimens available are NRTI (Nucleoside reverse transcriptase inhibitors) which includes stavudine, zidovudine, lamivudine etc, NNRTI (Non Nucleoside reverse transcriptase inhibitors) which includes nevirapine, efavirenz, protease inhibitors, fusion inhibitors and many more. In antiretroviral therapy, two NRTIs are combined with one NNRTI. As this is a combination therapy, several uncommon and serious adverse events are associated with it which include zidovudine induced anemia, stavudine induced peripheral neuropathy, lactic acidosis, hyperlactatemia, lipodystrophy, nevirapine induced rash, and other mild adverse effects including efavirenz induced nightmares, nausea, diarrhoea etc.\(^7,8\)

HIV infected patients are immunocompromised and this makes them prone to develop adverse reactions to drugs. Adverse reactions may damage confidence in antiretroviral therapy and affect patient adherence. Patients may stop taking these life-prolonging medicines leading to problems for themselves and for society as a
whole. Thus timely management of adverse drug reactions of antiretroviral drugs become essential to improve patient’s adherence towards treatment.

Antidiabetic treatment includes insulin and oral antidiabetic agents. Along with these drugs, diabetic patients generally take medications for dyslipidemia, hypertension and antiplatelet therapy. Therefore, due to administration of multiple drugs for different conditions, diabetic patients, especially the elderly ones are likely to develop adverse reactions. Adverse events associated with antidiabetic treatment are hypoglycemia, hypoglycemic coma, hepatotoxicity, drug induced erythema multiforme, photodermatitis etc\textsuperscript{9,10}.

India is a developing country and has special factors and conditions that are different from those of the developed world such as occurrence of diseases like TB, malaria, other infections, malnutrition, heavy reliance on traditional systems of medicine, absence of enough trained doctors, irrational use of drugs and medicine interactions due to which safety of drug may vary considerably. In addition, the local healthcare system is unaware of the importance of the pharmacovigilance and therefore very few studies are being performed. This has resulted in incomplete and insufficient data about possible adverse drug reactions with antiretroviral and antidiabetic drugs in the Indian population. The adverse drug reactions affect quality of life and compliance by the patients. This shows the need to study adverse drug reactions and to formulate risk minimization or risk management plans for preventable adverse reactions. Currently, there is no
such strong pharmacovigilance system in our set-up, especially in the field of antiretroviral and antidiabetic drugs.

The present study involved the establishment of a pharmacovigilance system to collect data on suspected adverse drug reactions; analyze the data; keep track of the incidence and intensity of known adverse drug reactions; examine data for signals of potential new harms; risk minimization of preventable adverse drug reactions and testing this established system by implementing a pharmacovigilance program to study adverse effects of antiretroviral therapy and antidiabetic treatment in HIV and diabetic patients respectively.