Chapter Six

Summary & Conclusions

Summary and conclusions

Pharmacovigilance has not been much developed in India. This may be due to the ignorance of healthcare professionals and also lack of training of drug safety monitoring. India is heavily dependent on the data generated in other countries, advisory notes issued and regulatory actions taken by regulators elsewhere. However, information obtained in one country may not be relevant to other parts of world where circumstances may differ. This makes it imperative upon us to generate Indian data, which would have greater relevance and educational value and may contribute to national regulatory decision making. Therefore, development of a strong pharmacovigilance system is important. The pharmacovigilance system comprises minimization of existing risks by providing training to healthcare professionals, safe care delivery of medical services, assessment of new risks by performing different methods of pharmacovigilance such as active or passive surveillance, analysis of safety data generated during pharmacovigilance methods, identifying preventable risks and development of risk minimization for such preventable risks.

The pharmacovigilance system was established by performing different studies for each component. This system was then used to develop the pharmacovigilance programme for anti-retroviral and anti-diabetic drugs at K.E.M. Hospital, Mumbai.

In the first objective, different components of the pharmacovigilance system were established. In the component of risk minimization, prescribing and dispensing

practices of teratogenic drug, i.e., isotretinoin was studied. Isotretinoin is a teratogenic drug and pregnancies exposed to isotretinoin can result into serious congenital malformations. There are different programmes available for risk management for such drugs in USA but not much attention is given in India though isotretinoin is widely prescribed by dermatologists and general practitioners. Therefore, a survey was performed to find out whether care is taken while prescribing and dispensing teratogenic drugs like isotretinoin by healthcare professionals and pharmacists in one urban and metro city in Maharashtra. A package inserts of various companies marketing isotretinoin in India were also assessed for completeness of information.

It was observed that very few dermatologists and general practitioners followed the complete procedure of performing pregnancy tests before prescribing isotretinoin. Pharmacists dispensed isotretinoin without prescription to females (including visibly pregnant female) without giving instructions of not becoming pregnant while on this drug. All package inserts mention about the need to take two prior pregnancy tests before putting any female patient on this medication; however, the patient information sheet did not mention anything about double contraception, i.e., one hormonal and the other barrier method to be followed to avoid any remote chances of pregnancy. Such ignorance by healthcare professionals put Indian women patients at risk; therefore, there is a need to educate and spread awareness among patients, prescribers, and pharmacists about the potential preventable harm from teratogenic drugs. Thus a simpler and practicable risk minimization method for married and unmarried women was

developed in which physician can avoid prescribing teratogenic drugs where other drug options can be used and the case where isotretinoin need to be prescribed, they need to interact with family members of patient to explain the precautions to be taken while on treatment.

In the component of analysis of pharmacovigilance data, National and International pharmacovigilance data was analyzed for potential signals. The spontaneous adverse drug reactions reporting forms reported under National pharmacovigilance programme were assessed for causality, seriousness, severity and entered into the WHO database by Vigiflow software. This data was assessed by WHO experts and certification for data entry into Vigiflow by WHO was done. ADR forms reported under the National Pharmacovigilance Programme were incomplete with respect to important information which led to the difficulty in carrying out the causality assessment. This is not only because healthcare professionals are unaware of the importance of ADR reporting but also due to the fact that the ADR form itself did not have columns to enter some important information required for causality assessment.

As part of the study, International safety data from African countries such as Botswana, Sudan and Zimbabwe were analyzed and entered into the WHO database. The quality of ADR forms received was average. Most of the cases had four criteria to make those cases valid but the information required to do causality assessment was missing.

It was observed that information about dechallenge and start date of the event was missing in Indian and African data and also information about the start and stop dates of co-suspects was not available, which made causality difficult. This quality issue developed could be due to less trained staff.

The content of ADR form in both India and African countries lacked some important fields. An ADR form of different countries generates a lot of discrepancy in data capture, leading to difficulty in signal detection process at the Uppsala Monitoring Centre. Therefore, there is a need to harmonise the ADR reporting forms of all the countries. This study also identified several unexpected adverse events, which need to be closely monitored to label it as potential signal.

Based on the experience of analysing and entering National and International safety data into Vigiflow, a study to perform assessment of adverse events following immunization (AEFI), development of instruction manual for AEFI data entry into Vigiflow software and training to healthcare professionals in India and Sri-Lanka were undertaken.

Vigiflow was earlier used to enter only drug-related adverse event. Special fields required to enter vaccine-related adverse events were not present in the software. Therefore, such special fields were identified and created into Vigiflow. A detailed instruction manual guide on how to enter AEFI into Vigiflow was prepared for official use for WHO and then healthcare professionals from India and Sri-Lanka were trained to enter AEFI entry into Vigiflow.

Powerpoint presentations and hands-on training were included in the training programme to make it more interactive. Hands-on training helped the participants as they encountered many practical difficulties while entering the case, which was solved readily. Different types of sample cases were asked to enter so that the participants could understand the process of data entry of a variety of cases in different scenarios. All the participants scored 50% and above in evaluation. Such trainings should be done on a regular basis for healthcare professionals for which they should be evaluated and further training should be imparted, if required.

The different components of the pharmacovigilance system were used to develop the pharmacovigilance programme for anti-diabetic and anti-retroviral drugs. The second objective was to develop a pharmacovigilance system for anti-diabetic drugs. The diabetic patients visiting the Endocrinology department in K.E.M. hospital were prospectively followed up for development of adverse drug reactions. It was observed that 38.63% of ADRs to hypoglycemic agents were preventable in nature and hypoglycemia was the commonly observed preventable ADR. The root cause analysis of ADRs showed that non-compliance of patients towards dietary instructions and wrong method of administration of insulin was responsible for the development of preventable ADRs. Although the department took all the necessary efforts to reduce preventable ADRs such as patients were provided with the necessary information about the possible adverse consequences of the treatment, proper method of administering insulin and dietary instructions to be followed while on treatment, patients were not able to understand the

instructions. Lack of comprehension and ignorance of patients could be a reason for non-compliance. Therefore short documentary should be prepared and played in OPDs giving all the information about diabetes, anti-diabetic treatment, it's possible side effects and steps to be taken in case of hypoglycemia, which could help reduce incidence of preventable ADRs.

The development of such a proper risk minimization programme consisting of patients and prescribers may reduce preventable adverse drug reactions, thereby increasing the patient's adherence towards treatment.

In the third objective, the prospective observational study was performed in which all the new and old patients attending the ART centre and taking anti-retroviral treatment were followed up for adverse drug reactions. Both active and passive surveillance methods were adopted. It was observed that the anti-retroviral therapy has many serious and life threatening adverse drug reactions that may affect a variety of organ systems. The prevalence of ADRs observed in new and old patients were 71.77% and 13.73%, respectively. This difference is because new patients were intensively monitored for ADRs. Thus, even mild ADRs were identified which might have gone unreported in old patients, where passive surveillance method were adopted. Most of the ADRs were moderately severe in nature and resulted into change of regimen. Maximum ADRs were associated with stavudine, nevirapine and zidovudine which included peripheral neuropathy, lipoatrophy, hyperlactetemia, anaemia, rash, SJ syndrome, etc.

The selection of HAART regimens was determined not only by treatment efficacy, but availability and affordability was also considered. Therefore, patients

with low haemoglobin levels started on d4T-based regimen; however, such patients should be substituted with AZT as soon as the haemoglobin reaches the normal level. Patients and healthcare providers should be adequately trained to recognize the signs and symptoms of possible d4T toxicity, including lipoatrophy, lactic acidosis and peripheral neuropathy, so that early recognition can lead to prompt treatment substitution. HIV patients on stavudine- and zidovudine-based regimens need intensive monitoring for early recognition of ADRs. Innovative treatment strategies should be established that can maximize the benefits and minimize the risk of drug toxicities for HIV-infected patients.

More studies are needed to establish the criteria to substitute and switch therapy, evaluate the best combinations for second line therapy, and direct treatment guidelines for resource constrained settings.

Active pharmacovigilance programme should be implemented and awareness should be created among physicians about reporting any suspected adverse drug reaction so that unreported ADRs and unknown risk factors could be identified and the ADR data generated will help Indian regulatory authority to take appropriate regulatory decisions which will benefit the people.