Chapter Five

Overall Discussion

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A new medicine gets approval by regulatory agencies after establishing its safety and efficacy. This safety and efficacy is measured during clinical trials and when regulatory agency gets sufficient evidences that drug will be safe and efficient in patients, they give marketing approval to the drug. The clinical trials are carried out on a sample set of people with restrictive inclusion criteria and therefore no data about safety of drug in special population like children, pregnant women, and elderly people is available before marketing of drug. Also, many delayed adverse events could not be detected in time bound clinical trials. So, to monitor the safety of medicines even after the launch to capture all the adverse reactions which are not detected during the trials and to generate safety data of drugs in special population becomes the purpose of pharmacovigilance.

The aim of pharmacovigilance is to foster the rational and safe use of medicines. After the Thalidomide tragedy in 1960, people became aware of the adverse reactions of the drugs and to study these reactions, a number of pharmacovigilance centres were established around the world. In early days, the spontaneous reporting system was used for ADR monitoring and regulatory decision making. However this method is completely dependent on the quality of ADR data and is inefficient due to the under-reporting of ADRs[2].

Pharmacovigilance is still in its infant stage in India. This may be due to ignorance and lack of awareness by healthcare professionals and lack of training about drug safety monitoring. Due to this, India does not have sufficient ADR data pertaining to local population, and we depend on the data collected in other countries. There are genetic and

environmental differences between India and other countries; therefore, regulatory decisions taken by agencies in other countries may or may not be relevant to India. Thus it is need of time to generate and maintain Indian ADR data in order to take appropriate regulatory decisions[3].

India has started its National pharmacovigilance programme in 2004 with different peripheral and regional centres under 2 zonal centers, Seth G. S. medical College & K.E.M. Hospital, Mumbai, and second one is AIIMS, New Delhi. These 2 centres collate ADR data from all over the country. Since July 2010 this programme has included medical colleges across the country to collect ADR data and to improve the size of data.[49] As a part of present research study, the pharmacovigilance system has been established by performing different studies. The developed pharmacovigilance system was then used for ADR monitoring of anti-diabetic and anti-retroviral medicines.

Risk minimization is the first objective of the pharmacovigilance system. It is essential to identify the risks and then to take corrective actions to minimize it. This was achieved with the study of the prescribing and dispensing practices of teratogenic drugs used by the prescribers and pharmacists for women of child-bearing age group. The results of this study were similar to studies carried out in developed countries which reveal that prescriptions for teratogenic medicines are given to women of child bearing age without any documentation of contraceptive counseling[48]. This becomes an important issue for the safety of Indian women for various reasons such as we do not have a strong pharmacovigilance system to keep an eye on adverse drug reactions of different drugs in special population and also the prescribers could not follow all prescribing instructions because of the unawareness among people about safe use of drug and the traditional

values followed in the country. For e.g. Physicians face a lot of difficulty to convince the families to get their unmarried daughter to do pregnancy test before prescribing the teratogenic drugs. All such factors put Indian women patients at risk but it is also one of the unavoidable facts that in a high population country like India, implementation of risk minimization programme like iPLEDGE become practically difficult. Therefore we came up with simple and feasible risk minimization method in which physician has to explain the need of performing pregnancy test to family members of the patient and also has to interact with unmarried female patient to understand whether she is planning to get married in very near future.

In addition to minimize existing risks, there was a need to establish a process which keeps on assessing any new risks so that appropriate method can be applied to minimize the risks. This was achieved by assessing the national and international pharmacovigilance data to identify any possible signals i.e. any serious expected or unexpected adverse drug reaction in which the ADR forms collected at K.E.M hospital were analyzed for causality and seriousness and they were entered into WHO database of Uppsala monitoring centre, Sweden. Similar study was performed on ADR forms collected from 3 different African countries. The signals generated through its assessment were communicated to respective countries so that they would take proper regulatory action based on the analysis of signals.

Many critical points were identified during this study. The first observation was that the assessment of adverse drug reaction was dependant on the quality of information captured on the ADR reporting form. The data obtained from spontaneous ADR reporting forms from KEM Hospital were not complete and this missing important information led

to the difficulty in carrying out the causality assessment. Most of the ADR forms were not having information about dechallenge or only information about drug withdrawn was available but whether patient recovered or not recovered was not available. This made causality as possibly related to the drug which could have been probably related if complete information would have been available.

The design of ADR reporting form is also a key factor as it is the only document which capture details of event and drugs on the basis of which further assessment of ADR is carried out. We performed a small study where we compared the important fields of ADR forms of different countries which showed that ADR forms of many countries lack fields required for assessment of ADR. The mandatory information required for causality assessment such as dechallenge was not asked in Pakistan and Australia where as rechallenge was not mentioned in Pakistan, Kenya and Australia. Indian ADR form don't have separate column for treatment of ADR. Information about action taken with the drug, outcome of the event, severity, pregnancy status were also not available on the Indian form.[51]

This shows that there is a need to harmonize the ADR reporting forms of all the countries because there is a lot of discrepancy in data capture by the existing ADR reporting forms as the design of these forms is different for different countries.[52] This incomplete data obtained results in inappropriate causality assessment of ADRs by Uppsala Monitoring centre and thus the healthcare professionals were trained to improve the quality of adverse drug reactions forms submitted at pharmacovigilance centre. The complete and uniform data received from all countries will enable WHO to draw meaningful conclusions.

It was essential to prepare some pharmacovigilance manual which would be useful for the healthcare professionals and will help to strengthen the pharmacovigilance system in India as well as in other countries. Therefore the training manual was developed to train healthcare professionals from India and Sri-Lanka to analyze and submit vaccine data in WHO database as a part of a Global network for PMS of pre-qualified vaccines, WHO. This training manual was tested in different countries like India, Sri-Lanka, Vietnam, Egypt. Out of these, India and Sri-Lanka trainings of AEFI entry into database were conducted by us. Powerpoint presentations and hands-on in training programme was used to make the training more interactive. Hands-on training proved to be useful for the participants as they encountered many practical difficulties while entering the case which were solved. Different types of sample cases were asked to enter so that participants could understand process of data entry.[54] Participants were from different background such as medical health professionals, clerk or computer operator. Therefore training was designed in such a way that it would be helpful to all of them. For example, power-point presentations on orientation to Vigiflow training, introduction to WHO UMC programme, overview of Vigiflow, coding terminologies, causality assessment of AEFI was done so that all the participants understood the database and in addition to that the medical and other health professionals also understood the AEFI coding conventions and causality specific to the AEFI.[55] This training manual was accepted by WHO to train healthcare professionals from different countries to initiate active AEFI reporting to WHO and increase vaccine safety across the globe.

After establishing different components of pharmacovigilance system such as how to identify risks by using different pharmacovigilance methods or by analyzing pharmacovigilance data and how to use proper risk minimization plan to reduce the risk, the established pharmacovigilance system was applied in endocrinology department and ART centre of KEM hospital, Mumbai. The prospective observational study was performed in diabetic patients. This study revealed that many patients developed hypoglycemia as preventable ADRs which affects compliance towards treatment. The root cause analysis of ADR showed that most of the ADRs developed because the patients were not following the dietary instructions and were not sufficiently trained to identify the hypoglycemia or the proper method of administration of insulin.

Most of the times patients were not able to understand the instructions and also physicians did not repeat the said instructions due to increased number of patients. Lack of comprehension and ignorance of patients was found to be the reason for non compliance. This problem of lack of awareness of patients and less available time to the physicians can be overcome by preparing education programme like short documentary or posters etc. which will educate the patients about every care they must take during the treatment. A similar educational documentary on Visceral leishmaniasis (VL) named as Kala Azar ki Kahani" which showed information on signs and symptoms of VL, its treatment, teratogenic effect and other adverse events to miltefosine and importance of contraception while on treatment was developed. This documentory was tested in Patna, Bihar where it was observed that patient's knowledge improved significantly after watching documentary and is accepted by WHO for the official circulation in India, Nepal and Bangladesh.

Similar pharmacovigilance system was applied to ART center of KEM Hospital. The risks of developing ADRs were identified by performing prospective observational study in new and old HIV positive patients through active and passive surveillance methods.

In active surveillance, every new patient on antiretroviral treatment was followed up for development of ADR where as in passive surveillance method, ADRs spontaneously reported by patients or their doctors were recorded. Prevalence of ADRs observed in these two groups was significantly different. Active surveillance method identified even mild ADRs which might have gone unreported in passive surveillance method. This shows that there is a great need to perform active pharmacovigilance studies in which every patient should be observed for development of ADR which will help doctors to give them the suitable and tolerable treatment. Unfortunately, it was observed that in India the selection of HAART regimens has been determined not only by treatment efficacy, but also considerations of availability and affordability which can be explained by the fact that the patients with good haemoglobin level also started with stavudine based regimen in case of zidovudine unavailability.

The low reporting rate of ADRs in passive surveillance indicates less awareness among healthcare professionals and even if some of the physicians report an ADR, they did not provide complete information required to assess the ADRs. Proper documentation of the drug safety data and continuous monitoring on ADRs of drugs is needed in countries which in turn could generate country specific data which will be helpful in good treatment outcomes.

The innovative treatment strategies should be developed so that the benefits could be maximized and the risk of drug toxicities could be minimized for HIV-infected patients.

The need of an hour is that the active pharmacovigilance programme should be implemented and awareness should be created among physicians about reporting any suspected adverse events so that unreported ADR and unknown risk factors could be identified and corrective measures can be taken.