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A REVIEW ON PHARMACOVIGILANCE; PAST, PRESENT AND FUTURE PROSPECTIVE IN INDIA

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ABSTRACT

The main responsibility of any drug regulatory authority is to ensure the quality, efficacy, and safety of all marketed products. The first two criteria can be established through data obtained from in vitro testing to ensure compliance with acceptable standards and data obtained from animal studies, preclinical and clinical trials involving humans. It is a well-established fact that pre-marketing clinical trials do not have the statistical power to detect rare adverse drug reactions (ADRs) nor do they have significant follow-up to identify delayed ADRs or effects from long-term exposure. In view of this, Pharmacovigilance plays a prominent role in establishing the safety profile of marketed drugs. Originally a modest appendix of drug regulation; it has become a major activity now.

KEYWORDS: Pharmacovigilance, adverse drug reaction, post-marketing surveillance, regulatory authorities.

DEFINITION

"Adverse drug reaction" or an "adverse reaction" means a response to a medicine in the humans or animals, which is noxious and unintended, including lack of efficacy, and which occurs at any dosage and can also result from an overdose, misuse or abuse of a medicine.

"Pharmacovigilance": As per World Health Organization (WHO), "Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems". Unfortunately, when this term is mentioned, it is very much a case of "Pharmaco what?" There is still a lack of understanding on this topic like how it functions, what are the benefits of sharing ADR knowledge and its purpose and importance.

On the other hand, the term "post-marketing surveillance (PMS) study" implies a scientifically rigorous study of a product that is approved for registration in a particular country, designed to produce reliable information about drug safety. It is not appropriate to apply the term to clinical trials of registered products or to studies designed primarily for marketing purposes regardless of the scientific validity of the study design.

Post-marketing surveillance studies are generally performed on the initiative of the sponsoring company, but may be suggested or requested by other parties. They should generally be designed to address a specific drug safety question or hypothesis (the latter often identified initially by voluntary reporting).

History and origin of pharmacovigilance

A new breakthrough in this field only happened after an episode occurring in 1937. In that year about 105 children and 71 adults were found dead after the consumption of syrup containing Sulphonamide and diethyl glycerol, where diethyl glycerol was incriminated. Sulphonamide was used since 1932 for treatment of streptococcal infection and was lowered as syrup and diethyl glycerol was added as solvent. Sulfanilamide (Prontosil), used since 1932 for treatment of Streptococcal infections, was launched as a syrup, containing diethyleneglycol as solvent. Although tested regarding, taste and odor, its safety was not evaluated before launching. This tragedy caused the American Congress to approve Food Drug and Cosmetic Act, in 1938 under which pharmaceutical product manufacturers would have to show scientific evidences of the safety of the drugs before releasing them for sale (Kulkarni, 2000).[1]

The thalidomide tragedy is a milestone in the origin and development of pharmacovigilance. Thalidomide was introduced in 1957 and widely prescribed as an allegedly harmless treatment for morning sickness and nausea. It was tested in approximately 300 patients without toxicity. It was soon linked to a congenital abnormality phocomelia, which caused severe birth defects in children of women who had been prescribed this

medicine during pregnancy. In 1962, after reports of numerous cases of phocomelia, it was discontinued (Hama, 2015).[2] In the same year, the Kefauver-Harris amendment was approved, requiring scientific evidences of efficacy and safety before drug tests in humans. As a means of pooling existing data on adverse drug reaction (ADRs), WHO's Programmed for International Drug Monitoring was started in 1968. Initially a pilot project in 10 countries with established national reporting systems for ADRs, the network has since expanded significantly as more countries worldwide developed, fallowing are chronological sequences as fallows (Allabi and Nwokirke, 2014).[3]

- 1937: Sulphanilamide disaster, where sulphonamide was dissolve in diethylene glycol leading to death of more than 100 people because of renal failure.
- 1938: The preclinical toxicity and pre-marketing clinical studies made mandatory by FDA.
- 1950: Aplastic anemia caused due to use of chloramphenicol.
- 1960: The FDA started hospital based drug monitoring program.
- 1961: Thalidomide disaster.
- 1963: 16th world health assembly recognized importance to rapid Action on ADR (Muhammad, 2016).[4]

The origin of pharmacovigilance in India goes back to 1986 formal adverse drug reaction (ADR) monitoring system consisting of 12 regional centers, each covering a population of 50 million, was proposed for India. However, nothing much happened until a decade later when in 1997, India joined the world health organization (WHO) adverse drug reaction Monitoring Programme based in Uppsala, Sweden. This attempt was unsuccessful and hence, from 1 January 2005, the WHO sponsored and World Bank-funded National Pharmacovigilance Program for India was made operational (Garlapati and Nagandla 2015)[5]

The National Pharmacovigilance Program established in January 2005, was to be overseen by the National Pharmacovigilance. Advisory Committee based in the Central Drugs Standard Control Organization (CDSCO), New Delhi. Two zonal centers-the South-West zonal centre (located in the Department of Clinical Pharmacology, Seth GS Medical College and KEM Hospital, Mumbai) and the North-East zonal centre (located in the Department of Pharmacology, AIIMS, New Delhi), were to collate information from all over the country and send it to the Committee as well as to the Uppsala monitoring centre in Sweden. Three regional centers would report to the Mumbai center and two to the New Delhi one. Each regional center in turn would have several peripheral centers reporting to it. Presently there are 26 peripheral centers. The program has three broad objectives (Preda, 2013).[6]

- The short-term objective is to foster a reporting culture.
- The intermediate objective is to involve a large number of healthcare professionals in the system in information dissemination.
- Long-term objective is for the program to be a benchmark for global drug monitoring.

Need of pharmacovigilance

1. There may be a need to monitor the effects of drugs during the clinical trials and after it in market.
2. Adverse events can even happen during the clinical trials and after its launch in the market
3. Monitor the quality of drugs.
4. Identify the health risks involved in the administration of certain drugs.
5. Prevent harm to people.
6. Research the efficacy of drugs.

Aim of pharmacovigilance

The major aims of Pharmacovigilance have been identified for human medicines (Stephens, 2000)[7]

1. Identification and quantification of previously unrecognized adverse drug reactions.
2. Identification of subgroups of patients at particular risk of adverse drug reactions, e.g. relating to species, breed, age, gender, physiological status and underlying disease.
3. Continued monitoring of the safety of a product in each species for which it is authorized, to ensure that the risks and benefits remain acceptable. This should include extension of monitoring to new indications and new species.
4. Comparing the adverse reaction profile with those of products in the same therapeutic class, both within and across species.
5. Detection of inappropriate prescription and administration, with respect to the latter, administration by specific groups, e.g. farmers or the public, may need to be monitored.
6. Further investigation of a drug or product's toxicological, pharmacological or microbiological properties in order to understand, where possible, the mechanisms underlying adverse drug reactions.
7. Detection of drug–drug interactions. This is particularly important for new drugs that are then co-administered with established products or even other new drugs.
8. Provision of appropriate information on adverse drug reaction data and drug–drug interaction information to veterinarians and others involved in the treatment of animals, e.g. veterinarians, farmers and other animal owners.

Assessment of ADR

The reports of ADRS are recorded as per the standard guidelines of Pharmacovigilance programme of India (PvPI). Causality, Severity and Types of ADR are assessed by using Naranjo Probability scale, Modified Hartwigs criteria and Rawlins &Thompson classification respectively, Seriousness of ADR is assessed by criteria given by WHO.

The causality assessment of the ADRs are done by Naranjo ADR probability scale[8]

Severity of ADRs are assessed at different levels using modified Hartwigs Criteria[9]

- Mild ADR belonged to level 1 and 2
- Moderate ADR belonged to level 3 and 4
- Severe ADR belonged to level 5 and above

Type of ADRs are identified by using Rawlins and Thompson classification[10]

Seriousness of ADRs are assessed by different criteria given by WHO[11-13] which is as follows

- Death
- Life threatening
- Hospitalization/Prolonged
- Congenital anomaly
- Disability
- Other medically important

ADR monitoring systems

Structural and Functional Aspects

The Pharmacovigilance concept rests on three pillars:

- Collecting new information from reliable scientific resources such as marketing authorization holders, healthcare professionals, consumers, international/public bodies, journals, published and updated literature, etc.
- Classifying and analyzing the above information.
- Circulating its contents as well as any action taken on specific drug to all health sectors

Four Elements of ADR Reporting

Any ADR report should have the following four main elements:

- Patient
- A drug
- An adverse reaction
- Composer/reporter of the report

Issues and Challenges Faced by Developing Countries

There is a long list of challenges faced by the developing countries.

These are as follows:

- As most drugs are developed in the West, most of the efficacy data are based on the Caucasians, with little or no information available on the Asians.

- There is no data on ADRs that may occur due to the interaction between the established medicines and traditional, herbal medicines and vaccines used locally.

- ADR reporting for traditional and herbal medicines, especially the multicomponent and adulterated ones is not done seriously and reports present are negligible.

- Attrition from local manufacturers who usually manufacture generics in carrying the burden of Pharmacovigilance when innovator products are taken off the market for economic reasons. In addition, most of them do not care to invest in ADR monitoring, as they believe they deal with off-patent products. But ADRs associated with generics although less in frequency, can still arise.

- It may require structural and policy changes within the drug regulatory authorities.

- Moreover, a lot of sensitization and setting up of new systems will consume resources such as good labs, patient's ability to pay for tests, infrastructure for proper causality assessment, identification of funding agency and certainty of funding, etc.

Success Factors

The success of any Pharmacovigilance system depends upon the following factors:

- Public awareness on need to report suspected ADRs.
- Government support and well-defined policies with proper financial assistance.
- Presence of national coordinator and an advisory committee.
- Trained healthcare workers.
- Quality control of laboratories.
- Free and open communication between public and the policy makers.
- Ability to have free flow of information, i.e. inquiries, feedback, etc

The National Pharmacovigilance Program will have the following milestones:

- **Short-term objectives**: To foster a culture of notification.

- **Medium-term objectives**: To engage several healthcare professionals and Non-Government Organizations (NGOs) in the drug monitoring and information dissemination processes.

- **Long-term objectives**: To achieve such operational efficiencies that would make Indian National Pharmacovigilance Program a benchmark for global drug monitoring endeavors.

  Periodic Safety Update Reports shall be expected to be submitted every 6 monthly for the first 2 years of marketing in India, and annually for the subsequent 2 years.

In addition, training programs and interaction meetings shall be held every 6 months after the initial training.

All data generated (including reporting forms) will be stored and preserved for the purpose of archiving for a minimum period of 5 years at the ZPCs. The reporting of

seemingly insignificant or common adverse reactions would be important because it may highlight a widespread prescribing problem.

Pharmacovigilance programme in india

In 1986, a formal adverse drug reaction monitoring system having 12 centres was proposed and there was no development and special attention on the Pharmacovigilance activity. (Camacho, 2016)[14] In the year 1997, India.

Participated in WHOs adverse drug reaction Monitoring Program organized at Uppsala-Sweden. This participation was not sufficient to promote Pharmacovigilance activity. Hence, on 14th July 2010 the Government of India started the Pharmacovigilance Program for India (PvPI). As part of PvPI, All India Institutes of Medical Sciences (AIIMS), New Delhi selected as National Coordinating Centre (NCC) to safe-guard public health by validating the safety of products. About adverse drug reaction monitoring centres were established in the year 2010 (Fujimoto, 2014).[15]

The NCC was transferred from AIIMS, New Delhi to IPC and Ghaziabad on 15th April 2011 for smooth and efficient functioning of program. Selected eligible medical colleges, hospitals and centres were approved as adverse drug reaction Monitoring Centres (AMCs). These AMCs collect the Individual Case Safety Reports (ICSRs), analyses and report it to regulatory authority. Till January 2017, 250 AMCs (government and non-government) have been established under PvPI. About 20 Anti-Retroviral Therapy (ART) and 17 Revised National Tuberculosis Program (RNTCP) centres were also established for spontaneous adverse drug reaction reporting. The technical associate from Medical Sciences, Banaras Hindu University is an authorized person for collecting ICSRs along with its follow up and online database entry in Vigi-Flow software.

All the primary health care centres (PHCs) and community health centres (CHCs) submit their adverse drug reaction reports to the regional centre. It was considered that the remedies from natural source are safe and devoid of adverse drug reaction. But "Charka Samheta", which is the heart of ayurveda illustrates that ADR can occur with herbal drugs also if they are compounded and dispensed inappropriately. Hence, to put PV for Ayurveda, Siddha, Unani (ASU) was highly essential to provide ADR data of AYUSH drugs as per WHO guidelines (Srivastava, 2011).[16]

Current scenario of pharmacovigilance

India is a vast country and there is a drug brand more than 6,000 licensed drug manufacturers and over 60,000 branded formulations. India is the fourth largest producer of pharmaceuticals in the world and is also emerging as a hub for clinical trials. Many new drugs are being introduced in the country, so there is an immense need to improve the pharmacovigilance system to protect the Indian population from potential harm that may be caused by some of the new drugs (Yerramili, 2014).[17] In the past, India's regulatory agencies and drug companies based their safety assessments on experiences derived from long-term drug use in the Western markets and there was no real urgency for the government to establish a strong pharmacovigilance system of its own. In recent years, however, the lag between when a drug is placed in the market and its subsequent availability in India has decreased considerably so that the much needed longer-term safety data is no longer available. In addition, India-based drug companies have increased their capacity to develop and launch new drugs through their own research efforts and this has heightened the importance of developing adequate internal pharmacovigilance standards to detect adverse drug events (Mishra *et al*., 2013).[18]

Inspections in all pharmaceutical companies operating in India all pharmaceutical companies should be instructed to maintain and submit to the DCGI the Summary of Pharmacovigilance System document operating within the company, which would serve as the base for future pharmacovigilance inspections. A high-level discussion with various stakeholders, i.e., Ministry of Health and Family Welfare (MHW), Indian Council of Medical Research (ICMR), Medical Council of India (MCI), Pharmacy Council, Nursing Council, Dental Council, Pharmaceutical Companies, Consumer Associations, Nongovernmental Organizations (NGOs) and Patient Groups should be initiated in order to make them aware of how the drug control general of India (DCGI) is planning to improve and develop a robust system in pharmacovigilance Strengthen the DCGI office with trained scientific and medical assessors for pharmacovigilance Intensive training should be given in all aspects of pharmacovigilance to officials working within the pharmacovigilance department of the DCGI and in the peripheral, regional and zonal centers. This should be an ongoing activity with training scheduled twice a year. Creating a single countrywide specific adverse event reporting form to be used by all (Salim. 2015).[19]

A single countrywide specific adverse event reporting form needs to be designed should not only be used by the National Pharmacovigilance Centers, but also by all registered hospitals (both private and government), teaching hospitals, Drug Information Centers and pharmacies throughout the country. It should also be made available to all primary healthcare centers (PHCs) in rural areas and all practicing general practitioners and physicians. Creating a clinical trial and post-marketing database. ADRs for signal detection and access to all relevant data from various stakeholders' full complete data should be made available to the DCGI and to the various stakeholders from the date of first registration of the clinical trial in the India.

This data should comply with consolidated standards of reporting trials guidelines including overall benefit-risk profile of the product. Current standards of safety reporting as outlined in Schedule and information about all adverse events (AEs) and adverse drug effects (ADRs) per study arm should be systematically included as well as detailed description of cases with previously unknown adverse events (AEs) adverse drug effects (ADRs) and the reasons for study withdrawals, for drugs already in the market, type and frequency of all adverse events (serious and non-serious) should be submitted in periodic safety update reports (PSURs) and also added to the summary of product characteristics (SPCs).

List all new drug indications by maintaining a standard database for every pharmaceutical company a list should be maintained by the regulatory authorities and pharmaceutical companies for all new drugs indications in the database. All new issues need to be put under heightened surveillance. Pharmaceutical companies in these circumstances should have meetings set up with the DCGI to outline their risk management plan (RMP) for the safety issues in question and describe how they would put effective strategies in place to mitigate the Education and training of medical students, pharmacists and nurses in the area of pharmacovigilance (Elhassan, 2015).[20]

There are several courses conducted by various organizations focusing in clinical research, but to date there is no course relevant to pharmacovigilance in the country. The various stakeholders including the MCI should incorporate a pharmacovigilance syllabus within the pharmacology and medicine curricula so that proper theoretical and practical training can be imparted to physicians. Similarly, nurses and pharmacists should also be trained in pharmacovigilance so that they are able to recognize adverse drug reaction (ADRs) and develop a culture of reporting ADRs in the future. An awareness program and a training schedule (both by distance education and face-to-face learning) covering all aspects of pharmacovigilance.

These are meant for the research and development (R and D)-based pharmaceutical companies, particularly those involved in new drug research, the medical profession, the pharmacists and chemist-druggist trades and the patients, to be alert in detecting ADRs and reporting them to the Indian regulatory agencies, who in turn will investigate and take timely corrective action. Collaborating with pharmacovigilance organizations in enhancing drug safety with advancements in information technology (IT), there has been the emergence of new opportunities for national and internationals collaborations that can enhance post-marketing surveillance programs and increase drug safety. The Uppsala Monitoring Center (UMC) is an example of an international collaboration to establish a harmonized post-marketing surveillance database. The system is based on the exchange of adverse reaction information among national drug monitoring centers in 80 countries. The information is transferred, stored and retrieved in a timely and secure way through the internet (Allabi and Nwokirke, 2014).[21]

The UMC database collectively contains over four million records with a large number of data fields. A similar database can be built for the DCGI with the help of experienced private firms from the safety data received from clinical trials and post-marketing surveillance. Building a network of pharmacovigilance and pharmacopeidemiologists in India core group of experts will need to be formed which will have representatives from multinational corporations (MNCs), Indian pharmaceutical companies and personnel from the regulatory authority (DCGI). Interaction with the IT sector in building a robust pharmacovigilance system for India Software programs developed can be used for collection and analyses of data sets, determining trends of drug usage in various disease areas, compliance, medication errors and drug interactions leading to ADRs (Patil, 2014).[22]

Future prospects

As future prospects increase, PV systems capable to detect new ADRs and taking regulatory actions are needed to protect public health. Little emphasis has been put into generating information that can assist a healthcare professional or a patient in the decision-making process. The gathering and communication of this information is an important goal of PV Information about the safety of drug active surveillance is necessary. When develop new methods for active post-marketing surveillance, one has to keep in mind that the important to collect complete and accurate data on every Serious reported event. Spontaneous reporting is a useful tool in generating signals, but the relatively low number of reports received for a specific association makes it less useful in identifying patient characteristics and risk factors PV methods must also be able to describe which patients are at risk of developing an adverse drug reaction (ADRs). As a source of information, the PV approach would be consistent with the growing patient involvement in drug safety (Flower, 2013).[23]

The PV could play a role in identifying individual risk factors for the occurrence of certain ADRs. In the future, PV has to concentrate on the patients as a source of information in addition to the more traditional groups, such as the health professionals. At present, the DCGI should act quickly to improve PV so as to integrate Good Pharmacovigilance Practice (GPP) into the processes and procedures to help ensure regulatory compliance and enhance clinical trial safety and post marketing surveillance. An appropriately working PV system is essential if medicines are to be used carefully. It will benefit healthcare professionals, regulatory authorities, pharmaceutical companies and the consumers. It helps pharmaceutical companies to monitor their medicines for risk. Post-marketing PV is currently a challenging and

laborious process, not only industry-wide, but also for regulatory agencies (Ghewari, 2014).[24]

The aim of the PV is to receive the information, documentation of the work and knowledge online while giving priority to the new and important safety issues. Non-serious events have less priority than serious events but important in comparing the changes in health, although they are also screened routinely in present time, GlaxoSmithKline has created a powerful new approach to Pharmacovigilance (PV), integrating traditional, case-based PV methods with disproportionality and data visualization tools. (Borja-Oliveira, 2015)[25]. These tools exist within a system framework that facilitates in-stream review, tracking of safety issues and knowledge management. This very innovative tool and the processes will help to advance PV by improving efficiency and providing new analytical capabilities. Similar approach may be adopted by pharmaceutical companies for prompt detection and analysis of ADRs. Transparency and communication would strengthen consumer reporting, which are positive steps towards involving consumers more in PV (Kalaiselvan, 2014).[26]

CONCLUSION

In India Pharmacovigilance (PV) system has increased awareness in people regarding ADR reporting. The issues of underreporting are resolving due to available reporting facilities like toll free dial number, message, mail and ADR form in vernacular languages. Various multinational companies have started the outsourcing of PV activity in India which is creating the good Pharmacovigilance (PV) culture. Various universities have incorporated PV courses in their curriculum as compulsory or elective subject. Still government needs to focus on the awareness and enhancement. Pharmacovigilance is comes under drug safety reporting and post marketing surveillance.

In this pharmacovigilance we can report the adverse drug events for efficacy of the drug product. Drug safety associate can investigate the case and reported to the drug regulatory affairs. Many pharmaceutical companies across the globe will maintain this pharmacovigilance reports. Pharmacovigilance is key for maintaining the drug safety.

India is now considered to be a hub for clinical research. The drug control general of India (DCGI) has shown its commitment to ensure safe use of drugs by establishing the National Pharmacovigilance Program. More and more clinical trials are now being conducted in India and business process outsourcing (BPOs) based in India are now also undertaking pharmacovigilance projects from multinational corporations (MNCs). Healthcare professionals, consumer groups, nongovernment organization (NGOs) and hospitals should appreciate that there is now a system in place to collect and analyze adverse event data. They should start reporting adverse events actively and participate in the National Pharmacovigilance Program to help ensure that people in India receive safe drugs. With the help and proper coordination of all stakeholders, we can definitely build a world class pharmacovigilance system in India.

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