ABSTRACT

Pharmacovigilance is an integral part and important for clinical research. It continues to play a crucial role, the challenges by the ever increasing range and potency of medicines. Medication safety requires that each drug should be monitored throughout its market life as early detection of its adverse reactions and lead to alerts that prevent patient harm. While big advancements of the discipline of pharmacovigilance have taken place in the west, not abundant has been accomplished in India. However, with more clinical research and clinical trials activity being conducted in India, there is an immense need to understand and implement pharmacovigilance. In India, pharmacovigilance has progressed from the situation as it was in past, but for different types of problems and limitations progress is yet not very rapid. Therefore awareness is required for improvement of pharmacovigilance as well as public health. This review is aimed to offer an analytical study of current problems and future aspects of pharmacovigilance in India. The necessity of implementation of appropriate pharmacovigilance, its requirements, problems, limitation and the process how it can be more improved have been emphasized. Even admitting pharmacovigilance is still in its adolescence in India, it is not new to India and still there exists actual bound ability about the discipline.

KEYWORDS: Pharmacovigilance, Pharmacovigilance in India, Future prospective of pharmacovigilance in India.

INTRODUCTION

Pharmacovigilance (PV) or Drug Safety is the branch of pharmacological science. This deals
with the collection, detection, assessment, monitoring and prevention of adverse effects of pharmaceutical products.\[^1\] The etymological origins for the pharmacovigilance are: Pharmakon = drug in Greek language, Vigilare = to keep watch in Latin and as per WHO, pharmacovigilance (PV) is defined as the sciences and activities, connecting to the finding, evaluation, understanding and prevention of adverse effects or any other drug-related problem.\[^2\] Before a product is marketed, experience of its safety and efficacy is limited to its use in clinical trials, which do not reflect practice conditions as they are limited by the patient numbers and duration of trial as well as by the highly controlled conditions in which clinical trials are conducted.\[^3\]

**Pharmacovigilance in India**

In India, according to the Medical Council of India (MCI), the total number of registered doctors in this country is 9,36,488 as on 31 December, 2014 and up to 20 November, 2015. A total number of hospitals are 18,365, having bed strength of 8,24,000. India is the fourth largest producer of pharmaceuticals in the world. It is also emerging as an important clinical trial hub in the world. Many new drugs are being introduced in our country after clinical trials. Therefore, there is a need for an active pharmacovigilance system in the country to protect the population from the potential harm that may be acquired by some of these new drugs. Clearly the awareness of abomination of Central Drugs Standard Control Organization (CDSCO) has initiated a well-structured and awful participative national pharmacovigilance programme. It is abundantly based on the recommendations made in the WHO document titled “Safety Monitoring of Medicinal Products – Guidelines for setting up and running a pharmacovigilance center”.\[^4\] The national pharmacovigilance programme was officially inaugurated by the Honorable Health Minister Dr. Anbumani Ramadoss on 23 November 2004 at New Delhi.\[^5\]

**Aims of pharmacovigilance**

1. Patient care and safety in relation to the use of medicines, all medical and Para medical interventions should improve.\[^6\]

2. Research the ability of drug and by monitoring the adverse effects of drugs right from the lab to the pharmacy and then on for many years.

3. Pharmacovigilance keeps track or clue of any drastic effects of drugs.

4. Improve public health and safety in relation to the use of medicines.

5. Contribute to the appraisal of benefit, harm, capability and risk of medicines, encouraging
their safe, rational and more effective (including cost effective) use.\[6\]

6. Promote understanding, education, clinical training in pharmacovigilance and its effective communication to the public.

7. The identification and quantification of ahead unrecognized adverse drug reactions (ADR), also identification of sub-groups of patients at particular and accurate risk of ADRs (the risk relating to dose, age, gender and basal disease).\[7\]

8. The connected monitoring of the safety of a product, throughout the continuance of its use, to ensure that its risks and benefits remain acceptable. This includes safety monitoring following significant newly approved indications.

9. The comparative adverse drug reaction profile of products within the same therapeutic class.

10. The detection of inappropriate prescription and administration.

11. The further elucidation of a product’s pharmacological/toxicological properties and the mechanism by which it produces adverse drug reactions.

12. The detection of significant drug–drug interactions between new products and co therapy with agents already established on the market, which may only be detected during widespread use.

These processes involved in the clinical development of medicines. Once these put onto the market, a medicine leaves the secure and protected scientific environment of clinical trials and is legally set free for consumption by the general population. At this point a lot of medicines will only have been tested for short-term safety and efficacy on a limited number of carefully selected individuals. In some cases as few as 500 subjects, and rarely more than 5000, will have received the product prior to its release.\[8\] In short, pharmacovigilance aims to improve patient care and safety, public health, assessment of benefit, harm, effectiveness and risk of medicines, promotes understanding, education, apprenticeship and clinical training.

**Importance of pharmacovigilance**

The Importance of pharmacovigilance mainly as follows.\[9\]


2. Drug monitoring.

3. Pharmaceutical preparations - adverse effects.

4. Adverse drug reaction reporting.

5. Product surveillance, Post marketing.

If a pharmaceutical drug is introduced in the market there are still a lot of things that are alien about the safety of the new drugs. These medicines are used by various patients for different types of diseases. People might be using several other drugs and must be following different traditions and diets which may abnormally affect the impact of medicine in them, also the different brands of same medicine might differ in the manner of their production and ingredients. To prevent all undue physical, mental and financial suffering by patients, pharmacovigilance proves to be an important monitoring system for the safety of medicines in a country by the support of doctors, pharmacists, nurses and other health professionals of the country.

Steps involved in pharmacovigilance programme

The specific aims of the pharmacovigilance programme

Contribute to the regulatory appraisal of benefit, harm, capability and risk of medicines, encouraging their safe, rational and more cost effective use.

- Improve patient care and safety in affiliation to use of medicines and all medical and paramedical interventions.
- Improve public health and safety in affiliation to use of medicines.
• Promote understanding, education and clinical training in pharmacovigilance and its more effective communication to the public.

The programmer aims to advance the ability of ADR notification in its first year of operation and afterwards aims to accomplish abounding based ADR data on the Indian population and allotment the information with global health-care community through WHO-UMC. Beneath the program 26 peripheral centers, 5 Regional Centers and 2 Zonal Centers were established. The Peripheral centers will record the adverse events (AE) and forward to the regional centers. They in about-face collate and scrutinize the data received from the peripheral centers and submit to the zonal centers. Data analysis and submit consolidated information to the national pharmacovigilance centre from the zonal centers. The zonal centre will also provide training, general support and coordinate the functioning of the regional centers. Pharmacovigilance is still in its adolescence in India and there exists very limited knowledge about the discipline. While major advancements of the conduct of pharmacovigilance have taken place in the western countries, not abundant has been achieved in India.[4]

India joined the World Health Organization (WHO) Adverse Drug Reaction Monitoring Programme based in Uppsala, Sweden in 1997. Three center’s mainly based in teaching hospitals were identified for ADR monitoring a national pharmacovigilance center located in the Department of Pharmacology, All India Institute of Medical Sciences (AIIMS), New Delhi and two special centers of WHO in Mumbai as KEM Hospital and Aligarh (JLN) Hospital, Aligarh Muslim University, the major role of these center were to monitor ADRs to medicines marketed in India. But this attempt was unsuccessful and hence, again from the 1st January, 2009, the WHO sponsored and world’s Bank funded National pharmacovigilance Program (NPP) for India was made operational.[10] The objectives of National pharmacovigilance Program were to absorb a large number of health care professionals in the process, inculcate the culture of reporting ADRs and to be a land mark for global drug monitoring.[10,11,12]

Current problems of pharmacovigilance in India
There are many current problems of pharmacovigilance in India. Which are as follows.[13]
1. Cardiovascular assurance of NSAIDs and selective COX-2 inhibitors.
2. Cardiac arrhythmias associated with antipsychotic drugs.
3. CosmoFer and top accident of anaphylactoid reactions.
5. Drotrecogin alfa (activated) (Xigris): risk benefit in the administration of sepsis.
6. Erythromycin and added macrolides: focus on interactions.[14]
7. Glucosamine adverse reactions and interactions.[15]
8. High dosage inhaled steroids: new admonition on accumulation of steroid treatment card.[16]
9. HRT and tibolone (Livial): amend on the accident of endometrial cancer.
10. Hypoglycaemia blindness on appointment insulin.
11. Intravenous human accustomed immunoglobulin (IVIg) and thromboembolic adverse reactions.
12. Isotretinoin (Roaccutane): psychiatric adverse reactions.
14. Local reactions associated with pre-school d/DTap-IPV boosters.
15. Osteonecrosis of the jaw with bisphosphonates.
16. Risk of QT breach assiduity with methadone.[17]
17. Rosuvastatin (Crestor): addition of 5 mg starting dosage.[18]
18. Salmeterol (Serevent) and formoterol (Oxis, Foradil) in asthma administration.[19]
19. Tamsulosin (Flomax) and Intraoperative Floppy Iris Affection (IFIS).[20]
20. Tenofovir (Viread): interactions and renal adverse effects.
21. Topical tacrolimus (Protopic) and pimecrolimus (Elidel): potential cancer risk.
22. NSAIDs and infertility.
23. Withdrawal of co-proxamol.[21]

Causes of failure of implementation of pharmacovigilance in India

The studies conducted throughout the world have demonstrated that the ADRs significantly abatement the quality of life, increase hospitalizations, prolong hospital stay and increase mortality.

A landmark study by Lazarou in 1998 described ADRs to be the 4th to 6th largest cause of death in the USA and ADRs are estimated to cause 3-7% of all hospital admissions.[22] More than half of these ADRs are not accustomed by the physicians on admission and ADRs may be responsible for death of 15 of 1000 patients admitted.[23] Furthermore, the financial cost of ADRs to the healthcare arrangement is also huge. With added new medicines being approved for marketing more quickly afterwards long-term safety studies by the regulatory authorities
and switching of prescription-only medicines (POM) to over-the-counter (OTC) to be acclimated more widely by patients for self-medication, the accepted general public is at risk of exposing itself to ADRs. In the past, Indian regulatory agencies and drug companies based their safety assessments on experiences acquired from long-term drug use in the western markets and there was no absolute 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 on the market and its subsequent availability in India has decreased appreciably so that the much needed longer-term safety data is no best available. In addition, India based drug companies have increased their capacity to develop and barrage new drugs through their own research efforts, has acute the importance of developing able internal pharmacovigilance standards to detect adverse drug events.\cite{24} Therefore, what needs to be more important forth with the funding is a focused vision and effective action for developing the pharmacovigilance systems, especially in the Drug Controller General of India Office, which is lacking. Traditionally, pharmacovigilance was never done in India in Pharmaceutical companies, be it Indian or MNCs, however, there is an immense shortage of knowledgeable people who will be able to advice the Drug Controller General of India on this matter, as pharmacovigilance is a very complex subject, intertwined with regulations and complex systems. The need is accordingly to engage a completely independent adviser who has an all-encompassing and practical knowledge on pharmacovigilance, who can act as a pharmacovigilance advisor to the Government of India to effectively implement the systems and behavior on pharmacovigilance. This will help the Drug Controller General of India to super-head the activities and implementation of pharmacovigilance. India is a vast country and there is a bellyful of drug brands-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 as well emerging as a clinical trials hub. Abounding 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 acquired by some of the new drugs. However, there are many issues and problems that accept prevented building a robust pharmacovigilance system, which are described following.\cite{4}

1. Pharmacovigilance systems are not well funded and organized for an all-inclusive country like India to serve patients and the public.

2. The information acquired to date in the zonal centers from various peripheral centers is generally poor and not well-analyzed. There is bereft research on ADRs in India, so the
exact incidence of specific ADRs is not known.

3. Understanding by healthcare professionals (both in rural and urban cities and hospitals) and ability and motivation for pharmacovigilance is about negligible. There is hardly any advance from the department of health to provide more specific training and create more awareness amongst them for better reporting.

4. In India, there are several consumers' groups who animate patients to report any adverse reactions encountered by them, although there is no information for patients to report ADRs directly to the regulatory authority.

**Future prospective of pharmacovigilance in India**

There is an immense need to understand the importance of pharmacovigilance and how it impacts the life cycle of the product, with more and more clinical trials and other clinical research activities being conducted in India. In this situation at present, the DCGI should act quickly to improve pharmacovigilance so as to accommodate Good pharmacovigilance Practice into the processes and procedures to help ensure regulatory compliance and enhance clinical trial safety and post marketing surveillance of drugs. Appropriately the working of pharmacovigilance system is essential if medicines are to be used safely. It will account all parties including healthcare professionals, regulatory authorities, pharmaceutical companies and the consumers. It helps pharmaceutical companies to monitor their medicines for risk and advice to implement effective risk management plans to save their drugs in difficult circumstances.\(^4\) Accepting advised the problems and challenges adverse the development of a robust pharmacovigilance system for India.

The following proposals ability is as follows

1. Building and maintaining a robust pharmacovigilance system.
2. Making pharmacovigilance reporting mandatory and introducing pharmacovigilance inspections time to time without intimations.
3. High-level discussions with various assorted personnel.
4. Strengthen of the DCGI office with trained scientific and medical assessors for pharmacovigilance.
5. Creating an individual country-specific adverse event reporting form to be acclimated by all.
6. Creating a specific clinical trial and post marketing database for SAEs/SUSARs and ADRs for signal detection and access to all accordant data from various stakeholders. List
all new drugs/indicated by maintaining a standard database for every pharmaceutical company.

7. Training and education of medical students, pharmacists and nurses in the area of pharmacovigilance.

8. Collaborating with pharmacovigilance organizations in acceptable drug safety with advancements in IT, there has been the actualization of new opportunities for national and international collaborations that can enhance post-marketing surveillance programs and increase drug safety.[25]

9. The Uppsala Monitoring Center (UMC) is an international collaboration to establish a harmonized post marketing surveillance database.[26]

10. Building a network between pharmacovigilance and pharmaco-epidemiologist in India.

CONCLUSION

In India, according to the Medical Council of India (MCI), the total number of registered doctors in the country is 9,36,488 as on 31 December 2014 and as on 20 November 2015, a total up to 18,365 hospitals, having bed strength of 8, 24,000.

India is fourth largest producer of pharmaceuticals in the world. It is emerging as an important Clinical trial hub in the world. Many new drugs are being introduced in our country. Therefore, there is a need for an active pharmacovigilance system in the country to protect the population from the potential harm that may be caused by some of these new drugs.[4] In recent USFDA announced safety warning on rosiglitazone, a drug approved to treatment for Type 2 diabetes. On 23rd May, The New England Journal of Medicine rushed out an analysis by prominent cardiologist Steven Nissan, of data about patients taking Avandia (rosiglitazone manufactured by GSK). It suggests that have a 43% higher chance of suffering a heart attack.[4]

We beforehand had Vaux, which created serious adverse events in patients taking this drug. This popular painkiller went on the market in 1999, in the same year as Avandia. The same scientist, Nissan, aloft some of the earliest concerns that tied Vaux to higher rates of heart attack and stroke. Afterwards Merck finally pulled Vaux off the market in 2004. The FDA whistle blower testified that the agency had bootless to heed abounding warnings. These examples show that after FDA certifies new drugs as safe and able based on clinical trials, adverse effects can show up when millions use them. Vaux acquired such problems. So, perhaps, has Avandia. In the further testifies the urgent need of a pharmacovigilance program
in India for even generic drugs which are already marketed abroad in the world. Pharmacovigilance has not best up able-bodied in India and the accountable is in its infancy. The rates in India below 1% in pharmacovigilance as against the world rate of 5%. This is due to ignorance of the subject and also lack of training. The office of the Drugs Controller General of India has attempted to apparatus a pharmacovigilance program in India afterwards much success. A regulation is must require to implement the system of reporting adverse events of drugs introduced in the Indian market by pharmaceutical companies. The government has to play an important role in ensuring the availability of safe medicines to the country.[27]

The apperception set of all including the bureaucrats and politicians and healthcare professionals need to be changed. The politicians and bureaucrats need must to support with full powers to the DCGI and the professionals. The deals of Zymogen with all aspects of pharmacovigilance and has also started functioning in India. With the help of all stakeholders, let us agreement to make this happen in India and build a world-class pharmacovigilance system and safe more life from new drug toxicity tragedy.

REFERENCES