

Pharmacovigilance - A Review

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ABSTRACT

Pharmacovigilance is an important and integral part of clinical research. Despite its 40 years history, pharmacovigilance remains a dynamic clinical and scientific discipline. It continues to play a crucial role in meeting the challenges posed by the ever increasing range and potency of medicines. When adverse effects and toxicity do appear especially, when previously unknown, it is essential that these are reported, analysed and their significance communicated effectively to an audience that has the knowledge to interpret the information, which carry an inevitable and some for all medicines there is a trade-off between the benefits and the potential for harm. The harm can be minimized by ensuring that medicines of good quality, safety and efficacy are used rationally and that the expectations and concerns of the patient are taken into account when therapeutic decisions are made. Taking medicines and prescribing them are among the commonest of activities of people who are unwell and of those who care for them. It makes sense that those medicines should be monitored to equally demanding standards as those evident in the development and evaluation of drugs and that prescribing habits and the extent of rational and cost-effective use should be reviewed. Responsibility for the holistic approach to drug safety that is encompassed in the science and practice of pharmacovigilance as reflected in this article has to be shared if ideal practice is to be achieved. The scientists, clinicians, pharmaceutical manufacturers, drug developers, regulators, public policy makers, patients and the general public all have their own complementary roles in achieving what is envisaged.

Keywords: Pharmacovigilance, National Pharmacovigilance Programme, Role of Pharmacovigilance, Pharmacovigilance Practice.

I. INTRODUCTION

The World Health Organization (WHO) defines pharmacovigilance as the science and activities relating to the detection, evaluation, understanding, and prevention of adverse reactions to medicines or any other medicine-related problems. The definition and scope of pharmacovigilance have evolved to recognize the importance of a systems approach for monitoring and improving the safe use of medicines.¹

Pharmacovigilance is a very important and inseparable part of clinical research. Both clinical trials safety and post-marketing pharmacovigilance (Popularly known as Post marketing studies or Phase IV clinical trials) are critical throughout the product life cycle. With a reasonably high number of recent high-profile drug

withdrawals, both the pharmaceutical industry as well as various regulatory agencies across the globe has raised the bar. Early detection of signals from the post-marketing surveillance studies and clinical trials in early phases have now been adapted by major pharmaceutical companies in order to identify the risks associated with their medicinal product/s as early as possible. If any such risk is present then effectively managing the risks by applying robust risk management plans throughout the life cycle of the product is adopted. These risk management plans are also widely known as Risk Minimisation Programmes/Strategies.²

II. METHODS AND MATERIAL

A. Story of Pharmacovigilance in India

It was not until 1986 that a formal adverse drug reaction (ADR) monitoring system consisting of 12 regional centres, each covering a population of 50 million, was proposed for India.² In 1997, India joined hands with the World Health Organization (WHO) Adverse Drug Reaction Monitoring Programme based in Uppsala, Sweden. Three centres for ADR monitoring were identified, mainly based in teaching hospitals : A National Pharmacovigilance Centre located in the Department of Pharmacology, All India Institute of Medical Sciences(AIIMS), New Delhi and two WHO special centres in Mumbai (KEM Hospital) and Aligarh (JLN Hospital, Aligarh Muslim University). These centres were to report ADRs to the drug regulatory authority of India. The major role of these centres was to monitor ADRs to medicines which are marketed in India. However, they hardly functioned as information about the need to report ADRs and about the functions of these monitoring centres were yet to reach the prescribers and there was lack of funding from the government. This attempt was unsuccessful and hence, again from the 1st of January 2005, the WHO- sponsored and World Bank-funded National Pharmacovigilance Program for India was made operational.³

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 centres-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 centre and two to the New Delhi centre. Each regional centre in turn would have several peripheral centers reporting to it. Presently there are 24 peripheral centers.

B. The Importance of Pharmacovigilance

Pharmacovigilance is an important and integral part of clinical research. Both clinical trials safety and post marketing pharmacovigilance are critical throughout the product lifecycle. Pharmacovigilance is still in its infancy in India and there exists very limited knowledge about the discipline. While major advancements of discipline of pharmacovigilance have taken place in the western countries not much has been achieved in India. There is an immense need to understand the importance of pharmacovigilance and how it impacts the life cycle of the product. This will enable integration of good pharmacovigilance practice in the process and procedures to help ensure regulatory compliance and enhance clinical trials safety and post marketing surveillance. Pharmacovigilance is not new to India and has in fact been going on from 1998, when India decided to join the Uppsala centre for adverse event monitoring. The importance of pharmacovigilance is withdrawals the regulatory agencies, media; consumers have become more aware about the benefit and risks of medicines.⁴ Spontaneous reporting of adverse drug reaction and adverse events is an important tool for gathering the safety information for early detection. In recent years many Indian companies are increasing the investment in research and development and are enhancing their capacity to develop and market new drugs with their own research efforts. Further India is becoming a hub for clinical research activities due to its large population, high enrolment rate and low cost. Moreover, the lag period when a drug is placed for the first time on the market in USA, Europe, and Japan or somewhere in the world and its subsequent availability in India has decreased considerably. As a result, for such drugs the long term safety data is not available and the time of their marketing in India. This is clear by the fact that all the high profile drugs that have been recently withdrawn were available in Indian market. In such cases, the Indian regulatory agencies cannot count on the experience of other market to assess benefit risk balance of a drug.⁵

C. Aim of Pharmacovigilance

1. Improve patient care and safety in relation to the use of medicines, all medical and Para medical interventions.
2. Research the efficacy 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 of any drastic effects of drugs.
4. Improve public health and safety in relation to the use of medicines.
5. Contribute to the assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost-effective) use.
6. Promote understanding, education, clinical training in pharmacovigilance and its effective communication to the public.⁶

These processes involved in the clinical development of medicines. Once 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 most 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.⁷

D. National Programme of Pharmacovigilance

Before a product is marketed, experience of its safety and efficacy is limited to its use in clinical trials, which are not reflective of 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. The conditions under which patients are studied during the pre-marketing phase do not necessarily reflect the way the medicine will be used in the hospital or in general practice once it is marketed. Information about rare but serious adverse drug reactions, chronic toxicity, use in special groups (e.g. pregnant women, children, elderly) and drug interactions is often incomplete or not available. Certain adverse drug reactions may not be detected until a very large number of people have received the medicine. Pharmacovigilance is therefore one of the important post-marketing tools in ensuring the safety of pharmaceutical and related health products.

- Assessing the risks and benefits of medicines in order to determine what action, if any, is necessary to improve their safe use.
- Providing information to users to optimize safe and effective use of medicines
- Monitoring the impact of any action taken

E. Resources for Pharmacovigilance Centres

The following books shall be provided to various centers as identified by the NPAC: Current editions of:

1. Meyler's Side Effects
2. 2.AHFS Drug Information hand book
3. 3. Martindale/online
4. 4.Davies Text Book of ADR
5. 5. Physician's Desk reference
6. British National Formulary

F. The National Pharmacovigilance Centres

At present, post-marketing surveillance of medicines is mainly co-ordinated by national pharmacovigilance centres. In collaboration with the Uppsala Monitoring Centre (UMC) the National Centres have achieved a great deal in:

1. Collecting and analysing case reports of ADRs
2. Distinguishing signals from background 'noise'
3. Making regulatory decisions based on strengthened signals
4. Alerting prescribers, manufacturers and the public to new risks of adverse reactions.
5. The number of National Centres participating in the WHO International Drug Monitoring Programme has increased from 10 in 1968 when the Programme started to 67 in 2002. The centres vary considerably in size, resources, support structure, and scope of activities. Collecting spontaneous reports of suspected ADRs remains their core activity.

G. National Pharmacovigilance Centres are Responsible for:

1. Promoting the reporting of adverse reactions.
2. Collecting case reports of adverse reactions.
3. Clinically evaluating case reports.
4. Collating, analyzing and evaluating patterns of adverse reactions.
5. Distinguishing signals of adverse reactions from "noise".
6. Recommending or taking regulatory action in response to findings supported by good evidence.
7. Initiating studies to investigate significant suspect reactions.
8. Alerting prescribers, manufacturers and the public to new risks of adverse reactions; and

9. Sharing their reports with the WHO Programme for International Drug Monitoring.

National centers have played a significant role in increasing public awareness of issues relevant to the safety of medicines. As a result, in some countries, pharmacovigilance is increasingly being seen as much more than a regulatory activity as it also has a major part to play in clinical practice and the development of public health policy. This development is partly attributable to the fact that many national and regional centres are housed within hospitals, medical schools or poison and medicine information centres and is in collaboration with a Medicines Regulatory Authority (MRA). The scope of activities of national centers has expanded to include communication of information about the benefits, harm and effectiveness of medicines to practitioners, patients and the public.⁸

III. RESULT AND DISCUSSION

Current Problems in Pharmacovigilance¹⁰

1. Topical tacrolimus (Protopic) and pimecrolimus (Elidel): potential cancer risk.
2. Duloxetine (Yentreve, Cymbalta): need for monitoring.
3. Tenofovir (Viread): interactions and renal adverse effects.
4. Linezolid (Zyvox): severe optic neuropathy.
5. CosmoFer and high risk of anaphylactoid reactions.
6. Drotrecogin alfa (activated) (Xigris): risk benefit in the management of sepsis.
7. Rosuvastatin (Crestor): introduction of 5 mg starting dose¹¹.
8. Osteonecrosis of the jaw with bisphosphonates.
9. High dose inhaled steroids: new advice on supply of steroid treatment cards^{12,13}.
10. Local reactions associated with pre-school d/DTap-IPV boosters.
11. Salmeterol (Serevent) and formoterol (Oxis,Foradil) in asthma management¹⁴.
12. Risk of QT interval prolongation with methadone
13. Tamsulosin (Flomax) and Intraoperative Floppy Iris Syndrome (IFIS)¹⁵.
14. Cardiovascular safety of NSAIDs and selective COX-2 inhibitors.
15. Erythromycin and other macrolides: focus on interactions

16. Glucosamine adverse reactions and interactions
17. Isotretinoin (Roaccutane): psychiatric adverse reactions.
18. Cardiac arrhythmias associated with antipsychotic drugs.
19. HRT and tibolone (Livial): update on the risk of endometrial cancer.
20. Hypoglycaemia unawareness on transferring insulins.
21. Withdrawal of co-proxamol .
22. Intravenous human normal immunoglobulin (IVIg) and thromboembolic adverse reactions.
23. NSAIDs and infertility.
24. Patients across the UK may report suspected adverse reactions.

IV. CONCLUSION

Pharmacovigilance and risk management are an essential part of pharmaceutical product development and commercialization, the activities of which are highly regulated in many part of the world. Rare adverse events may not be identified until large numbers of patients receive the product, so pharmacovigilance and risk management must extend throughout the product's life cycle. Benefit and risk must be continually assessed as more is learned about the product through its use. Building pharmacovigilance and risk management capacity requires a systematic approach to ensure that all safety aspects are monitored and addressed properly. Since capacity building takes time and resources, outsourcing of certain activities may enable capacity building to proceed before all capabilities can be done in-house. The use of a limited number of safety centers is a viable and cost-effective option, provided there are good processes, good tools, and good communication of responsibilities and events.

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