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Pharmacovigilance - A Review

Debjit Bhowmik[1,*], S.Duraivel[2], Rajalakshmi A.N[3] and K.P.Sampath Kumar[3]
[1]Nimra College of Pharmacy, Ibrahimpatnam, Vijayawada, Andhra Pradesh.
[2]Mother Theresa Post Graduate and Research Institute of Health Sciences, Puducherry.
[3]Department of Pharmacy, Coimbatore Medical College, Coimbatore.

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ABSTRACT

Pharmacovigilance is an important and integral part of clinical research. Pharmacovigilance is defined as the pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, particularly long term and short term adverse effects of medicines. Pharmacovigilance will certainly help identifying risks and risk factors in the shortest possible time so that harm can be avoided or minimised. Pharmacovigilance is the science and activities relating to detection, assessment, understanding and prevention of adverse effects or any other possible medicine related problem. Today its importance cannot be sidelined at all, given the number of new medicines being introduced in the market.

Introduction

There is a need to monitor the effects of drugs before and after it's successfully tested and launched in the market. Pharmacovigilance involves monitoring and assessing the quality of drugs, detection and preventing of any adverse effects of drugs. Pharmacovigilance involves evaluating information provided by health care providers, pharmaceutical companies and patients in order to understand the risks and benefits involved with a particular drug. Pharmaceutical companies spend millions of dollars and a considerably long time in developing new drugs. They again spend a lot of money in conducting clinical trials before the drugs are approved and launched in the market. It is recognized that information technology (IT) has entered and transformed the world of health careand clinical medicine in which the work of doctors and the care of patients proceed with higher quality, efficiency and lower costs. It is also no secret that IT has merged in to clinical safety practice and sparks the creation of worldwide pharmacovigilance systems for safety signal detection. The IT transformative force and health it adoption have fundamentally changed the conduct of clinical research, practice of medicines, and medicinal safety monitoring. In today's world, pharmacovigilance pushes new boundaries and it is no longer sufficient to simply report adverse events along with efficacy and quality requirements.

Aims of Pharmacovigilance

1. Early detection of increases in frequency of previously unknown adverse reactions and interactions and other noxious drug induced problems.
2. Detection of increase in known adverse reactions.
3. Identification of predisposing risk factors and possible mechanisms underlying adverse reactions.
4. Estimation of quantitative aspects of risk benefits analysis and dissemination of information needed to imp-rove drug prescribing, use and regulation.

Goals

1. To assess and communicate risk and benefits of drugs on the market.
2. To promote rational and safe use of medicines.
3. Educate and inform the patient.

All drugs undergo a significant amount of testing and evaluation before marketing to ensure their effectiveness as well as safety. Marketed drugs undergo trials in animals (pre-clinical testing) and humans (clinical trials) to establish their efficacy, safety, and quality.

Pre- Evaluation Marketing

Pre-marketing evaluation involves animal studies and clinical trials in humans. Studies in two or more animal species are conducted to test whether the drugs are harmful and whether they may for instance induce cancer, damage an unborn child etc. Once scientists are sure that the drug is safe, they start studies in human beings and these studies are known as Clinical Trials. Pre-marketing clinical trials take place in three phases – phases I, II and III. These trials are studies of the effects of drugs on humans under rigorously controlled conditions. All clinical trials will assess safety of the drug in question. A brief description of each phase of clinical trial is given below:

- Phase I—Single dose studies in healthy volunteers, using low doses of the drug. Subsequently, larger doses and multiple sequences are evaluated.
- Phase II—Efficacy is the primary objective of phase II trials, but safety is also continuously monitored and evaluated.
- Phase III—Evaluations of safety in groups of patients with the disease.

Each phase involves increasing number of patients and by the end of full pre-marketing clinical trials about 5000 patients would have taken the drug. However, when the drug is marketed millions of people will take the medicine. There is therefore the question of whether clinical trials involving just about 5000 people provide enough information to extrapolate the safety of a new drug to millions of people. Pre-marketing safety evaluations have two significant drawbacks:

Tele:
E-mail addresses: debjit_cr@yahoo.com

Under-identification of adverse drug reactions:

ADRs which occur infrequently are difficult to identify. Statistically, reactions with an incidence of less than 1% are frequently not identified.

Over-identification of ADRs:

Many adverse drug reactions that are identified in pre-clinical studies are not proven to be related to the drug, but are nevertheless listed in the product literature as potentially causing the ADR. This provides some measure of legal protection for the pharmaceutical company but is misleading to practitioners and patients, as many of these reactions are not definitely proven.

Post-marketing Surveillance (PMS):

It is not possible to have identified all of the safety-related problems that may exist with a new drug during pre-market testing and evaluation. After drugs have been released on the market, National Agency for Food and Drug Administration and Control(NAFDAC), the manufacturers/importers and health care professionals are responsible for post-marketing surveillance of these products. Drugs released to the market will be used not only by more people, but also by different categories of people other than those in whom the drug was tested. The marketed drug will be used by older people, those with more serious illness, those from different ethnic groups, pregnant women and also by children in whom drugs are rarely tested. The medicines may also be used under many different dose regimens (not necessarily the correct and approved dose) and they could also be deliberately misused. These circumstances inevitably lead to a potential for more adverse drug reactions. For these reasons, it is obvious that the safety of a drug requires long-term surveillance after marketing.

Rationale for Pharmacovigilance

Drug safety monitoring gained world-wide attention following the thalidomide incident in the 1960s. Thalidomide was a drug given to pregnant women to prevent "morning sickness". The babies born to some of these women were badly deformed and it took a while before the link between the deformed babies and the drug was made. Once this link was established the drug was banned and regulatory authorities all over the world became aware of the fact that seemingly safe drugs could have potentially serious adverse effects. The WHO therefore called for closer monitoring of the adverse effects of all drugs.

By continuously monitoring all drugs used in Nigeria, it is possible to detect any drugs causing unwanted ADRs and to control them. This can only be done effectively if health care professionals report all suspected ADRs to the National Pharmacovigilance Center.The effectiveness of any Pharmacovigilance activity is dependent on the active participation of all health professionals. Health professionals are in the best position to report suspected ADRs observed in their every day patient care. All health care professionals should report suspected ADRs as part of their professional responsibility, even if they are doubtful about the precise relationship between the reaction and the given medication. NAFDAC on its part assures the safety of all products before registration. However, some safety issues only come up after registration when the product is in use. There is therefore need for continuous monitoring for further safety assurance.

The magnitude of the problem

It has been demonstrated by a number of studies that medicine induced morbidity and mortality is a major problem of which health professionals and the general public are becoming increasingly aware. It has been estimated that ADRs are the 4th to 6th largest cause of death in the USA.1 Studies conducted in developed countries have consistently shown that approximately 5% of hospitalised patients are admitted into hospital as a result of an ADR while 6-10% of in-patients will experience a serious ADR during hospitalisation. ADRs cause the death of several thousand patients each year. The percentage of hospital admissions due to ADRs in some countries is about or more than 10%.Norway 11.5% ,France 13.0% UK 16.0% Even these startling figures do not represent the whole picture. These studies generally excluded ADRs caused by other drug related problems such as, overdose, drug abuse, misuse, poisoning, medication errors and therapeutic failures. In addition, treatment of ADRs imposes a high financial burden on health care. Some countries spend up to 15-20% of their hospital budget dealing with drug complications.

Pharmacovigilance In India

Pharmacovigilance is fastest emerging as an important approach for the early detection of unwanted effects of the drugs and to take appropriate regulatory actions if necessary .This may ensure the safer use of drugs.Historically, Indian market has always, except in very few cases, seen the launch of only products, which have been earlier approved and marketed in U.S.A., Western Europe or Japan. Until now, the time lag between the first marketing of a new drug in a foreign country and India has been on an average around 4 years, and hardly any new drug was introduced for the first time in ndia. In that kind of scenario, it was not too critical that there was in place a system of pharmacovigilance inIndia, since reports of side-effects from outside India would have helped our regulatory agencies to assess the rationale of continuing the drug in the Indian market. Thus in the past, action on marketed drugs has been triggered on the basis of reports on the harmful effects of drugs marketed abroad. In a few cases, drugs, which have been banned or withdrawn in foreign markets, were allowed to be kept in the market in India. For example, Chloramphenicol, Phenyl Butazone, Clioquinol, Phenformin, Cisapride, all continue to be prescribed in India on the basis of a conscious decision by the Regulatory Agency that the benefit to risk ratio is in favour of the former.The evolution of a new Patent regime in the Indian Pharmaceutical Industry (the Post-2005 scenario) as a consequence of India being a founder member of WTO, and her obligations under Trade Related Intellectual Property Rights and Services (TRIPS), makes it incumbent that ndia can no longer copy patented products and market them without licence from the innovator company. The leading Indian companies realizing the compulsions of the new regime have already initiated investments of substantial resources for the discovery and development of new drugs needed for both Indian and International markets. This in turn means that during the coming years R&D by the Indian Pharmaceutical companies will hopefully lead to new drugs based on pre-clinical and clinical data generated mostly in ndia. In such cases, the Indian regulatory agencies cannot count on the experience of other markets to assess the incidence and prevalence of adverse reactions from drug usage, and therein lies the importance of a properly designed pharmacovigilance system in India. For an effective Pharmacovigilance system to be functional and efficient all the stakeholders need to be alert and attentive through out the lifetime of the drug in the market.

National Pharmacovigilance Programme

The National Pharmacovigilance Programme was officially inaugurated by the Honorable Health Minister Dr.Anbumani Ramadoss on 23 November, 2004 at New Delhi. The National

Pharmacovigilance Programme for India, sponsored by the World Health Organization (WHO) and funded by the World Bank, became fully operational in January 2005.The Programme aims to foster the culture of ADR notification in its first year of operation and subsequently aims to generate broad based ADR data on the Indian population and share the information with global health-care community through WHO-UMC.The nation wide programme, sponsored and coordinated by the country's central drug regulatory agency – Central Drugs Standard Control Organization (CDSCO) – to establish and manage a data base of Adverse Drug Reactions (ADR) for making informed regulatory decisions regarding marketing authorization of drugs in India for ensuring safety of drugs.Under the program 26 peripheral centers, 5 Regional Centers and 2 Zonal Centers were established. The Peripheral centers will record the Adverse Events (AE) and send to the Regional Centers.They in turn collate and scrutinize the data received from the Peripheral Centers and submit to the Zonal Centers. The Zonal Centers will analyze the data and submit consolidated information to the National Pharmacovigilance Centre. The Zonal Centre will also provide training, general support and coordinate the functioning of the Regional Center.

Peripheral Pharmacovigilance Centres:

Primary pharmacovigilance centers. Relatively smaller medical institutions including individual medical practitioners' clinics, private hospitals, nursing homes, pharmacies etc. First contact ADR data collection unit at a health care facility. They would be identified and coordinated by RPCs / ZPCs in consultation with CDSCO. Regional Pharmacovigilance Centers (RPCs): Secondary pharmacovigilance centers. Relatively larger healthcare facilities attached with medical colleges. They would act as second level centers in the administrative structure of the NPPI. They will function as first contact ADR data collection units also. They would be identified and coordinated by ZPCs in consultation with the CDSCO.

Zonal Pharmacovigilance Centre (ZPCs) :

Tertiary pharmacovigilance centers. Large healthcare facilities attached with medical colleges in metro cities identified by the CDSCO for the purpose. They would act as third level centers in the administrative structure of the NPPI. They will function as First contact ADE data collection units also.

The National Pharmacovigilance Advisory Committee (NPAC):

Oversee the performance of various Zonal, Regional and Peripheral Pharmacovigilance centers as well as recommend possible regulatory measures based on the data received from various centers. It also oversees data collection and assessment, interpretation of data as well as publication of ADR monitoring data. The Committee also periodically evaluates their protocol compliance levels to ensure that the data received is homogenous and can be scientifically pooled for informed regulatory decisions. Wherever necessary, NPAC also seeks the opinion of experts in various specializations. The specific aims of the Pharmacovigilance Programme are to:

1. Contribute to the regulatory assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost effective) use.
2. Improve patient care and safety in relation to use of medicines and all medical and paramedical interventions.
3. Improve public health and safety in relation to use of medicines.
4. Promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public.
5. Monitoring medicines as used in everyday practice to identify previously
6. unrecognized adverse effects or changes in the patterns of their adverse effects
7. Assessing the risks and benefits of medicines in order to determine what action,
8. if any, is necessary to improve their safe use
9. Providing information to users to optimize safe and effective use of medicines
10. Monitoring the impact of any action taken

Scope And Opportunities Of Pharmacovigilance

Pharmacovigilance is the science relating to the detection, assessment, understanding and prevention of adverse effects, particularly long term and short term side effects of medicines. Generally speaking, it is the science of collecting, monitoring, researching, assessing and evaluating information from healthcare providers and patients on the adverse effects of medications, biological, herbalism and traditional medicines with a view to:

1. Identifying new information about hazards associated with medicines
2. Preventing harm to the patients.

armacovigilance is a great career option for life science and pharmacy graduates. It is a scientific discipline that is primarily concerned with reporting and analyzing of drug side effects. It is primarily due to the work of Pharmacovigilance professionals that the drugs in the market that we consume are mostly safe and those that are found harmful are taken off the market. Pharmacovigilance professionals continuously monitor the safety of the drugs in clinical trials as well as the drugs already being sold in the market. After a drug side effect is reported, the Pharmacovigilance professionals enter the event in relevant databases, follow up with the case to gather more information and forward these reports to regulatory authorities and other applicable bodies. The Pharmacovigilance professionals identify signals in data that may point towards a potential side effect and probe the case further.Setting up of stringent laws by regulatory bodies (e.g. US-FDA, DCGI, EMEA etc.) has led to the adoption of a systematic Pharmacovigilance framework worldwide. This in turn had led to the creation of large number of jobs pertaining to this field.Worth of Pharmacovigilance market worldwide was US $186 million in 2008 and is estimated to reach US $ 2,253 by the year 2015.At present, India is the fourth largest producer of pharmaceuticals in the world and therefore is a surfeit of drug brands with more than 6,000 licensed drug manufacturers and over 60,000 branded formulations. India offers unique advantages for the growth of Pharmacovigilance that include:

1. Rapid induction of New Chemical Entities (NCEs) and high technology pharmaceutical products in market
2. Abundance of patients with genetic diversity
3. Presence of Lakhs of formulation in domestic market
4. Presence of large number of licensed drug manufacturers in India
5. Potentially large world scale Adverse Drug Reaction (ADR) database

Job description:

A Pharmacovigilance professional does the following:

1. Track all adverse event reports received and completed;

2. Review and assess all source documents, and compile data in an adverse event report;
3. Data enter report into the safety database;
4. Code adverse events in the safety database;
5. Perform labeling assessment of adverse events, comparing adverse event to adverse events previously reported and contained in the product label;
6. Release report to safety database

Job prospects:

Starting salaries for freshers are substantially a function of their educational background, varying from year to year as well as across organizations and domains.

The following represents the typical work place hierarchy.

1. The Entry level job for life science graduate is DSA (Drug Safety Associate). DSAs are mainly involved in case creation, checking for MSI (Minimum safety information – a patient, a reporter, a suspect drug and a adverse event), reconciliation and follow-up process, data entry of all information available in the document and medical coding
2. Once an individual acquires an experience of 2-3 years in that position and builds the required skill sets (Medical coding, narrative and scientific writing, good understanding of medical terms and basic understanding of regulatory affairs, ICH-GCP and compliance etc) he can go on to become a DSS (Drug Safety Scientist).
3. Individuals once having acquired a good narrative writing experience can pursue it on a larger frame, moving from individual cases like writing for PSUR(Periodic Safety Update Report) and PADER(Periodic Adverse Drug Experience Reports) and as well as becoming a Aggregate report scientist.
4. With an overall of 7-10 years experience in this position individuals can easily become a Team lead or Team manager based on the company.
5. Lastly, individuals end up acquiring the position of a Director or Vice-President with an experience of 9-10 years.

Growth prospect:

Individuals trained in Pharmacovigilance will find good job options in the following sectors:

1. Pharmaceutical Companies (MNCs & Indian) & Biotech companies.
2. Clinical Research Organizations.
3. KPOs like Accenture & Quintiles.
4. Regulatory Agencies like DCG (I) & CDSCO
5. Pharmacovigilance units in Medical colleges & Hospitals

Conclusion

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem. Pharmacovigilance heavily focuses on adverse drug reactions, or ADRs, which are defined as any response to a drug which is noxious and unintended, including lack of efficacy, which occurs at doses normally used for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function. Medication errors such as overdose, and misuse and abuse of a drug, are also of interest because they may result in an ADR.

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