International Journal of Pharmacology and Clinical Research (IJPCR)

IJPCR |Volume 6 | Issue 2 | Apr-Jun - 2022
www.ijpcr.net

Review article *Clinical research*

ISSN: 2521-2206

A review on healthcare professional approaches in adverse drug reaction monitoring and reporting system

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ABSTRACT

Pharmacovigilance is a practice aimed to monitor drug safety in real life conditions and capture adverse drug events during the post marketing phase of drug's life cycle. But under reporting of adverse reactions is a major cause of concern and a threat to the pharmacovigilance systems. The present article looks into the major obstacles affecting the spontaneous reporting of adverse drug reactions (ADRs) in India and the possible solutions. As per available scientific literature, the major impediments to ADR reporting are inadequate knowledge and awareness among health professionals, clinicians' perceptions towards reporting, problems with establishing reporting systems in hospitals and insufficient training to recognize ADRs.Measures to improve the situation include greater involvement of nurses, pharmacists as well as consumers in the reporting of ADRs, making the process simpler and faster through electronic means, introducing educational interventions and training programs for health care providers and spreading awareness about the reporting system amongst caregivers and receivers alike. Providing a momentum to the pharmacovigilance system and ensuring a robust reporting process is a challenge but proper planning, feasible solutions and focussed efforts can help bring about the change ensuring patient safety - the ultimate goal of pharmacovigilance.

Keywords: Adverse drug reactions, spontaneous reporting, Case Reporting

INTRODUCTION

Pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse drug effects (ADRs) or any other drugrelated problem. The purpose of pharmacovigilance is to detect, assess and understand, and to prevent the adverse effects or any other possible drug-related problems, which is not only confined to chemical drugs, but extended to herbal, traditional and complementary medicines, biologicals, vaccines, blood products and medical devices. [1,2]

The aims of pharmacovigilance are to enhance patient care and patient safety in relation to the use of medicines and to support public health programmes by providing reliable, balanced information for the effective assessment of the risk-benefit profile of medicines. WHO established its Programme for International Drug Monitoring in response to the thalidomide disaster detected in 1961. Central Drugs Standard Control Organization (CDSCO), Ministry of Health and Family Welfare, Govt. of India launched the National Pharmacovigilance Program (NPP) in November, 2004, appreciating the importance and benefits of pharmacovigilance based on the recommendations made in the WHO. Under this programme, the whole country is divided into zones and regions for operational efficiency. The National Pharmacovigilance Advisory Committee (NPAC) oversees NPP which is sponsored by the WHO and funded by the World Bank. [3]

NPAC has 24 peripheral centers reporting to five regional centers which reports to the South-West zonal center in KEM Hospital, Mumbai and the North-East zonal center in AIIMS, New Delhi. Data received at the peripheral centers are forwarded to the respective regional centers which carry out the causality analysis and forward informations to the zonal centers from where forwarded to the CDSCO and WHO database. The WHO, Uppsala Monitoring center, Sweden, is

maintaining the international database of ADR reports received from several National Centers. [4]

An adverse drug reaction (ADR) can be defined as 'an appreciably harmful or unpleasant reaction resulting from an intervention related to the use of a medicinal product; adverse effects usually predict hazard from future administration and warrant prevention, or specific treatment, or alteration of the dosage regimen, or withdrawal of the product'.[5] Since 2012, the definition has included reactions occurring as a result of error, misuse or abuse, and to suspected reactions to medicines that are unlicensed or being used off-label in addition to the authorized use of a medicinal product in normal doses.[6] While this change potentially alters the reporting and surveillance carried out by manufactures and medicines regulators, in clinical practice it should not affect our approach to managing ADRs.

Pharmacovigilance is defined by the WHO as the science and activities relating to the detection, assessment, understanding and prevention of adverse reactions or any other drug-related problem. National systems for reporting drugs' adverse reactions can be found in almost every country [7-8]. Spontaneous reporting of medical staff regarding the occurrence of adverse reactions is the major source for monitoring and investigating adverse reactions of marketed drugs. However, only 1 in 20 adverse reactions is actually detected and defined as a real side effect; this leads to the erroneous assumption that the incidence of adverse reactions is much lower than it actually is [9]. Inadequate ADR reporting may lead to loss of clinical information that could prevent substantial damage to patients and consequently minimize health costs.

Objective of Pharmacovigilance: ADR monitoring

Pharmacovigilance is related to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems. It is the science of collecting, monitoring, researching, assessing and evaluating information from healthcare providers and patients on the adverse effects of medications. Safety and efficacy are the two major concerns about any drug. It is fast emerging as an important approach for the early detection of unwanted effects of the drugs and to take appropriate regulatory actions if necessary to ensure the safer use of drugs. [10]

Pharmacovigilance is a useful tool in post marketing surveillance, to identify, evaluate and responding to ADRs and safety issues about medicinal products. The monitoring of adverse effects of drugs while used in the population is called post marketing surveillance. Pharmacovigilance is therefore one of the important post-marketing tools to ensure the safety of pharmaceutical and related health products.

ARD Reporting Sources for Pharmacovigilance

The activity that is most essentially associated with pharmacovigilance is adverse event reporting. ADR reporting involves the receipt, triage, data entering, assessment, distribution, reporting and archiving of data and documentation. The source of ADR reports include spontaneous reports from healthcare professionals (doctors, nurses, pharmacist, paramedics), solicited reports from patient support programs, clinical or post marketing studies by pharmaceuticals, literature sources of academic researches and reports of drug regulatory authorities themselves. For pharmaceutical companies ADR reporting is a regulatory requirement in India for 4 years after marketing a new drug entity.

Health Care professionals

Most countries legally oblige spontaneous reporting by physicians. In India ADR reports can be sent only by health care workers to any one of the nearest pharmacovigilance center. Peripheral centers forward ADR data to the respective regional centers for causality analysis which is further forwarded to the CDSCO and WHO database via the zonal centers.

Spontaneous Reporting

Healthcare professionals identify and report any suspected ADR to their national pharmacovigilance center or to the manufacturer spontaneously. Spontaneous reporting is the core data generating system of international pharmacovigilance programme. Spontaneous reports play a major role in the identification of adverse signals which not detected in earlier clinical trials or other pre-marketing studies. [10]

Case Reporting

There are some distinct adverse events known to be rarely associated with drug therapy, such as anaphylaxis, aplastic anemia, toxic epidermal necrolysis and Stevens - Johnson syndrome. Practicing clinician can notify regarding a disorder in a patient suspected to be drug-related and in case different doctors independently report the same unknown and unexpected adverse experiences with a particular drug this can be indicated as an important signal.

Pharmaceutical Industry

Early detection of ADR signals from both clinical trials and post marketing surveillance studies mandatorily conducted by pharmaceutical companies have been adapted by regulatory agencies to identify the risks associated with the medicinal product. Pharmaceutical companies submit Periodic Safety Update Reports (PSURs) for all new chemicals drugs in every 6 monthly for the first 2 years of marketing in India, and annually for the subsequent 2 years. The purpose of the programme is to collate data, analyze it and use the inferences to recommend informed regulatory interventions, besides communicating risks to healthcare professionals and the public. Manufacturers are also required to submit all the reports they receive from healthcare providers to the national authority.

Stimulated Reporting

Pharmaceutical industries facilitate online reporting of adverse events based on a pre-designed method by health professionals in specific situations (e.g., in-hospital settings) on new products for a limited time periods. For the early post-marketing reporting phase companies notify healthcare professionals about new therapies and provide safety information for the general population (e.g., Early Post-marketing Phase Vigilance, EPPV in Japan).

Targeted Clinical Investigations

To elucidate the benefit-risk profile of a drug outside of the formal/ traditional clinical trial setting and/or to fully quantify the risk of a critical but relatively rare adverse event the targeted investigations conducted on population. Targeted

studies are conducted to investigate potential drug-drug and food-drug interactions based on pharmacological properties and the expected use. These studies include population pharmacokinetic studies to determine and quantify the magnitude of the risk or benefit in large populations. Potential risks or unforeseen benefits of drugs in special populations might be identified from the large simplified studies as children, elderly and co-morbid patients metabolize drugs differently than patients typically enrolled in clinical trials.

Descriptive Studies

Descriptive studies provide background data on rate of outcome events and/or establish the prevalence of the drug use in specified populations.

Drug Utilisation Study

Drug utilization studies explore the marketing, prescription and used pattern of a drug in a population and its influence on clinical, social and economical factors. These studies provide data on specific populations, such as the elderly, children, or patients with hepatic or renal dysfunction, often stratified by age, gender, concomitant medication, and other characteristics.[11]

Academia

Academicians and researchers carry out intensive, focused programmes concentrating on new drugs or controversial drugs. Some studies focus on the prescribing habits of doctors or involve pharmacists in reporting. All of these generate potentially useful information about ADR of drugs but also on reporting pattern of doctors.

Active Sentinel Sites Surveillance

Active surveillance ascertains the complete profile of adverse events via a continuous pre-organized process by followingup the patients treated with a particular drug through a risk management program. Patients are asked to complete a brief survey form and give permission for later contact32. Sentinel site specific reviewing of patients medical records or interviewing patients and/or physicians provides complete and accurate data on adverse events. Active surveillance with sentinel sites is most efficient for those drugs used mainly in institutional settings such as hospitals, nursing homes, haemodialysis centers, etc. Intensive monitoring of sentinel sites can also be helpful in identifying risks among patients taking orphan drugs.

Drug Event Monitoring

Patients are identified from electronic prescription data or automated health insurance claims for drug event monitoring to collect detailed information on adverse events from a large number of physicians and/or patients. A follow-up questionnaire sent to each prescribing physician or patient at pre-specified intervals to obtain outcome information on patient's demographics, indication for treatment, duration of therapy, dosage, clinical events and reasons for discontinuation etc.

Registries

Disease registry maintain list of patients with the same disease characteristics like for blood dyscrasias, severe cutaneous reactions, or congenital malformations which help data collection on drug exposure and other factors associated with a clinical condition. These registries are used to collect battery of information using standardized questionnaires in a prospective fashion. Drug registry maintains data related to specific populations exposed to drugs of interest. Patients are followed over the time to include in cohort studies to collect data on adverse events using standardized questionnaires.

Observational Studies

Traditional epidemiologic methods like are cross-sectional studies, case-control studies, and cohort studies are useful in validating signals from spontaneous reports or case series for evaluation of adverse events. Data collected on a population of patients at a single point in time (or interval of time) regardless of exposure or disease status constitute a cross-sectional study. Case-control studies are particularly useful to investigate whether there is an association between a drug and one specific rare adverse event, as well as to identify risk factors for adverse events. Cohort studies are useful to explore the incidence rates of adverse events in addition to the relative risks of adverse events. Multiple adverse events are also investigated using the same data source in a cohort study.

Adverse Event Reporting Types

Spontaneous Reporting

The healthcare professionals spontaneous report any adverse events to their national pharmacovigilance center, health authority or to the drug manufacturer itself7. In most parts of the world adverse event reports are submitted electronically using a defined format. Spontaneous reports are a crucial element in the worldwide pharmacovigilance system and form the core of the WHO Database. [12]

Aggregate Reporting

Aggregate or periodic reporting plays a key role in the safety assessment of drugs. Cases that do not involve a serious, unlabelled adverse event is subjected to non-expedited or periodic reporting. Aggregate reporting involves the compilation of safety data for a drug over a prolonged period of time. The advantage of aggregate reporting is to provide a broader view of the safety profile of a drug. Worldwide, the most important aggregate report is the PSUR.

Expedited Reporting

Reporting of Individual Case Study Reports involves serious and unlabelled event related to use of a drug is termed as expedited reporting. In most countries the timeframe for reporting expedited cases by the drug company after receiving notification of such a case is 15 calendar days. Within clinical trials the Suspected Unexpected Serious Adverse Reaction is an event that involves a life-threatening or fatal event is subject to be reported within 7-days.

Clinical Trial Reporting

Safety information from clinical studies is used to establish safety profile of drug in humans. Serious Adverse Event (SAE) occurring to any study patients (subjects) during conduction of clinical trials is the key component for the drug regulatory authorities in the decision-making to grant or deny market authorization for a drug. SAE informations are forwarded to the sponsoring pharmaceutical company that is

responsible for the reporting to the drug regulatory authorities.

Reporting Backdrops

The major weakness of the spontaneous reporting system by clinician is under-reporting, though the figures vary greatly between countries and in relation to minor and serious ADRs. ADR reporting behavior varies greatly between countries and in relation to the seriousness of the events, but in general probably less than 5-10% of all adverse events that occur are actually reported. Another problem is that overworked medical personnel do not always see reporting as a priority, especially if the symptoms are not serious. Even if the symptoms are serious, they may not be recognized as the possible side effect of a particular drug9. Though spontaneous reports are submitted voluntarily although under certain circumstances these reports may be encouraged or stimulated, by media reports or articles published in medical or scientific publications or by product lawsuits. Pharmacists and paramedics are not trained enough for detecting and reporting ADR and mostly not having the ADR reporting form assessable and other contact details of pharmacovigilance centers.

One limitation of this targeted clinical investigation method is that the outcome measure might be too simplified and this might have an impact on the quality and ultimate usefulness of the trial. Important limitations of these studies can include a lack of clinical outcome data or information of the indication for use of a product. The selected sentinel surveillance sites can provide information data from specific patient subgroups that would not be available in a passive spontaneous reporting system. Some of the major weaknesses of sentinel sites are problems with selection bias, small numbers of patients and increased costs. Limitations of drug event monitoring include poor physician and patient response rates and the unfocused nature of data collection, which can obscure important signals. [13]

A randomized, cross-sectional, observational, questionnaire based study was conducted at a 550-bed tertiary care teaching hospital in Moradabad, India on ARD reporting and pharmacovigilance awareness. The study involves the paramedical staff (pharmacist and nurses) along with senior (professor and associate professor) and juniors (assistant professor, senior resident and junior resident) doctors. This study showed poor knowledge, attitude and practices of pharmacovigilance among medical professionals urging the need to improve the awareness of pharmacovigilance among the healthcare professionals. [14]

A questionnaire based study was conducted to evaluate the awareness of pharmacists working in Delhi regarding pharmacovigilance, ADR and it's reporting among the hospital pharmacists, community pharmacists and medical representatives. Pharmacists were found to be not very much aware of pharmacovigilance. Majority of pharmacists did not report the ADRs noticed by them and were not having information that reporting can be done at national monitoring center and/ or regional monitoring centers. ADR reporting is done by pharmacists at places other than official monitoring centers like physicians, manufacturing industry, product management team and chief pharmacist. Education and training of pharmacists is essential to improve the ADR reporting. [15]

Suggested Measures to Encourage ADR Reporting Culture

• A single countrywide specific adverse event reporting form has been designed by CDSCO, for use by all registered doctors working in hospitals (both private and government), medical colleges, Drug Information Centers and pharmacies throughout the country. ADR reporting form should be made easily available to all primary healthcare centers in rural areas and to all practicing general practitioners, physicians, pharmacists and paramedics.

• NPP can act towards positively changing the mindset of the participators so that ADR reporting becomes an accepted and common routine practice. All the newsletters, leaflets and journals covering pharmacovigilance activities should sent to all the hospitals. Periodic meeting of NPP experts with nurses, pharmacists and paramedics will motivate them for ADR reporting. Each hospital should build local pharmacovigilance unit for disbursement and collection of ADR reporting forms and can also have ADR form drop boxes at strategic sites. Facilitation of eleceronic submission of ADR reporting form by uploading in website or Email or fax will further increase the reporting frequency. The NPP can also periodically collect ADR forms from hospitals by sending representatives.

• The various stakeholders including the Medical Council of India should incorporate a pharmacovigilance syllabus within the pharmacology and medicine curricula so that proper theoretical and practical training can be imparted to health care providers. Nurses, pharmacists and paramedics should also be trained in the regular curriculum about pharmacovigilance practice so that they are able to recognize ADRs and develop a culture of reporting ADRs in the future.

• An awareness program and a training sessions covering all aspects of pharmacovigilance meant for the research and development based pharmaceutical companies, particularly those involved in new drug research should be extensively implemented. The medical professionals, the pharmacists, chemist-druggist traders and the also the patients should be make alert in detecting ADRs and reporting them to the Indian regulatory agencies.

• To effectively managing the ADR related risks of drugs PSUR reporting done by pharmaceutical companies only for initial 4 years of marketing should be made mandatory throughout the life cycle of the product with due relaxation. There are many example of drug withdrawing or banning after a long period of regulatory approval and marketing i.e. clioquinol, rosiglitazone, sibutramine, rimonabant, nimesulide, cisapride, phenylpropanolamine while they were assumed to be safe. Spontaneous reporting program by health care professionals, a common method of drug surveillance, alone is not capable of recognizing ADRs in the daily medical practice, as under-reporting and absence of information on number of people actually exposed to the drug are its disadvantages.

• The students of health care system need to be trained in drug safety to build up a habit of rational drug use. Continuing medical education programme for physicians and other health professionals should be conducted to make them accustomed to the methodologies and other technical aspects of the ADR monitoring process. The pharmacist and paramedical staff could play an important role in ADRs reporting, because they are close to the patient and are responsible for drug administration and recording side effects. They can alert the

responsible physician about possible ADRs without time gap. Conduction of workshops for pharmacists and paramedics to train them regarding pharmacovigilance, ADR identification, ADR reporting forms, reporting centers, procedure of reporting and benefits of reporting will be of great benefit.

• Spontaneous ADR reporting is the most important input for post-marketing surveillance of medicines and is vital for maintaining drug safety. The MHRA run the UK's spontaneous ADR reporting scheme called the Yellow Card Scheme to receive reports of suspected ADR from healthcare professionals and patients. Patients, carers or parents can use the Yellow Card Scheme to report any side effects they have experienced from a medicine, and individuals can use it to report any side effects on behalf of a child or adult in their care. NPP has spontaneous reporting system only for health care personnel's; individuals are not allowed to report ADR. Introduction of ARD reporting by the patients and related person will definitely tremendously increase the reporting of cases. A simultaneous verification process can be adopted to validate that the ADR reported by the patients are actually related to use a particular drug in use.

• Making pharmacovigilance reporting mandatory and introducing pharmacovigilance inspections can only ensure 100% reporting of ADRs. MHRA has a well defined procedure for pharmacovigilance reporting and inspection. The Government of India's Health Ministry should also need to pass a law and make pharmacovigilance reporting mandatory to ensure that pharmaceutical companies are meeting their legal responsibilities. A department for Pharmacovigilance Inspections should be incorporated within the DCGI with the view of starting inspections in all pharmaceutical companies operating in India.

CONCLUSION

Effective implementation of pharmacovigilance in India is a need of the hour because of increased trend of outsourced clinical trials and new researches going on in clinical field. Pharmacovigilance collects, records, codes ADRs, analyses and assesses the reports, to promotes the safe use of drugs, creates appropriate structures and means of communication needed to perform its tasks. ADR reporting should be intensively taught during undergraduate study, and this should be reinforced at the start of internships as well as periodically thereafter through continual education programs. For improving pharmacovigilance in India, a new scheme was introduced as 24 hour telephone and online advice in which people can telephone a helpline to report suspected adverse drug reactions. Reports from patients themselves are of high value. The confirmation of these events by a healthcare professional is considered to increase the value of these reports. Hence it is important not only for the patient to report the ADR to health care provider, but also report both to the pharmaceutical company and the FDA. Education and training of medical students, pharmacists and nurses in the area of pharmacovigilance will encourage reporting without bias. Pharmaceutical companies are required to have a life-cycle approach to their products and patient safety issues associated with them.

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