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Review Article

PHARMACOVIGILANCE: A PRACTICAL APPROACH FOR RESHAPING PATIENT SAFETY

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ABSTRACT

Ensuring patient safety and efficacy of medicines is one of the top challenges in health-care today. Numbers of adverse effects, drug interactions, and risk factors have been reported later in the years of drug release and hence postmarketing surveillance is today's need. Pharmacovigilance (PV) is the important and vital part of clinical research dedicated to minimize the risk of drug-related events to patient. PV covers the science and practice related to the recognition, estimation, understanding, and anticipation of adverse effects of drugs or any other possible drug-related problems. The objective of this article is to provide a concise review on the importance of PV practice to ascertain and maintenance of rational use of drugs within the domain of pharmacotherapy. Thus, in summary, this review attempts to stress that systematic PV is essential to buildup reliable information network on the safety of medicines to boost confidence about their safety. 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, Adverse drug reaction, Drug interactions.

INTRODUCTION

Modern medicines have changed the way in which diseases are managed and controlled with systematic approach. However, in spite of all their benefits, evidence continues to mount that adverse reactions to medicines are a common, yet often preventable, cause of illness, disability and end with even death. Pharmacovigilance (PV) also known as drug safety, is the pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, particularly long- and short-term side effects of medicines and traditional medicines [1].

It is extensively acknowledged that a drug has to go through various phases of clinical trial to establish its safety and efficacy before it is marketed commercially. PV is a very imperative and indivisible part of clinical research. Both clinical trials safety and postmarketing PV (popularly known as Postmarketing studies or Phase IV clinical trials) are critical throughout the product life cycle. However, the clinical trials propose various limitations such as strict criteria of inclusion and exclusion make it to be used in a very selective group of patients; special population groups such as children, pregnant woman, and old age population are not studied during the trials; and other factors causing drug reactions such as genetic factors, environmental factors, and drug-drug interactions may not have been studied during the clinical trials. No medicine is absolutely free from harmful effects and polypharmacy increases the risk of reactions related to drug use, adverse drug reactions (ADRs), and ADRs as consequence of drug-drug interactions [4].

PV plays significant various roles such as, identification, quantification, and documentation of drug-related problems which are responsible for drug-related injuries. Further, National PV Programmes (NPP) have been introduced which occupies a key role in increasing the public awareness about drug safety. 5 years roadmap of PV Programme of India with initiation phase in 2010 followed by expansion with consolidation, maintenance, optimization, and finally achieved stage of excellence in 2015 with creation of center of excellence for PV in Asia Pacific [1,2].

PV program organized with the broad objective as:

- The short-term objective is to foster a reporting culture
- The intermediate objective is to involve a large number of healthcare professionals in the systems for information provision (reporting) and in information dissemination
- The long-term objective is for the program to be a benchmark for global drug monitoring.

AIM OF PV

Once the product is manufactured and marketed overall safety of medicine is unknown, and postmarketing surveillance necessitates on the priority basis. To allay inappropriate or unsafe use of medicine, minimize unnecessary patient suffering and financial loss of patient, its today's need to establish effective monitoring system as PV to reshape and ensure patient safety with involvement and support of health-care professionals - doctors, pharmacists, nurses, and other health professionals in the country. The Department of Health's Essential Drug Programme is dedicated to improving drug safety through ADR monitoring system. Through the NPP, adverse reactions expected should be reported on a daily basis in proper channels.

PV Programme of India (PVPI) was launched in July 2010 with purpose to ensure that the benefits of use of medicine prevail over the risks and thus defend the health of the Indian population.

- Improve patient care and safety in respect to the use of medicines, all medical and Paramedical interventions
- To promote systematic and rational use of medicines and to boost confidence for safety
- Evaluate the efficacy of drug and monitoring the adverse effects of drugs
- PV keeps pathway of any severe effects of drugs
- Promote public health and medicine use safety
- Contribute to the assessment of benefit, adverse effect, efficacy and hazard of medicines, promoting their safe, rational, and more effective (including cost-effective) use
- Promote understanding, education, clinical training in PV, and its effective communication to the public [2].

NEED OF PV

Patient suffering with many different diseases, using several other drugs simultaneously, different lifestyle, traditions, and diet react to medicines. Different brands of medicines possess diversity in manufacturing and ingredients exploited. The ADRs and poisonings associated with traditional and herbal remedies also need to be monitored in each country. With the severity of adverse events related with drugs its need

hour to acquaint with the PV system for patient safety. PV is prime tool that will reshape patient safety after postmarketing surveillance. Concerns focusing on need of PV as mentioned below:

- Humanity concern - Insufficient evidence of safety from clinical trials, animal experiments, and Phase 1-3 studies before marketing authorization
- Medicines are supposed to save lives, i.e., dying from disease sometimes unavoidable but dying from medicine is unacceptable
- ADRs and events may cause sudden death and are expensive
- To promote rational use of medicine and adherence
- To ensure public confidence.

Ethics to know of something that is harmful to another person; who does not know and not telling is unethical [2,3].

CONSEQUENCES OF MEDICINES

Since from longer time drugs effectively used to treat and prevent illness and have modernized health-care system. As one coin has two sides every drug has its benefits and side effects no any medicine is free from harmful effects and polypharmacy increases ADR and reactions related to drugs including drug-drug interactions. In general for society and individuals, ADRs due to drug interaction pose a serious health problem [1].

As per WHO, an adverse reaction (ADR) is defined as any response to a drug which is noxious and unintended and occurs at doses used in man for diagnosis, prophylaxis, and treatment. Gastrointestinal bleedings, central nervous system complications, cardiovascular disorders, and hemorrhages are the most commonly occurring ADRs for patient that takes place after administration of respective drug. Drug-related administrations causing ADRs some of pharmacological classes include nonsteroidal anti-inflammatory drugs (NSAIDs), antithrombotic drugs, sedatives, and cardiovascular agents including cardiac stimulants, and antiarrhythmics [2,3].

Drug-drug interaction occurs when two drugs are administered simultaneously or prior administration of another drug results in alteration of effect of one drug. In general, drug-drug interaction explains the effect of one drug changed either enhanced or reduced in the presence of another drug, herbal drug, food, drink or by environmental chemicals. The effects of drug combination may be synergistic or additive; antagonistic or reduced; or altered or idiosyncratic, and it may result in beneficial effects or adverse reactions. An adverse drug interaction is a drug-drug combinations causing ADR or therapeutic failure of one of drug. Drug interaction mechanism divided into two main groups pharmacokinetic and pharmacodynamic, depending on behavior of drug in body [3]. One of the most popular clinically important interactions discovered were food-drug interaction between patient consuming cheeses and monoamine oxidase (MAO) inhibitors resulting in hypertensive crises.

During the hospital stay, it was found from survey that the majority of drug-related reactions were pharmacodynamic (91.7%), pharmacokinetic (5.3%), and had both (3%). Potentially serious drug interactions reported with drugs are cardiovascular agents (e.g. enalapril, digoxin, furosemide) and anti-inflammatoric drugs (acetylsalicylic acid and other NSAIDs (diclofenac) and anticoagulants (such as warfarin). Fatal and serious reactions have been reported for more number of times for anticoagulants and antiplatelets. One of the specific herbal drug and their adverse effect include if ginko biloba adverse effect of bleeding taken along with aspirin it retards absorption of aspirin [4]. It is provoked that polypharmacy enhances the risk of adverse reactions related to drug use, and ADRs as consequence of drug interactions.

PROCESS OF PV

- What to report
  The NPP shall encourage reporting of all suspected drug related adverse events, including those suspected to have been caused by herbal, and traditional or alternative remedies [5].

The program particularly solicits reports of:

- All adverse events suspected to have been caused by new drugs and "drugs of current interest" (list to be published by CDSCO from time to time)
- All suspected drug interactions
- Reactions to any other drugs, which are suspected of significantly affecting a patient's management, including reactions suspected of causing: Death, Life-threatening, hospitalization, disability, congenital anomaly, and required intervention to prevent permanent impairment or damage.
- Who can Report?
  Any health care professionals (Doctors including Dentists, Nurses, and Pharmacists) may report suspected adverse drug events. The program shall not accept reports from lay members of the public or anyone else who is not a health-care professional [5,6].
- Where to Report?
  After completion, the form shall be returned/forwarded to the same PV center from where it was received. Reporting can be conducted to any one of the country vide PV centers nearest to the reporter (complete list of PV centers is available at: www.cdsco.nic.in). In case of doubt, the form may be sent to the national PV center at: CDSCO, New Delhi [7,8].

WHAT HAPPENS TO THE INFORMATION SUBMITTED?

Information submitted to the center of PV in a prescribed format shall be handled in strict confidence. Peripheral PV centers forward adverse event form to the Respective Regional PV centers for the purpose of causality analysis. This information shall be preceded to the Zonal PV centers. Data obtained will be analyzed statistically and forwarded to the global PV database managed by WHO Uppsala Monitoring Centre in Sweden. The final report based on the analyzed data will be periodically reviewed by the National PV Advisory Committee constituted by the Ministry of Health and Family Welfare. The Committee is entrusted with the responsibility to review data and suggest any regulatory interventions that may be required with respect to the drug/drugs or class of drugs [9,10].

- Process of PV
  The process of PV starts from collection and record of data and ends with communication to stakeholder regarding safety issue of drug.

The process of PV involves 5Cs as below:

- Collect and record of AEs/ADRs [11,12].
  Collect and record of AEs/ADRs integral part of PV process. Spontaneous reporting system (SRS) is the basic and broadly used method to report ADRs. It has great importance to identify ADRs yet under-reporting remains the major limitation, accounts for 90-95%. Other limitations include quality of report, reporting bias, and reporting only short latency events. SRS is effective way for ADRs reporting and able to safeguard the patient safety. A variety of reasons counted for under-reporting as reporting considered as additional burden as little obvious or immediate return and time consuming, it avoid scrutiny of professional competence and insufficient awareness/training to health care professionals.

AEs/ADRs reporting sources:

- From health-care professionals (voluntary)-high incidence of under reporting
- Published scientific literature: Pubmed, Scopus, etc.
- Periodic safety update report.

Methods for collecting AEs/ADRs:

A. Active surveillance
   - Site surveillance (hospitals, pharmacies, nursing homes, etc.)
   - Focused ADR monitoring of drugs
   - Prescription event monitoring
   - Disease registries from public health program.

B. Comparative observational studies
   - Cross sectional survey
   - Case control study
   - Cohort studies
   - Large safety tria
   - Drug utilization study
   - Causality assessment and analysis of ADRs.

A national ADR or PV advisory committee provides assistance on causality assessment, risk management, risk management case investigation, and crisis communication.

Most case reports suspected ADRs is the intrinsic problem in PV. Adverse reactions are rarely specific for the drug, diagnostic tests are usually absent and a recalling is rarely ethically justified. In practice few adverse reactions are "certain" or "unlikely;" most are somewhere in between these extremes, i.e., "possible" or "probable." To cope up with this problem many systems have been developed for structured and balanced assessment of causality. None of these systems, however, have been shown to produce a precise and reliable quantitative estimation of relationship likelihood. Nevertheless, causality assessment has become a common routine procedure in PV. The advances and limitations of causality assessment are reviewed. The WHO-UMC system has been developed in consultation with the National Centers participating in the Programme for International Drug Monitoring and is meant as a practical tool for the assessment of case reports [15,16]. It is basically a combined assessment taking into account the clinical pharmacological aspects of the case history and the quality of the documentation of the observation.

- Collate and code in database
  - After reporting of ADR/event firstly enters it into database
  - Once entered into database AEs/ADRs assign code. Method for coding as below Adverse Events: WHO-ART, MedDRA. Drugs: WHO-Drug dictionary.
- Compute risk-benefit and suggest regulatory action
  As per reporting of AEs/ADRs compute risk-benefit ratio that will propose evolutionary report either based on one man's meat is another man's poison. It will bring signal on reported information casual alert relationship between adverse event and drug or unknown relationship or incomplete documentation. Suggest warning and alert for regulatory agencies for patient safety [8].
- Communicate for safe use of drugs among stakeholders [9,10]
  Communicate regarding AEs of drugs among various stakeholders – Patient, physician and medical association, pharmaceutical industry and association, policy maker, press and public for minimizing suffering and creating awareness.

PARTNERS INPHARMACOVIGILANCE

Key players of PV in national drug policyare: Government, industry, hospitals and academia, medical and pharmaceutical associations, poisons and medicines information centers, health professionals, patients, consumers, media and World Health Organization, Uppsala monitoring centre [8].

ROLE AND RESPONSIBILITIES

National PV center will be responsible for the development of PV in the public health system. It promotes PV in the PHPs and sensitizes professionals and public health staff to the reporting of adverse reactions and irrational use of medicines to ensure patient safety.

Pharmacist

- Participate in spontaneous reporting of adverse events, also report (even if no adverse event)
- Evaluation and reporting of medication errors with respect to drug interaction, ADR, and allergic reaction
- Exposure of medicines during pregnancy and lactation
- Monitor clinical status of patients
- Identify the correct ADRs not side effects related with medicine
- Get more information about adverse events and details of particular medicine
- Investigate adverse event at hospital level
- Assist and encourage physicians to fill-up the forms for reporting event
- Keep patient's record if more information needed [9,10].

Patients and the public

The patient adherence to pharmacotherapy is of prime importance for efficient recovery. Public awareness about adverse event, early reporting, and management are crucial to make sure patient confidence and compliance. The patient reporting of ADR considered as part of feedback communication link and need to be separate from involvement of patient interest group [8,10].

Primary health-care workers

Public awareness about adverse reactions, early reporting and management are essential for ensuring patient confidence, in and adherence to, pharmacotherapy. It is the responsibility of the primary health-care provider to detect, investigate, manage, and report ADRs. These staff will need training on the importance of adverse reactions, diagnosis, basic principles of causality assessment, and the important elements of the adverse reactions reporting form [11].

Primary health-care workers

Ensuring and reshaping patient safety its responsibility of primary health-care provider is to detect, investigate, manage, and report ADRs. To cope up with the serious issue of ADRs staff need training on the importance of adverse reactions, diagnosis, basic principles of causality assessment, and the important elements of the adverse reactions reporting form including patient education. Counseling and explanation about adverse reaction will definitely promote patients' confidence and adherence. Continuous guidance and encouragement is indispensable for reporting adverse reaction [12]. It is imperative to accomplish a positive attitude toward PV. To encourage reporting, the following steps should be of help:

- Easy availability and access to reporting forms and training
- Acknowledgement of receipt of a report and provision of feedback to the reporter
- Participation of reporting staff in PV meetings and of PV staff in professional meetings [13,14]
- Collaboration with the national PV center.

Other health-care workers

Health-care workers outside the government system should also report adverse reactions. These would include among others, non-governmental organizations, and Charitable health facilities [15,16].

RECOMMENDATIONS

Based on these observations, there are several ways we can move forward in attempting to embrace PV systems:

- Introduce PV concepts into the curriculum at the undergraduate and postgraduate level [17]
- Encourage studies on drug safety
- Create awareness about the science of PV among physicians, patients, and paramedical staff
- Development and validation of scales to assess the causality of the reported reactions to herbal and Ayurveda medicines [18,19].

The need of the hour is to educate the physicians and encourage them to analyze and report any adverse effect that occurs in a patient. The industry should take concrete steps to generate confidence and reliability for its products [19].

CONCLUSION

PV is the practical approach to ensure safety of drug and reshape patient safety. It plays an important role in meeting the challenges offered by

the increased range and potency of medicines. The success of any PV system lies in its ability to prevent further adverse events of drug on the basis of information received. This will be possible only when health care professionals are vitally alert to the onset or offset of any ADRs. They need to prioritize their contributions to make the PV program for medicines a success.

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