Review on Pharmacovigilance

Gite Poonam Sambhaji*, Miss. Bhavana Hon, Dr. Megha Salve.

Department of Bachelor in Pharmacy
Shivajirao Pawar College Of Pharmacy, Pachegaon, Ahmednagar-413725.

ABSTRACT
Pharmacovigilance play an important role in the healthcare system Through monitoring and interaction of drugs and there effects in the Human body. In this article includes good manufacturing practices (GCP) and (ICH) guidelines for pharmaceuticals for human use are Examined as an important aspects in the transformation of clinical trial To the objective of pharmacovigilance In pharmaceutical production India becomes third largest country in the world. Nowadays in India Pharmacovigilance gives awareness about adverse drug reactions (ADR) and this review gives information about implementation for Solving current problems. This article summarized objective and Methodology used in pharmacovigilance with their overview of Existing in India and their challenges and future expectance

KEYWORDS: pharmacovigilance, adverse drug reactions, ADRs assessment.

I.   INTRODUCTION:
Drugs have changed the way in which diseases are treated. Despite all the advantages of pharmacotherapy, adverse reactions are a recognized hazard of drug therapy. Adverse drug reactions (ADRs) are a common, frequently preventable cause of illness, disability and death. An ADRs may be defined as "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of product" [1]. Pharmacovigilance has been described as "the science and activities relating to the detection, assessment , under-standing and prevention of the adverse effects of drugs or any other possible drug-related problems. It is a fundamental component of effective drug regulation systems, public health program and clinical practice" [2]. In 1968, ten countries (Australia , Canada, Czechoslovakia, Germany, the Netherlands , Ireland, new Zealand, Sweden, united kingdom, and USA), with national drug monitoring centers, collaborated And joined the world health organization (who) pilot research project for international drug monitoring [3]. In 1972, a report was published that formed the basis of the current international system of national centers collaborating in the who program [3, 4, 5].

IMPORTANCE OF PV:
It is the science which deals with the complex process of the understanding and explaining the nature of ADR occurred in a patient taking either oral or parenteral or intravenous (I.V) drugs for an ailment. The drugs being marketed worldwide underwent a whole array of tests and also underwent clinical trials in animals and human subjects to assess the safety of the drug for a particular disease and to know the exact side effects associated with it. Still there is a major part of it goes undetected and some of the ADR are detected in post marketing surveillance. It is estimated that there is significant amount of ADRs which decreases the quality of life, increase hospitalization stay and increases the mortality. A landmark study by in 1998 described, ADRs to be the fourth to sixth leading cause of death in the US and ADRs are estimated to cause 3-7% of all hospital admissions [6].

AIMS OF PHARMACOVIGILANCE:
1. Increase society's protection from new drugs
2. Contribute to the assessment of the effectiveness, benefits and risks of drugs.
3. Promote healthy communication with the community.
4. Promote the rational and safe use of medicines.
5. Effectiveness of drugs and monitoring of drug side effects.
6. Pharmacovigilance avoids the drastic effects of drugs.

. Improving public health and safety by promoting understanding, education and clinical training in pharmacovigilance.

GOALS OF PV:
Short term goals:
1. Develop and implement a pharmacovigilance system in India
2. Encourage healthcare professionals to report adverse reactions to drugs, vaccines, medical devices and biological products
3. Collect case reports and data
4. The programs were conducted by all MCI-accredited medical schools [7]

Long term goals:
1. Expansion of pharmacovigilance program to all hospitals and public health program centers in India
2. Introduction of mandatory reporting of adverse reactions for healthcare professionals.
3. Development of an electronic reporting system.

ADVERSE DRUG REACTION (ADR):
Adverse drug reactions (ADRs) At normal doses, administered drugs can sometimes harm the patient. Adverse drug reactions (ADRs) [8] are different from side effects. The assessment of adverse events is crucial in the field of pharmacovigilance

Adverse drug reactions (ADRs) have been classified in to two ways;
A. PREDICTABLE (TYPE-A) REACTIONS:
These are based on pharmacological properties of drug like augmented but quantitatively normal response to the drug which include side effects, toxic effects and consequences of drug withdrawal. [9, 10]

B. UNPREDICTABLE (TYPE- B) REACTIONS :
These are based on indication of patient and not on drug's known actions such as allergy and idiosyncrasy. They are more serious and require withdrawal of drug .for example anaphylaxis to penicillin.
A list of some suspected and known drugs associated with adverse effects

Sr. No	Drug	Adverse Drug Reaction(ADRs)
1.	Thalidomide	Pocomania, multiple defects
2.	Methotrexate	Multiple defects, death
3.	Androgen	Civilization, limb, esophageal ,cardiac defects
4.	Progestin	Civilization of female fetus
5.	Stilboestrol	Vaginal carcinoma in teenage female offspring
6.	Tetracycline	Discolored or deformed teeth, retarded growth
7.	Warfarin	Nose eye and hand defects , growth retardation
8.	Phenytoin	Various malformations
9.	Lithium	Fetal goiter cardiac and other abnormalities
10.	Aspirin/ Indomethacin	Premature closer of ductus arteriosus

Chart no. 1 Drug and Adverse drug reaction (ADRs) [11]

ADVERSE DRUG REACTIONS (ADRS) REPORTING:
When the adverse reaction to drugs is potentially serious or clinically important, all health care workers including doctors, pharmacists, nurses and other health experts are requested to clarify it. It is necessary to report an adverse drug reaction to pharmacovigilance.

PV PROGRAMMED :
1. Management body: Steering Committee, Technical Assistance Committee, Strategic Advisory Committee.
2. National Photovoltaic Center: Zonal Photovoltaic Center, Regional Photovoltaic Center, Peripheral Photovoltaic Center
3. ADR Observatory: MCI recognized medical institute, private hospital/health center and autonomous structure [12]

BENEFITS OF ADR MONITORING:
1. It caters information about quality and safety of pharmaceutical products.
2. It initiates risk-management plans.
3. It prevents the predictable adverse effects and helps in measuring ADRs adherence.

4. It instructs health care team i.e., patients, pharmacists and nurses about adverse drug effects and creates awareness regarding ADRs.

The main objective of ADRs monitoring is to disclose the quality and frequency of ADRs and to identify the risk factors that can cause the adverse reactions. [13]

DRUGS BANNED BY CDSCO:

Sr.no	Drugs	Reason for ban
1.	Terfenadine	Cause cardiac arrhythmia
2.	Rofecoxib and its formulation	Myocardial infraction was reported
3.	Valdecoxib and its formulations	Heart attack and stroke
4.	Cisapride	Caused cardiac arrhythmias
5.	Gatifloxacin formulation	Cause hyperglycemia and liver damage
6.	Tegasérod and its formulations	Cardiovascular ischemic events occurred followed by heart attack
7.	Nimusulide-basedformulations for human use in children below 12 years of age	Hepatotoxicity
8.	Cisapride and its formulations for human use	Fast heartbeat , convulsions , irregular heartbeat, QT prolongations
9.	Sibutramine	Cardiovascular risk increases by its use
10.	Dextropropoxyphene + formulations	Cardiac toxicity
11.	Fixed dose combination of Flupenthixol + Melitracen for human use	Potential risk to human life

Chart no.2 Drugs and Reason for Ban [14]

THE PRINCIPLE OF ICH:
Formulation of India's pharmacovigilance guideline:
Many countries around the world have developed their own pharmacovigilance guidelines aimed at a systematic safety reporting process. The ICH has six guidelines that cover various aspects of drug safety:
1. Clinical trials must be conducted in accordance with the ethical principles of the Declaration of Helsinki and in accordance with applicable GCP and regulatory requirements.
2. Before a trial begins, the foreseeable risks and disadvantages must be weighed against the expected benefits for the test subject and society. A study should only be initiated and continued if the expected benefits justify the risks.
3. The rights, safety and well-being of study participants are the most important issue and must take precedence over the interests of science and society.
4. The non-clinical and clinical information available on the investigational medicinal product must be sufficient to support the planned clinical study. Clinical studies must be scientifically justified and described in a clear and detailed protocol.
5. The study must be conducted according to a protocol that has received prior approval/positive opinion from the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).
6. A qualified doctor or, if necessary, a qualified dentist should always be responsible for your medical care and the medical decisions made on your behalf.[15]

AS PER INTERNATIONAL CONFERENCE HARMONIZATION EFFICACY GUIDELINES (ICHE2E) GUIDELINES. THE PHARMACOVIGILANCE METHODS CAN BE CATEGORIZED AS:
PASSIVE SURVEIL:
1. Spontaneous reporting system (SRS): a report of an ADR received directly from healthcare professional/patients/consumers.

2. Case series stimulated reporting: series of case reports can provide evidence of an adverse event. More useful for generating hypothesis than for verifying of an association between drug exposure and outcome

ACTIVE SURVEILLANCE:

Sentinel Sites	Drug Event Surveillance	Registry Comparative Observational Studies
Selected sites may provide information such as data on specific patient subgroups.	Patients-electronic prescription. Questionnaire-specified time details about clinical events indication of treatment, duration of therapy.	A registry is a list of patients presenting with the same characteristics. A) Disease registry eg: registries for blood dyscrasias. B) Specific exposure (drug register)

METHODS:-
- **Hypothesis Generating Methods-**
1. Spontaneous ADR reporting
2. Prescription event monitoring

- **Hypothesis testing Methods:-**
1. Case control study
2. Cohort studies
3. Randomized controlled trials.

PHARMACOVIGILANCE METHODS:
Many researchers developed different methods of causal assessment of ADRs by utilizing different criteria like chronological relationship between the administration of the drug and the episodes of the ADR, screening for non- drug related causes, confirmation of the reaction by in vivo or in vitro tests, and antecedent information on homogeneous events attributed to the suspect drug or to its therapeutic class, etc., to define ADRs in different categories. Currently, there is no universally

Accepted method for assessing causality of ADRs currently, there are many algorithmic methods of causality assessment but no single algorithm is accepted as the gold standard because of the shortcomings and division that subsist between them. We would explicate them in short as list [16]

DANGAUMOU'S FRENCH METHOD:
This rule of thumb has been used by the French government agency since 1977. The way of doing thing separates an intrinsic imputable (possible case between abused substance and dispassionate event) from an extrinsic imputable[17]

(bibliographical data) by the agency of seven criteria (three connected and four semi logical) in two different tables. The criteria are:

1. Drug challenge.
2. De challenge
3. Re challenge by the overall score of four possible categories.

The semi logical criteria are:
1. Semi logical (clinical signs) using per se (suggestive or other),
2. Favoring component.
3. Arbitrarynon-drugrelated (none or possible)
4. Laboratory tests show with three possible outcomes (positive, negative or no test for the event- drug pair).

KRAMER ET AL. METHOD :
This method applies when the offending drug is administered and a single adverse drug event has taken place. Each adverse event is assess independently and assessment is prepared. One of the Advantages of this algorithm is its transparency. However, certain levels of experience, expertise, and time are required to use this method effectively [18]

NARANJO ET AL. METHOD:
It is utilized to verify causality in a variety of clinical situations utilizing the categories and definitions of definite, probable, possible, and doubtful. It consists of ten questions which are answered as yes, no and unknown. The event is assigned to a probability category predicated on the total score after totaling. A total score of ≥ 9 is definite, probable is 5-8, and possible is 1-4.[19]

BALANCED ASSESSMENT METHOD :
This method evaluates a case report on various visual analog scale (vas) models that each criterion is fulfilled individually. It has an added advantage that it considers an alternative causative factor as a possibility and not just as a separate factor. Each case is assessed independently by different assessors and the evaluation depends on the assessor's skills knowledge.[20]

CIBA-GEIGY METHOD
Expert consensus meetings have resulted in Ciba-Geigy method. Experts used their clinical judgment to assess adverse drug events and assign causality on a vas. This method uses a checklist which is composed of 23 questions, which is split into three sections: (1) history of present adverse reaction, Patient past adverse-reaction history, and (iii) monitoring-physician's experience. This updated method was found to have a high degree of agreement (62%) when compared with evaluator's Assessments [21]

LOUPI ET AL. METHOD :
This method developed to assess the teratogenic potential of drug. The first sections of the algorithm sanction for the drug to be omitted if not implicated in the inception of the abnormality. The second section weighs the bibliographical data. The three questions consider alternative etiological Candidates other than the drug; chronology of the suspect drug and other bibliographical data, to arrive at a conclusion on causality.[22]

ROUSSEL UCLAF CAUSALITY ASSESSMENT METHOD :
This method is used in disease states such as liver and dermatological problems. A retrospect assessment of the reproducibility of this method among four experts had showed a 37-99% agreement rate. [23]

AUSTRALIAN METHOD
Australian method involves the evidence which helps in to draw the conclusion, such as timing, and laboratory information from case reports presented and the antecedent cognizance on the suspect drug profile is deliberately omitted in the assessment.[24]

II. CONCLUSION:
India is the fourth largest pharmaceutical producer and is emerging as an important clinical research center worldwide (25). With the introduction of new drugs in our country, a powerful pharmacovigilance system is now required to protect the population from potential risks. The damage and side effects are due to the action of some new pharmaceutical molecules. Pharmacovigilance plays a central role in addressing the challenges arising from the ever-increasing diversity and effectiveness of medicines. However, the Pharmacovigilance system is not well developed in India. Despite the recent implementation of a well-organized pharmacovigilance program in India that is in line with the objectives and recommendations of the CDCSO, the desired success still remains a distant dream. 16 However, increased awareness and education of the public and healthcare professionals, establishment of strict standards for reporting adverse reactions, effective implementation and joint efforts by government, regulators, pharmaceutical companies, healthcare professionals
And patients can lead to an effective pharmacovigilance system. India ensures availability of safe medicines to the public.

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