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RESEARCH ARTICLE

PHARMACOVIGILANCE: A REVIEW

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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.

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Introduction:-

Clinical research industry has grown around the world in past years. The main aim of pharmaceutical company is innovate new drugs in market, the company has to conduct clinical trials as per ICH GCP guidelines .pharmacovigilance is integral and important part of clinical trials.1 Pharmacovigilance was officially introduced in December 1961 was publication of a case report in the Lancet by W. McBride, the Australian Doctor who first boosted a causal link between serious fetal deformities (Phocomelia) and thalidomide a drug used during pregnancy: Thalidomide was used as an antiemetic and sedative agent in pregnant women . In1968, the World Health Organization (WHO) promoted the "Programmed for International Drug Monitoring", a pilot project aimed to centralize world data on adverse drug reactions (ADRs). In particular, the main aim of the "WHO Programmed" was to identify the earliest possible PV signals. The term PV was proposed in the mid-70s by a French group of pharmacologists and toxicologists to define the activities promoting "The assessment of the risks of side effects potentially associated with drug.2 Pharmacovigilance is a very important and inseparable part of clinical research. Both clinical trials safety and post-marketing pharmacovigilance potential 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 industries as well as various regulatory agencies across the globe have 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 products as early as possible. If any such risk is present then effectively managing the risks by applying powerful risk management plans throughout the life cycle of the product is acquired. These risk management plans are also widely known as Risk Minimization. PV is particularly concerned with ADRs, which are drug responses that are noxious and unintended, and which occur at doses normally used for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function. Continuous monitoring of drug effects, side effects, contraindications and outright harmful effects which could result in a high degree of morbidity

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and mortality, are essential to maximize benefits and minimize risks. No degree of care and caution at the pre-clinical and clinical testing stages can guarantee absolute safety, when a drug is marketed and prescribed to large populations across the country and outside. Because clinical trials involve several thousands of patients at most, less common side effects and ADRs are often unknown at the time a drug enters the market. Post marketing PV uses tools such as data investigation of case reports to identify the relationships between drugs and ADRs. The drug regulatory agencies have the responsibility of having a well-established PV system to monitor ADRs during the drug development phase and later during the life time of a marketed drug.

Aims of pharmacovigilance:

1. To Increase public protection from the new drugs
2. To contribute to assessment of benefit efficiency and risk of medicines.
3. Endorse healthy communication to the community.
4. To promote rational and safe use of medicines.
5. Efficacy of drug and their monitoring about adverse effects of drugs.
6. Pharmacovigilance keeps way of any drastic effects of medicines.

Improve public health and safeties in relation to the use of promote understanding, education and clinical training in pharmacovigilance.

History (2):

Year	Events
1747	First reported clinical trials by James Lind, proving the effectiveness of lemon juice in preventing scurvy
1937	Death of 107 children due to sulfanilamide toxicity
1950	Aplastic anemia reported due to chloramphenicol
1961	Global disaster due to thalidomide toxicity
1963	16th World Health Assembly recognize important to rapid action on ADR
1968	WHO pilot research project for international drug monitoring
1996	Clinical trials of global standards started in India India joined WHO Adverse Drug Reaction Monitoring programme
1998	Pharmacovigilance initiated in India
2002	67th National Pharmacovigilance Center established in India
2004	National Pharmacovigilance Program launched in India
2005	Conduct of structured clinical trials in India
2009-2010	PVPI Initiated

List of definations (3):

TERM	DEFINTION
Adverse event	An adverse event is defined as any un toward medical occurrence that may present during treatment with a drug but which does not necessarily have a relationship with its use.
Adverse drug reaction	An adverse drug reaction (ADR) is any noxious, unintended and undesired effect of a drug, which occurs at a dose used in human for prophylaxis, diagnosis, therapy or modification of physiological function
Post marketing surveillance	Post-marketing surveillance (PMS) is the practice of monitoring the safety of a pharmaceutical drug or device after it has been released in the market.
Clinical trials	Clinical trials are sets of tests in medical research and drug development that generate safety and efficacy data (or more specifically, information about adverse drug reactions and adverse effects of other treatments) for health interventions (e.g., drugs, diagnostics, devices, therapy protocols).
Safety signals	Safety signal refer to a concern about an excess of adverse events compared to what would be expected to be associated with products use, which can arise from post marketing data and other sources, such as pre-clinical data and events associated with other products in the same pharmacological class.
Pharmacoepidemiology	Study of the uses and effects of drugs in large populations.
Pharmacology	Study of the uses, effects and modes of action of drugs

Pharmacovigilance	The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problem.
Side effect	Any unintended effect of a pharmaceutical product occurring at normal dosage which is related to the pharmacological properties of the the drug.
Poly-pharmacy	The concomitant use of more than one drug, sometimes prescribed by different practitioners.

Adverse drug reactions (adrs):

An adverse drug reactions (ADRs) can be defined as an unintended and noxious responses to a health product which causes at the doses usually used or tested for the diagnosis, prevention or treatment of a disease or the alteration of an organic function n drugs, this scale fails to identify the offending agent. 4 TYPES OF ADRS:

1. Predictable (Type-A) Reactions- These are based on pharmacological properties like augmented but quantitatively normal response to the drug which include side effects, toxic effects and consequences of drug withdrawal. These reactions are dose dependent examples are bleeding with anticoagulants.
2. 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.

Advice about reporting:

Report adverse experiences with medications:

1. Report serious adverse reaction : Reaction is serious when patient outcome is – Death ,life threatening ,hospitalization ,required intervention to prevent permanent impairment or damage
2. Who can report: Any health care professional (doctors including dentists, nurses, and pharmacists) Where to report: please return the completed form to the nearest Adverse Drug Reaction Monitoring Center or to National Coordinating center.
3. What happens to the submitted information: information provided in this form is handled in strict confidence. The causality assessment is carried out at ADR monitoring centers by using WHO –UMC scale .the analyses form forwarded to national centers through ADR database.
4. The report are periodically review by national coordinating centers. The information generated on the basis of this report helps in continuous assessment of the benefit risk ratio of medicines.

The information is submitted to steering committee of PvPI constituted by the Ministry of Health and Family Welfare.

A list of some suspected and known drugs associated with adverse effects (5):

Drugs	**Adverse Drug Reaction**
Thalidomide	Phocomelia, Multiple Defects.
Methotrexate	Multiple defects, Fetal death.
Androgen	Virilization of limb, esophageal, cardiac defects.
Progestin	Virilization of female fetus
Stilbesterols	Vaginal carcinoma in teenage female offspring
Tetracycline	Discolored or deformed teeth, retarded bone growth
Warfarin	nose, eye and hand defects, growth retardation
Phenytoin	Various malformations
Lithium	Fetal goiter, cardiac and other abnormalities
Aspirin/Indomethacin	Premature closer of ducts arteriosus
Quinidine	Ringing in ear
Alcohol	Low IQ baby, growth retardation
Carbamazepine	Neural tube defects
Rifampicin	Orange color urine
Chloramphenicol	Grey baby syndrome.
Anticancer drugs	Cleft palate, multiple defects.
Valproate sodium	Spina bifida, limb abnormalities.
Isotretenoin	Heart and CNS defects.

Pv Programme In India **(6):**

PV Programme:

1. Administrative Body: Steering committee, Technical support committee, Strategic advisory committee.
2. National PV center: Zonal PV center, regional PV center, peripheral PV center
3. ADRs monitoring center: MCI approved medical college, private hospital\health center, and autonomous institution.

Goals of pvpi:

Short term goals:

1. To develop and implement pharmacovigilance system in India
2. To encourage the health professionals in reporting of adverse drugs, vaccines, medical devices, and biological products
3. Collection of case reports and data.
4. All MCI approved medical colleges conducted the programs.

Long term goals:

1. To expand the pharmacovigilance programme to all hospitals and centers public health programs located in India
2. To make ADR reporting mandatory for healthcare professionals.
3. To develop and electronic reporting system.

Drugs banned by cdsco (7):

Drugs	Reason for ban
Terfenadine	Cause cardiac arrhythmia
Rofecoxib and its formulations	Myocardial infarction was reported
Valdecoxib and its formulations	Heart attack and stroke
Cisaprid	Caused cardiac arrhythmias
Gatifloxacin formulations	Causes hyperglycemia and liver damage
Tegaserod and its formulations	Cardiovascular ischemic events occurred followed by heart attack
Nimusulide formulations for human use in children below 12 years of age	Hepatotoxicity
Cisapride and its formulations for human use	Fast heartbeat , convulsions, irregular heartbeat, QT prolongations
Sibutramine	Cardiovascular risk increases by its use
Dextropropoxyphene+ formulations	Cardiac toxicity
Fixed dose combination of flupenthixol + melitracen for human use	Potential risk to human life

Role of various regulatory agencies (8):

Agencies	Role of Agencies
Drug Controller General of India (DCGI)	Implementation the National Pharmacovigilance Program (NPP) in India.
Central Drugs Standard Control Organization (CDSCO)	Operate under the supervision of the National Pharmacovigilance Advisory Committee to recommend procedures and guidelines for regulatory interventions
Department of Biotechnology	Provides product evaluation and validation through support for limited and large scale field trials for agriculture products and clinical trials for health care products.
Ministry of Environment & Forests (MOEF)	PAC (Project advisory committee) approves guidelines for making data entries of the information provided by the environmental experts through the field trials for agriculture products and clinical trials for health care products.
Indian Council of Medical Research (ICMR)	Brought out the 'Policy Statement on Ethical Considerations involved in Research on Human Subjects' in 1980 and revised these guidelines in 2000

	as the 'Ethical guidelines for Biomedical Research on Human Subjects'.
Central Bureau of Narcotics (CBN)	Closely monitored all clinical trials, which require additional narcotics compliances relating to storage, import-export quotas and movement of the investigational drug
National Pharmacovigilance(NPAC)	To collate, analyze and archive adverse drug reaction data for creating healthy environment for the regulatory authorities to analyze the drug to be marketed in India
Ministry of Health and Family Welfare (MHFW)	An autonomous body for setting of standards for drugs, pharmaceuticals and healthcare devices and technologies in India

The principle of ich:

Formulation of India's pharmacovigilance guideline (9):

Globally, many countries have formulated their own pharmacovigilance guidelines with the aim to have a systematic process of safety reporting. The ICH has six guidelines pertaining to various aspects of drug safety:

E2A	Clinical Safety Data Management: Definitions and standards for expedited reporting
E2B	Clinical Safety Data Management: Data elements for transmission of individual case safety reports
E2C	Clinical Safety Data Management: Periodic safety update reports for marketed drugs
E2D	Post-approval Safety Data Management: Definitions and standards for expedited reporting
E2D	Pharmacovigilance planning
E2F	Development Safety Update Report

1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
3. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.
4. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
5. Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
6. A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favorable opinion.
7. The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
9. Freely given informed consent should be obtained from every subject prior to clinical trial.
10. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
11. Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.
12. Systems with procedures that assure the quality of every aspect of the trial should be implemented.
13. All clinical trial information should be recorded, handled ,and stored in a way that allow it's reporting, interpretation and verification.

As per International Conference on Harmonization Efficacy Guidelines (ICHE2E) guidelines9.

The pharmacovigilance methods can be categorized as:

Passive surveillance:

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 Monitoring	Registries Comparatives observational studies
The selected sites can provide information, such as data from 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 registry)

Pharmacovigilance methods can be also classified as hypothesis generation methods and hypothesis.

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.

Pharmacovilance Methods (10):

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:

Dangaumou's French method (11):-

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 (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. Dechallenge
3. Rechallenge 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 assessed 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.

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.

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.

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: (i) History of present adverse reaction, (ii) patient's 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.

Loupe 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.

Russell Clef 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.

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.

Role of pharmacist:
1. Participate in spontaneous reporting of adverse events.
2. Review prescriptions
3. Manage the adverse effects of drugs
4. Monitor drug interactions
5. Recommend changes to regimen
6. Pharmacist contributes to the drug safety by preventing, identifying and reporting ADRs report.

Major challenges in pharmacivigilance:
Pharmacovigilance facing the challenges in healthcare delivery because of not getting priority. Biasness of drug in healthcare delivery system is also a big issue (12). Poor staffing, poor funding and mostly political pressures creating barrier in implementing of pharmacovigilance programme. Other challenges are associated with health professionals are few in number but many prescriber. Lack of continuing medical education and difficulties in availability of drug information is another big issue. Some drug use problems contributing to the barriers in pharmacovigilance programme of India are availability of many types of drugs in households and dispensing the drugs by untrained persons (13) Some other drug use problems are wide spread use of injections, high levels of antibiotic use, inadequate treatment guidelines, poor prescribing .Diseases like tuberculosis, HIV/AIDS, malnutrition requires multiple drug therapy and adverse event occurs due to drug interactions and can lead to severe health hazard. Due to the above reasons risk of adverse drug events are very high. So following challenges can be avoided by implementing proper rule and regulation of pharmacovigilance programme strictly everywhere. Improvement of communication regarding pharmacovigilance between public and health professionals creates awareness and adverse occurring can be minimized. Proper knowledge on pharmacovigilance would help to health professionals to understand the effectiveness or risk of medicines that they prescribe and ensure a better healthcare to patient (14).

Following are the few points due to lack of such a point of pharmacovigilance is not attained:
1. Globalization.
2. Web –based sales and information.

3. Broader safety concerns .
4. Public health versus pharmaceutical industry economic growth
5. Developing and emerging countries.
6. Attitudes and perceptions to benefit and harm.
7. Detection of ADRs.
8. Assessment of ADRs.

Applications:

Pharmacovigilance in Clinical Practice (13):

Safe monitoring of medicines in common use should be an integral part of clinical practice. The degree to which physicians are informed about the principles of pharmacovigilance, and practice according to them, has a large impact on the quality of health care. Education and training of health professionals in drugs safety, exchange of information between national pharmacovigilance centers, the coordination of such exchange, and the linking of clinical experience of drugs safety with research and health policy, all serve to enhance effective patient care. A regular flow and exchange of information in this way means that national pharmacovigilance programmers' are ideally placed to identify gaps in our understanding of drugs-induced diseases.

Pharmacovigilance in disease control health programme:

The monitoring of medicine safety in countries where there is no safety monitoring system in place, or any health care surveillance or infrastructure, has been identified as a matter for concern. The problems are especially apparent in situations that involve the use of medicines in specific communities, for example, for the treatment of tropical diseases such as malaria, leishmaniasis and schistosomiasis and for the treatment of HIV/AIDS and tuberculosis. Pharmacovigilance should be a priority for country with a public health disease control programme.

Conclusion:-

India is the fourth largest producer of pharmaceuticals and now emerging as an important clinical trial hub in the world (15) with introduction of new drugs, a energetic pharmacovigilance system is need of the hour in our country to protect the population from the potential harm and adverse effect due to some of the new drug molecules. Pharmacovigilance plays a major role in meeting the challenges posed by the ever increasing range and potency of medicines. But the pharmacovigilance system in India is still not well developed. Disfavor of recent implementation of a well-structured pharmacovigilance program in India in accordance with the objectives and recommendations of WHO by CDSCO, desired success is still a distant dream. 16However increased awareness and training of public and medical professions, framing of strong regulations for reporting of ADRs, effective implementation and collaborative efforts between government, regulatory officials, pharmaceutical companies, health care professionals and patient may lead to an effective pharmacovigilance system in India to insure the availability of safe medicines to public.

To achieve this is to:

1. Educate health professionals to understand the effectiveness/risk of medicines.
2. Ensure that at risks in drug use are anticipated and managed.
3. Provide regulators with the necessary information to amend the recommendations on the use of the drugs.
4. Improve communication between the health professionals and the public.

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