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REVIEW ON PHARMACOVIGILANCE: DRUG SAFETY & MONITERING

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ABSTRACT:

Pharmacovigilance defined as "the science and activities relating to the detection, assessment, understanding, monitoring and prevention of adverse effects related to drugs. Pharmacovigilance play important role in public health by monitoring and interaction of drug and there impact on human being. Aim of Pharmacovigilance is patient safety. This review article contain guidelines such as Good Clinical Practice (GCP) and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).India becomes third largest country in world for pharmaceuticals production. In India these days Pharmacovigilance bring to public attention importance about reporting of adverse drug reaction. This review article brief about activities related to the pharmacovigilance. [1]

Keywords: Pharmacovigilance, Drug Safety, Spontaneous Reporting, Adverse Drug Reaction**.**

INTRODUCTION:

In this past year clinical research industry has grown all over the world. Main goal of pharmaceutical industries is to introduce novel drug into the market and the company needs to conduct the clinical trial in accordance with ICH GCP guidelines. In clinical trial .pharmacovigilance is essential and integral part. [2].

Pharmacovigilance was introduced in December 1961 was publication of report in Lancet by Australian Doctor, W. McBride who first raise causality between serious congenital anomaly (Phocomelia) and thalidomide a drug used during pregnancy. Thalidomide was prescribed as an antiemetic and sedative agent in pregnant women for morning sickness. In1968, the World Health Organization (WHO) publicized the "Programmed for International Drug Monitoring" which aimed to centralize world data on adverse drug reactions (ADRs). The main goal of the "WHO Programmed" was to recognize the earliest potential PV signals.

The term PV was introduce in the 70s decade by a French group of toxicologists and pharmacologists to define the activities promoting "The assessment of the threat of side effects potentially associated with drug. [3]

Pharmacovigilance is a integral and major part of clinical research.

PV is particularly engrossed with ADRs, which are drug responses that are noxious and unintended, and which occur at doses normally used for the prevention, diagnosis or therapy of disease, or for the modification of physiological function. Continuous surveillance of drug effects, side effects, contraindications and outright harmful effects which could result in a high degree of morbidity and mortality, are essential to maximize advantages and minimize risks or threat. At the pre-clinical and clinical testing stages no one can assurance absolute safety, when a drug is marketed and prescribed to massive populations across the universe.

Because clinical trials concern thousands of volunteers at most, less common side effects and ADRs are often not known at the time a drug enters the market. Post marketing surveillance uses tools such as data investigation of case reports to determine the causality between drugs and ADRs.

Main Goals of pharmacovigilance:

1.To improve the public safety and health in relation to uses of medicinal drugs.
2.To contribute to determination of benefit efficiency and risk of medicinal products.
3.To aid rational and safe use of medicines.
4.Promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public.

HISTORY OF PHARMACOVIGILANCE IN ASIAN NATION (4)

Year	Developments
1747	Very first known clinical trials by James Lind, proving the usefulness of lemon juice in preventing scurvy.
1937	Death of more than 100 children due to toxicity of sulfanilamide.
1950	Aplastic anemia reported due to Chloramphenicol toxicity.
1961	Worldwide tragedy due to thalidomide toxicity
1963	16th World Health congregation recognize significant to rapid action on Adverse Drug Reactions (ADRs)
1968 .	WHO research project for international drug monitoring on pilot scale.
1996	Global standards level clinical trials initiated in India.
1997	India attached with WHO Adverse Drug Reaction Monitoring Program
1998	Initiation of Pharmacovigilance in India.
2002	67th National Pharmacovigilance Center established in India.

2004-05	India launched National Pharmacovigilance Program.
2005	Accomplishment of structured clinical trials in India.
2009-10	Pharmacovigilance Program (Pv. PI) started.

List of Definition's : (5)

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 Population.
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 effects	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.

Serious Adverse Event

A serious adverse event (SAE) in human drug trials are defined as any untoward medical occurrence that is caused at any dose

(a) Results in death
(b) Is life threatening
(c) Require in-patient hospitalization
(d) Prolongation of existing hospitalization
(e) Causes congenital anomaly/birth defect.[6]

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.

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.

A list of some suspected and known drugs associated with adverse effects (7):

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

Pv Programme In India (8):

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 initiate 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 programmed 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 (9):

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
Sibutramine	Cardiovascular risk increases by its use

Role of various regulatory agencies (10):

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 (11):

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

STEPS IN PHARMACOVIGILANCE PROGRAMME

1. Finding the risk of a drug
2. Clinical trials
3. Pharmacoepidemiological study
4. Case report
5. Developing case series
6. Analysis of case series
7. Use of data mining to identify product- event combination
8. Spontaneous reporting.

ACTIVITIES IN PHARMACOVIGILANCE OPERATIONS

Case Registry

• Triage

• Registry

• Enrollment

Processing

• Data Entering

• Coding

• Labelling

Medical Review

• Serious Case Medical Review

• Non Serious Listing Review

• Aggregate Report Review

Aggregate Reports

• Analysis And Creation of IND/NDA Reports

• Analysis And Creation of Pader Reports

• Analysis And Creation of Psur & Bridge Reports

PARTNERS IN PHARMACOVIGILANCE

A complex and vital relationship exists between wide ranges of partners in the practice of drug safety monitoring. Sustained collaboration and commitment are vital if future challenges in pharmacovigilance are to be met in order to develop and flourish.

- Government
- Industry
- Hospital and academia[12]
- Poison information centers
- Health professionals[13,14]
- Patients
- Consumers
- Media

Conclusion:-

India is the fourth enormous producer of pharmaceuticals and now emerging as an important clinical trial hub in the world (15) with development of new drugs, an active pharmacovigilance system is need of the hour in our country to protect the population from the potential injury 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 grow. 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. However 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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