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BRIEF OVERVIEW OF PHARMACOVIGILANCES

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ABSTRACT

Drugs safety profile monitoring is an essential element for the effective use of medicines and for high quality medical care. Pharmacovigilance (PV), is the pharmacological science relating to the collection, detection, assessment, monitoring, and prevention of adverse effects with pharmaceutical products. The PV comes in picture after elixir sulphanilamide tragedy of 1937 and in the late 1950s and early 1960s, more than 10,000 children in 46 countries were born with deformities such as phocomelia as a consequence of thalidomide use has opened the eyes of drug regulators as well as consumers to establish a way to ensure drug safety. The hospitalization due to adverse drug reaction (ADR) in USA is about or more than 10%. In addition, it is Estimates that 1520% of the hospital inpatient suffers from ADRs. Now the pharmacovigilance system is globalised, strengthen and systematized after the establishment of World Health Organization (WHO) Programme for International Drug Monitoring. The patient safety is now becoming the priority area of pharmaceuticals. In this article, we are describing brief history and introduction of PV that will help to understand PV for beginners.

INTRODUCTION

An important part of clinical research starting from drug discovery. The drug discovery is mainly based on preclinical and clinical trials.

Pre-clinical:- Its is based on a laboratory test of a new drug or a new medical device, usually done on animal subjects, to see if the hoped-for treatment really works and if it is safe to test on humans.

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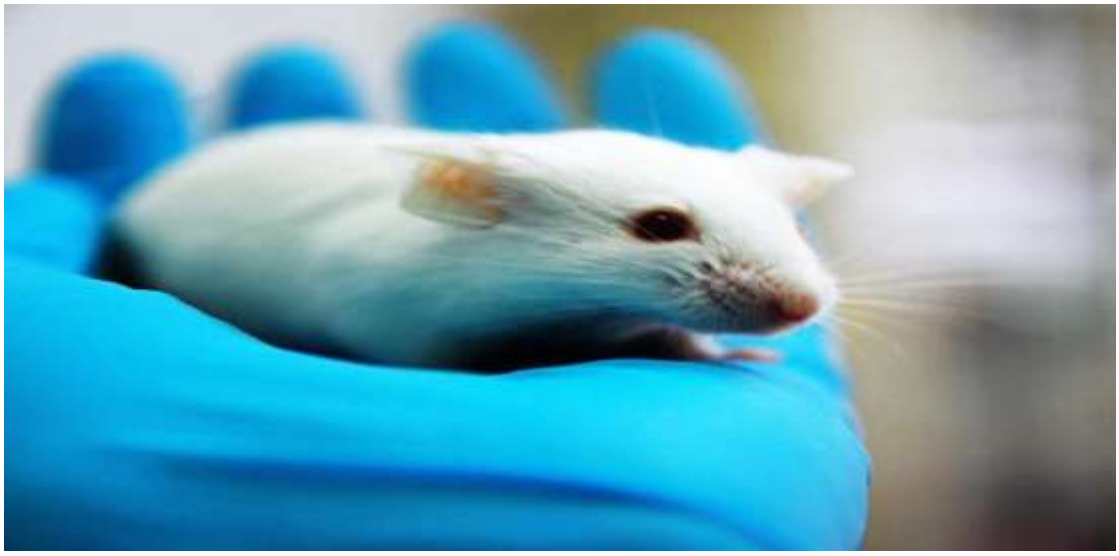

Many preclinical tests include pharmacokinetics - the study of how drugs move through living organisms. Four processes are examined in pharmacokinetic studies: absorption, distribution, metabolism& excretion.

Before a new drug comes to the market, it is extensively tested in animals and in vitro studies for safety and efficacy. If th drug is found to be promising in these studies, an Application called IND (Investigational New Drug) is filed with the United States Food and Drug Administration (main regulatory authority). If the permission is granted, then drug is tested in humans. This testing is called clinical trials.

Clinical

The International Conference on Harmonization defines a clinical trials as, "Any investigation in humans subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product, and/or to identify any ADR to an investigational Drugs, and/or to study ADME of drug with the objective of ascertaining the safety and efficacy. This is also termed as randomized control trial Clinical trials are a set of procedures in medical research conducted to allow safety and efficacy data to be collected for health interventions.

It includes number of Phase.

1. **Phase 0 trials:- (Microdosing studies)**
2. **Phase 1 trials:- (Human Pharmacology)**

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3. **Phase 2 trials:- (Therapeutic exploratory)**
4. **Phase 3 trials:- (Therapeutic confirmatory)**
5. **Phase 4 trials:- (Post Marketing Surveillance)**

Phase 1

Here, the drug is tested in normal human volunteers (extremes of ages; elderly and children are excluded). As the drug is not tested in the patients, so we cannot determine efficacy in this phase. This is mainly for toxicity and pharmacokinetic studies. This is first in human study. The idea of testing the new drug in normal humans is based on the fact that healthy persons are more likely to tolerate the adverse effects of the drug than diseased persons. Because anticancer drugs can produce unacceptable toxicity and we cannot expose healthy humans to such a toxicity, the phase-1 trials for anticancer drugs are done in the patients.

Phase 2

The drug in this phase is tested in small number of (20-200) patients. We can determine both efficacy and safety in this phase. This is first in patient study.

Phase 3

Here the drug is tested in large number of patients at several central to include patient with different genetic makeup. This is done to generalize the results of the study to variable genetic and ethnic groups.

If the drug is found to be safe and effective in these trials, then another application is filed with FDA (New Drug Application or NDA) to market the drug. If approval is granted, the drug is marketed.

Phase 4

This is post marketing surveillance of a drug to know the rare adverse effects or those occurring with prolonged use of the drug. In this phase ethical clearance is not required.

Phase 0:-

These are also called microdosing studies. Here, a very low dose 1/100th of human dose; maximum 100 µg) of the drug is administered to healthy volunteers. As the dose is subtherapeutic, so safety and efficacy cannot be known in phase 0.

However, the drug is radiolabelled and thus movement of drug in the body can be known.

This could avoid costly phase I studies for candidate drugs with unsuitable pharmacokinetics.

All phases of clinical trials must follow the ICH-GCP (Good clinical practice guidelines given by International Conference for Harmonization, so that the data generated is credible and interest of the patients/volunteers can be safeguarded.

Pharmacovigilance (Phase 4)

According to WHO, Pharmacovigilance can be defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems.

The Central Drugs Standard Control Organization (CDSCO), New Delhi, under the aegis of Ministry of Health and Family Welfare (MOHFW) has initiated the PVPI in July 2010. Initially National coordinating centre (NCC) was AIIMS, New Delhi but it was shifted to Indian Pharmacopoeia commission (IPC), Ghaziabad (U.P.) in April 2011. The vision of PVPI is to improve patient safety in Indian population by monitoring drug safety and there by reducing the risks associated with the use of medicines.

Adverse drug reaction Monitoring Centres (AMCs) play a vital role in PVPI. These AMCs include MCI approved medical colleges and hospitals, autonomous institutes and even corporate hospitals. AMCs are responsible for collecting the ADR (adverse drug

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reaction) reports from patients and sending it to NCC via entry in a software called Vigi-flow. NCC then assesses the ICSR (individual case safety reports) by various methods of causality assessment like Naranjo scale, and if found valid will commit to Uppsala Monitoring centre (UMC) in swede.

Prior identification of adverse drug reactions is most important for safety of a patient taking medicine. The information received from health care providers, pharmaceutical companies and patients should be evaluated in order to assess the risk and benefits involved with respect to a particular drug. A careful monitoring of drug usage at every step such as pharmacovigilance inspection, reporting of ADR, periodic collection of safety report, postauthorization safety studies is required. The information technology supports very effectively for development of health-care industry. In fact, clinical safety practices have improved by strong support of IT. Thus, safety, efficacy, and cost reduction of drugs are very much important. Presently pharmacovigilance plays very critical role in drug development process.

This is most important for post marketing evaluation of drugs. Due to evolution of epidemiological methods and changes in the definition of ADRs, or due to variation in marketing and promotional techniques, pharmacovigilance and pharmacoepidemiology sciences have become complementary to each other. Out of all the methods in pharmacovigilance spontaneous reporting is the most traditional one and is considered as the foundation method for post-marketing surveillance. This is useful for making hypotheses regarding safety of drugs. These hypotheses can be further analysis and verified with additional pharmacoepidemiology studies.

Historical Background Pharmacovigilance

Several disasters led to an awareness that drugs not only can heal but also can harm including sudden death caused by chloroform anaesthesia in 1877 and fatal hepatic necrosis due to arsenicals in 1922.

Chloroform

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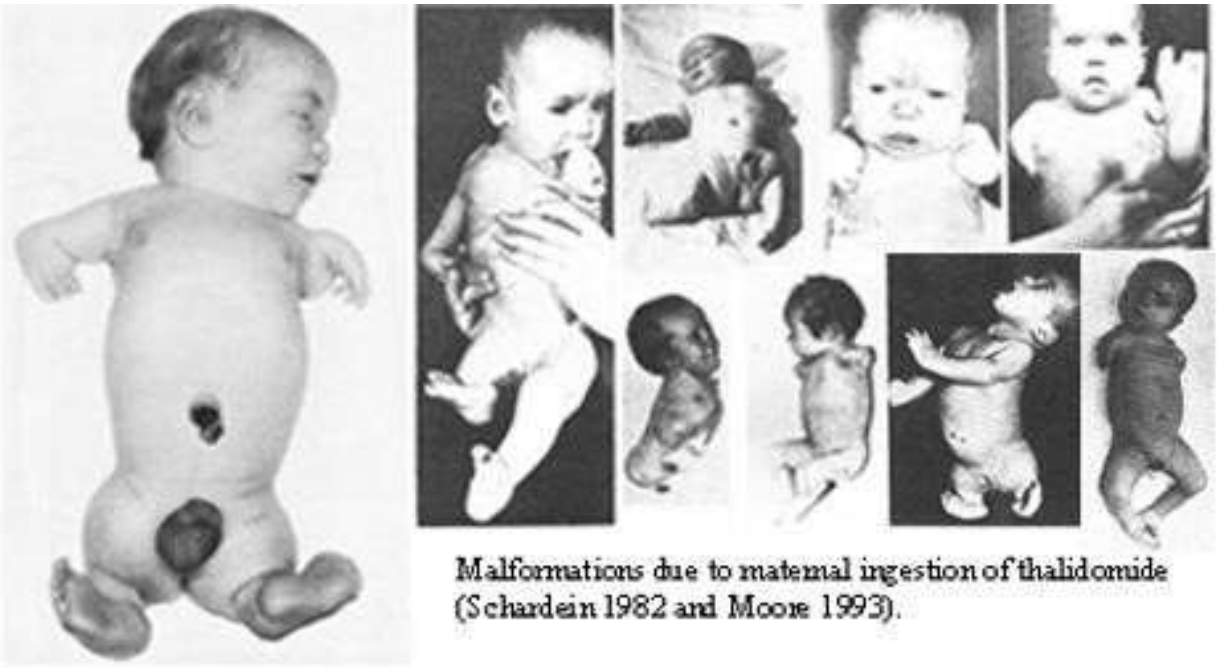
Fatal Hepatic Necrosis

In the United States a tragic mistake in the formulation of a children's syrup in the late 1930s was the trigger for setting up the product authorisation system under the Food and Drug Administration (FDA).

FDA had the authority to review new drugs for safety, by scrutinizing animal studies and small human volunteer trials for any signs of serious hazards. Child deaths after diethylene glycol was mistakenly used to solubilise sulphonamides in 1937 led to the first enactment of legislation on adverse reactions.

Following 100 deaths in France in 1952 after diethyl tin diiodide and the thalidomide tragedy of the 1960s, in England and in Germany with reports of foetal abnormalities (phocomelia and Micromelia) in relation with the use of a new sleep-inducing thalidomide,



Phocomelia (Used of Thalidomide)

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there was a rapid increase in laws, regulations and guidelines for reporting and evaluating the data on safety, quality and efficacy of new medicinal products. In the Summer of 1962 a new bill amending the 1938 Food, Drug and Cosmetic Act, the Kefauver-Harris Amendments, gave the FDA the power to approve or disallow the introduction of new drugs and the continued marketing of established compounds based on substantial evidence of their therapeutic efficacy as well as safety. Around 1980 it became compulsory to record side effects (adverse drug reactions. by the regulatory authorities in many countries to allow for a continual monitoring of the risk and benefit of products both in the investigational phase before authorization and as post marketing surveillance when the product is commercialised as an authorized product.

The consequences of this are that over the last 30 years there have been continued instances of drug recalls or precautionary statements due to the discovery of potential hazards during their use, some more notable examples include. Practolol and the mucocutaneous syndrome, Benoxaprofen and hepatic disorders / deaths in the elderly, temafloxacin and haemolytic Anemia, fenfluramine /phentermine and valvulopathy or pulmonary hypertension, terfenadine or cisapride and potential cardiac arrhythmias (especially in association with interacting agents), cerivastatin (Lipobay) and rhabdomyolysis, Vioxx with increased risk of cardiovascular events.

Key Events resulting in Laws and Regulations of pharmacovigilance.

1820 Physicians concerned about the quality of domestic and imported drugs convened the first U.S. Pharmacopeia (USP) convention. This convention wrote guidelines for the formulation of drug products, resulting in the publication of the U.S.P. which contains information about drugs including source, physical and chemical properties, tests for purity and identify, assay method of storage, category and dosage 1848 The Import Drugs Act of 1848 allowed U.S. Customs officials to inspect shipments of imported drugs. This function was later assumed by federal agents of the Bureau of Chemistry (renamed the FDA in 1930) 1877 Sudden death caused by chloroform anaesthesia 1898 The Bayer Company sold heroin as “a superior cough suppressant”

1906 Pure Food and Drugs Act of 1906: Problems with medicines and foods outraged the public and Congress. Required manufacturers to list ingredients contained in their products, meet standards of strength and purity established in the U.S.P. Amended over next 30 years to make labeling drugs with false claims a crime and to require physicians to have a license number to prescribe narcotics 1911 In Germany evaluation of marketed medicines was the responsibility of the Congress of Internal Medicine later known as Medicines Commission of the German Medical Profession.

Aim:- To identifying new information about hazards as associated with medicines.

Objectives

To monitor Adverse Drug Reactions (ADRS) of medicines with population. To improve public health and safety. To contribute to the assessment of benefit, harm, effectiveness and risk of medicines. To promote understanding, education and clinical training. To create awareness amongst health care professionals. To monitor benefit-risk profile of medicines Generate independent, evidence based recommendations on the safety of medicines Support the CDSCO for formulating safety related regulatory decisions for medicines Communicate findings with all key stakeholders Create a national centre of excellence at par with global drug safety monitoring standards.

Rationale of the study

Pharmacovigilance is one of the most important and challenging area for the pharmacist. When a pharmaceutical drug is introduced in the market there are still a lot of things that are unknown about the safety of the new drugs. These medicines are used by various patients for different diseases These people might be using several other drugs and must be following different traditions and diets which may adversely affect the impact of medicine in them. Also the different brands of same medicine might differ in the manner of their production and ingredients.

Additionally, adverse drug reactions might also occur when drugs are taken along with traditional and herbal medicines that has also to be monitored through pharmacovigilance. In some cases, adverse drug reaction of certain medicines might occur only in one country or region’s citizens. To prevent all undue physical, mental and financial suffering by patients, pharmacovigilance proves to be an important monitoring system for the safety of medicines in a country with the support of doctors, pharmacists, nurses and other health professionals of the country.

Scope Of Pharmacovigilance.

It has relevance on the suspicion of ADRs sent by the clinicians and subsequent analysis of the reports by physicians, clinical pharmacologists, and practicing pharmacists.

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Partners in Pharmacovigilance

The management of the risks associated with the use of medicines demands close and effective collaboration between the key players in the pharmacovigilance. Sustained commitment to such collaboration is vital if the future challenges in pharmacovigilance are to be met, and if the discipline is to continue to develop and flourish.

Those responsible must jointly anticipate, describe and respond to the continually increasing demands and expectations of the public, health administrator policy officials, politicians and health professionals However, there is little prospect of this happening in the absence of sound and comprehensive systems which make such collaboration possible. The constraints typically include lack of training, resources, political support and most especially scientific infrastructure. Understanding and tackling these are an essential prerequisite for future development of the science and practice of pharmacovigilance.

The key partners is given below

o Government o Industry o Hospitals and academia o Medical and pharmaceutical associations o Poisons and medicines information centres o Health professionals o Patients

Institution of Pharmacovigilance practice

There are many organizations in the U.S. and the international community that have pharmacovigilance programs designed to monitor drug use statistics, identify risks and adverse effects, and educate the medical, scientific and lay communities regarding drug safety to best protect the health of patients.

Some of these organizations include

WHO
International Society of Pharmacovigilance
FDA

NATIONAL PROGRAMME OF PHARMACOVIGILANCE

Before a product is marketed, experience of its safety and efficacy is limited to its use in clinical trials, which are not reflective of practice conditions as they are limited by the patient numbers and duration of trial as well as by the highly controlled conditions in which Clinical Trials are conducted. The conditions under which patients are studied during the premarketing phase do not necessarily reflect the way the medicine will be used in the hospital or in general practice once it is marketed.

Information about rare but serious adverse drug reactions, chronic toxicity, use in special groups (e.g. pregnant women, children, elderly) and drug interactions is often incomplete or not available. Certain adverse drug reactions may not be detected until a very large number of people have received the medicine.

Pharmacovigilance is therefore one of the important post-marketing tools in ensuring the safety of pharmaceutical and related health products.

Assessing the risks and benefits of medicines in order to determine what action, if any, is necessary to improve their safe use. Providing information to users to optimise safe and effective use of medicines. Monitoring the impact of any action taken.

Pharmacovigilance plan

For most products, routine pharmacovigilance (i.e., compliance with applicable post market requirements under the FDCA and FDA implementing regulations) is sufficient for post marketing risk assessment. However, in certain limited instances, unusual safety risks may become evident before approval or after a product is marketed that could suggest that consideration by the sponsor of a pharmacovigilance plan may be appropriate. A 30 In the vast majority of cases, risk communication that incorporates appropriate language into the product. labeling will be adequate for risk minimization. In rare instances, however, a sponsor may consider implementing a Risk MAP. Please refer to the Risk MAP Guidance for a complete discussion of Risk MAP development. pharmacovigilance plan is a plan developed by a sponsor that is focused on detecting new safety risks and/or evaluating already identified safety risks. Specifically, a pharmacovigilance plan describes pharmacovigilance efforts above and beyond routine post marketing spontaneous reporting, and is designed to enhance and expedite the sponsor's acquisition of safety information. The development of pharmacovigilance plans may be useful at the time of product launch or when a safety risk is identified during product marketing. FDA recommends that a sponsor's decision to develop a pharmacovigilance plan be based on scientific and logistical factors, including the following:

1. The likelihood that the adverse event represents a potential safety risk;
2. The frequency with which the event occurs (e.g., incidence rate, reporting rate, or other measures available);
3. The severity of the event;

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4. The nature of the population(s) at risk;
5. The range of patients for which the product is indicated (broad range or selected populations only.

Pre And Post Marketing Clinical Trails

Pharmacovigilance system studies the long term and short term adverse drug reaction or simply stated- side effects of medicines. Pharmacovigilance system involves collection, monitoring, researching upon, assessing and evaluating information received from health care workers such as doctors, dentists, pharmacists, nurses and other health professionals for understanding the adverse drug reaction. Pharmacovigilance definition includes monitoring of all pharmaceutical drugs and also other medical products including vaccines, X-ray contrast media, traditional and herbal remedies etc. especially when the reaction is unusual, potentially serious or clinically significant.

Pre-Marketing Clinical Trials

Safety monitoring in clinical trials involves collecting adverse events, laboratory investigations and details of the clinical examination of patients. Pharmacovigilance staff may be involved to varying degrees in all phases of clinical trials, including the planning, execution, data analysis and reporting of safety information. Safety issues from animal pharmacology and toxicology studies, findings in phase I studies, known ADRs with similar drugs, signals from other studies and special patient groups, (e.g. the elderly) need to be addressed. The practice of collecting all adverse events rather than suspected ADRs arose from the failure of clinical trials to detect serious reactions with practolol and after several years -experience this is now the approach adopted by companies in most studies. The involvement of pharmacovigilance staff in clinical trials also includes an important responsibility for the expedited reporting of individual cases and safety updates required by the UK Medicines Control Agency (MCA) and other regulatory authorities.

Well conducted clinical trials should be able to identify and characterize.

Common type A (pharmacologically mediated) ADRs, indicate how these Are tolerated by patients, determine a relationship between ADRs and dose Or Plasma concentration and identify pre-disposing (risk) factors if at all Possible.

These issues will usually be presented and discussed in an integrated safety analysis and clinical expert report in the Marketing Authorisation Application submitted by the company and will be the basis of ADRs, warnings and precautions included in the prescribing information i.e. Summary of Product Characteristics (SPC) or data sheet.

However, clinical trial programmes before marketing are limited in their power to detect rare, particularly type B (non-pharmacologically mediated) ADRs. This is because of the limited number of patients that are studied before marketing, the frequent exclusion of patients who may be at greater risk e.g. the elderly and those with significant concurrent disease, and the structured nature of clinical trials where drugs are given at specific doses for limited periods of time by experienced investigators. Only with wider experience after marketing during routine clinical practice and possibly in larger studies will the less common ADRs and other 'at risk' groups be identified. Post-marketing surveillance (PMS) by companies is therefore essential.

Clinical Practice of Pharmacovigilance

Pharmacology curricula should give a higher priority to the study of the safety of medicines. This would lead to an enhanced awareness of the balance between the benefits and harms of medicines. An integrated approach to therapeutic decision-making might be encouraged. Excessive and irrational drug use contributes to adverse reactions. The misuse of medicines is largely caused by the poor quality and inaccessibility of drug information available to practitioners. These problems are worsened by:

- Aggressive and inaccurate marketing and advertising
- Uninformed patient use and their demands for the latest medicines
- Lack of accurate drug information.

Indicators of inappropriate drug use can be obtained from spontaneous reports of ADRs. Case examples may serve as useful teaching tools for improving the safe use of medicines. In some countries an overwhelming volume of information (as opposed to effective communication of critical information) can serve as a deterrent to rational use. Medication errors and ADRs are well documented in hospitalized and non-hospitalized patients, and they contribute substantially to morbidity and mortality. They also contribute to the number of hospital admissions and are known to occur in the community setting. Many are predictable and preventable. This suggests considerable opportunity for minimizing the risks of ADRs through rational use, monitoring and follow-up. Early detection is important, particularly in hospitals where systems for detecting ADRs and medication errors will save lives and money. Such systems might be linked to institutional, regional or national pharmacy and therapeutics committees so that information can be used to educate professional staff in safe drug use. Prospective hospital-based surveillance reduces the risk and severity of ADRs.

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Product safety information, the way it is currently presented, often consists of lists of adverse reactions, perhaps rated in order of frequency, without real description of how these might affect quality of life. Moreover, prescribers should be free to practice without being subjected to the vested interest of manufacturers and any conflict in interest.

Difficulties in communication between patients and healthcare providers represent an important and preventable potential source of harm. The following elements are likely to reduce significantly the risks of adverse effects and their severity:

- An adequate drug history of the patient
- Rational prescribing and dispensing
- Proper counseling
- The provision of clear and understandable drug information.

Methods of PMS used by the Pharmaceutical Industry

The general process is basically that utilised by regulatory authorities and other parties working on drug safety matters. The first step is signal generation, i.e. processes that can identify possible new ADRs. There may then be a period of signal strengthening and in the second step such signals are subjected to hypothesis testing, i.e. processes that determine whether the signal does indeed indicate a new ADR, or whether it is false. Whereas the signal generation process is, in principle, relatively simple if the right systems are in place, the hypothesis testing process is challenging and often time consuming and may require a variety of different approaches. The key problem encountered is 'signal vs noise'—many adverse events observed in treated patients in the end turn out to be related to factors other than the treatment.

The Signal Generation Process

Signals may be generated through four different methods: spontaneous reporting published case reports, cohort studies and post-marketing clinical trials.

Spontaneous Reporting

Recording and reporting clinical observations of a suspected ADR with a marketed drug is known as spontaneous or voluntary reporting. The national system in the UK is the 'yellow card' scheme where doctors, dentists, and recently, hospital pharmacists are encouraged to report all suspected reactions to new medicines and serious suspected reactions to established medicines.

The culture of reporting varies greatly between countries in terms of the quantity, quality and source of reports. In the UK and Sweden most doctors report directly to the national regulatory authority rather than pharmaceutical companies, although some report to both. In other countries such as Germany and the USA the majority of reports go initially to companies who then report to the authority in that country. The proportion of reports received by companies directly from patients also varies considerably between countries and is highest in the USA.

Published Case Reports

Publishing case reports of suspected ADRs in medical journals is an established way of alerting others to possible drug hazards. However, it has limitations as only a very small proportion of cases can be published, reports are sometimes poorly documented, publication depends on editorial selection and there is often considerable delay between occurrence and publication. Companies and some regulatory authorities actively monitor the published literature for such reports. This will involve screening key journals where ADRs are described, monitoring publications such as 'Reactions Weekly' (ADIS International) and running regular standard searches on databases such as Medline and Excerpta Media. With efficient regulatory and company safety surveillance it is now relatively rare for a new ADR to be signalled primarily through published cases, however, publication of well characterised ADRs still fills an important function in alerting physicians. A more recent development is reports of possible ADRs appearing on the Internet and many companies are still determining how they should best handle them.

Cohort Studies

Companies may set up or sponsor prospective, non-interventional cohort type studies either to answer safety questions raised after marketing or as a general hypothesis generating and testing tool to be used as need arises. In the past, company sponsored studies were considered poor at detecting new safety issues mainly because of slow recruitment and lack of control groups. Since 1994 such studies in the UK have been subject to the SAMM (Safety Assessment of Marketed Medicines) guidelines which have ensured a closer dialogue between companies and the MCA.

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Post-Marketing Clinical Trials

Large randomized clinical trials with wide entry criteria (similar to SPC indications) can be valuable in assessing the safety of marketed products as well as confirming efficacy. Because patients are randomised to different treatments they do not have some of the problems inherent in cohort studies, for instance whether the control group is truly comparable. Companies can choose to set up or sponsor such studies to address particular safety issues. To make them sufficiently large to provide more information than the trials performed for product registration purposes may make them prohibitively expensive, hence a simple protocol and study plan with limited observations is desirable.

Pharmacovigilance is particularly concerned with adverse drug reactions.

Introduction of ADR (Adverse Drug Reaction)

According to world health organisation (WHO), an ADR can be defined as any response of a drug which is noxious and unintended, that occurs at doses used in humans for the prophylaxis, diagnosis or therapy of disease or for the modification of physiologic function purposely, excludes therapeutic failures, overdoes, drug abuse, non-compliance, and medication errors. Moreover, it has been regarded as an appreciable harmful reaction which results from an intervention related to the use of a medical products. An adverse effect, which occurs as overstate of the desired therapeutic effect, forms a part of ADR, whereas, side effects are generally related to the therapeutic activities of a drug which may be beneficial as well as harmful. Thus, it may be suggested that an ADR is a harmful reaction or unwanted reaction that is followed by the administration of a medicinal product or a combination of drugs under normal conditions of use.

However, various type of ADRs have been reported which include Type A, Type B and Type C, adverse reactions.

Type A, ADRs are commonly related to dose which enhance the normal therapeutic effect of drug, with common reasons of overdose and alteration of the dose, whereas.

Type B, have been considered as the idiosyncratic responses that are usually uncommon, unpredictable and not related to the pharmacological actions of the drug.

Type C ADRs have been suggested to be connected with long-term drug therapies in which both serious and common effects on public health takes place.

Mechanisms of adverse drug reactions An ADR

the unpleasant and harmful reaction resulting from an intervention after receiving the medication. The mechanism of adverse reactions can be divided into direct toxicity studies and hypersensitivity reactions that occur due to the pharmacokinetic and pharmacodynamic alterations of the drug products. Direct toxicity reactions may be attributed to the toxic effects of a compound or its metabolites which are apparent in various organ systems, inducing noxious chemical reactions, physiological dysfunction, DNA damage or injury to cellular structures and tissues. On the other hand, hypersensitivity reactions can be determined after the immune system of the individual shows an exaggerated response to a drug or its metabolites, which include allergy and anaphylactic reactions. It has been suggested that the results of direct cytotoxicity and excessive immune reaction are noticeable in various organs like skin, liver, lungs, bone marrow and kidneys.

Types of Adverse Drug Reactions

the types of adverse reaction can be studies in two main headings, i.e., more common ADRs including type A and B reactions; and less common ADRs which include type C, D and E reactions.

Type A

Adverse reactions have been commonly related to dose which enhance the normal therapeutic effect of drug. Moreover, the pharmacokinetic or pharmacodynamic factors of the drugs have been found to be responsible for type A ADRs. The pharmacokinetic causes of type A reactions may be attributed to the genetic variations in order to cause ADRs. Moreover, hepatic diseases have been noted to cause pharmacokinetic variations

Type B

Adverse effects have been noted in marginal number of patients and are often sensitive or idiosyncratic reactions. Moreover, type B adverse reactions have been suggested to be unforeseen and unpredictable; showing less or no relationship with the dosage

The pharmacokinetic causes of type-B ADRs remains scarce, that can be an aspect to bizarreness of absorption or distribution, which suggests that the bioactivation of drugs yield reactive species responsible for a significant preparation of type-B adverse effects.

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Type C

Adverse reactions have been attributed to both serious and common effects having notable outcomes on public health from chronic disease toxicities. Moreover, type C reactions have been regarded as the reactions with chronic effects related to long-term drug use, such as analgesic nephropathy or extrapyramidal effects.

Type D

also termed as delayed ADRs, are the reactions that have been found to be apparent after sometime of the treatment. The development of secondary cancers in patients treated with alkylating agents like cyclophosphamide is the best example of type D adverse reactions. In addition, type E ADRs have been known to occur when drug treatment has been terminated suddenly, the examples of which include withdrawal seizures on terminating anticonvulsant therapy and adrenocortical insufficiency subsequent to glucocorticoids termination

Type E :

Termination of treatment

Ex: Tachyphylaxis.

Detection of ADR

Patients susceptible to adverse drug reactions must be properly identified and monitored. However, specific group of patients include:

1. Those having multiple disease processes.
2. Those patients taking multiple medicines in large number 3) Those having history of adverse drug reactions.
3. Those patients already suffering from kidney or liver diseases
4. Paediatric or geriatric patients
5. Patients who are undergoing treatment with medicines having high incidence of adverse effects
6. Patients treated with medicines having low therapeutic index
7. Patients undergoing treatment with medicines already known to be associated with serious adverse effects
8. Patients having abnormal investigation results.

Subsequently the ADRs might act through the same pathological and physiological pathways for different diseases there it becomes sometimes difficult or impossible to distinguish that whether the toxic effect is due to pathological effect or physiological effect.

However, the following step-wise approach might be helpful in assessing possible drugrelated ADRs :

1. It must be ensured that the ordered medicine is correct and is actually administered to the patient at the advised dose.
2. The onset of the suspected reaction must be verified that it occurred after and not before the administration of drug and also the observation made by the patient must be carefully discussed.
3. It helps in determining the interval of time between the beginning of treatment of drug and the onset of the event;
4. Suspected ADR must be evaluated after the drug is discontinued or the dose is reduced and then after the status of the patient must also be monitored. However, if found suitable, then the drug treatment must be restarted and relapse of any adverse events must be monitored regularly.
5. Alternative causes must be analysed (other than the drug) that could have caused the reaction on their own.
6. Relevant updated literature and personal experience as a health care worker on drugs and their adverse reactions must be used and also must be verified that whether there are any earlier conclusive reports on the same reaction.
7. The Drug regulation authority and National Committee are very important resources to obtain information on any type of adverse drug reactions. The drug manufacturer can also be a resource to consult.
8. Any suspected ADR to the person nominated for ADR reporting must be exported in the hospital or directly to the health District.

Detection Method of ADRs

1) Pre-marketing studies
2) Assessing Causality
3) Postal Survey Method.
4) Post-marketing surveillance
5) Communicating ADRS

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Reporting to ADR

ADR or adverse event reporting involves the triage, receipt, data entering, distribution, assessment, archiving and reporting of adverse event data and documentation.

Procedure

1. All healthcare professionals including clinicians, dentist, pharmacist, nurses,
2. All non-healthcare professionals including consumers, patients, etc.
3. ADR should be reported immediately.
4. The report can be incorrect and unreliable if the ADR reporting is delayed.

Who can Report

Physician, physiotherapist, Nurses, Pharmacist etc.

What to Report

1. All ADRs as a result of Prescription and Non-Prescription medicinal products
2. All suspected ADRs irrespective so product information delivered by the company.
3. Unpredicted reaction of the ADRs along with the product irrespective of their nature and severity.
4. A serious reaction (whether expected or not)
5. All suspected ADRs related with drug-drug. drug-food or drug-food supplements interactions.
6. Overdose or medication error leading to ADRs.
7. Uncommon lack of efficacy or detection of suspected pharmaceutical flaws.

How to Report

1. Standardised ADR reporting form should be used for reporting.
2. ADRs in the reporting from should be filled appropriately in case an ADR is encountered.
3. Separate forms with complete information should be used for every individual.
4. The completely filled ADR form should be then returned to the nearest adverse drug reaction monitoring Centre (AMC) or to National Coordinating. Centre.
5. Any follow-up information should be forwarded by another ADR form, in case of an ADR case that has been reported already. It can also be communicated by telephone, fax or email.
6. Follow-up reports should be recognisable including following points:

i. Follow-up Information
ii. Date of Original Report
iii. Patient Identity

What Happens to Submitted Information

1. At Adverse Drug Reaction Monitoring Centres (AMCS) by using UMC scale the causality assessment should be carried out.
2. The analysed forms should be forwarded to the National Coordinating Centre via ADR database.
3. At last the data should be examined and sent to the Global Pharmacovigilance Database that is managed by the WHO Uppsala Monitoring Centre in Sweden.
4. The reports should be revised from time to time by the National Coordinating Centre (PvP).
5. The information produced based on these reports aids in continuous evaluation of the benefit-risk ratio of medicine

Causality Assessment

Causality assessment can be defined as the assessment of relationship between the treatment with any drug treatment and incidence of an adverse reaction or event. It helps in checking and also evaluating that whether the particular treatment due to which an adverse event or reaction has occurred is co-related with the drug or not. Causality assessment is an important part of ADR reporting system and important task, conducted by National Pharmacovigilance Programme in every country.

What is the causality assessment methods for pv.

Methods of causality Assessment

1. Expert Judgement / Global Introspection
2. Agie Algorithms (standardized Assessment 3) Probabilistic Bayesian Approaches.

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1) Expert Judgement / Global Introspectrum

In this Method, the experts express their opinion about the possibility of causation of the 'rean (ADP drug causing") by considerations all the Available data regarding the suspected ADR. The assessment and evaluation of ADRS by these experts is purely based on Knowledge and experience. their respective Experts involved. are: clinical Pharmacologist and physicians. Ex: WHO- Uppsala Monitoring centre causality. Assessment criteria (WHO-UMC). Visual Analogue Method... Swedish Method Regulatory Agency WHO- UMC This is a Method that is globally accepted. It is practical tool for detecting unknown and unexpected ADR. The Walti offer assessment. The assessment is based on 4 criteria 4) Time relationship between the drug use and the adverse event. Absence of other competing causes (Medication) B) Response of drug Response & to withdrawal on dose Reduction • drug re-administration. The level of causal assessment is grouped into 4 categories based on the no. of above criteria being met. The categories as follows: are lot of out of certain when all 4 criteria a b c d met. eg Injection site rea" after 30 sec. Following a subcutaneous injection o
Probable→→→ When criteria a, b clare met. eg: Diarrhoea and Ampicillin, Possible When only a criteria met. eg: Abnormal liver function test after taking antihistamine lens
unlikely → When criteria and a and b met. eg: colon cancer diagnosed after 3 doses of an antibiotic.

2) Ag Algorithms / standardised Assessment Method

Algorithms consist of some quest … eg:- Dangau mous French Method. Naranjo scale. "! Summary Time plot..
A) Naranjo Scale •It is widely accepted method. The Method is used to
B) determine whether.
C) ADR is actually due to the drug rather than the result of other.
D) factors -The scale consists of to questions that are answered as 'yes' or 'moor "dont know?..
There answers are -assigned via a score termed definite, probable, possible or doubtful.
This score gives the probability of. ADR. Naranjo scale is given, Definite When scale is 2
Probable when scale is 5-8 Possible -When scale is 1-41614
3) Probabilistic Approaches ⇒ This Method involves the transformation an of prior probability at into a post erion probability. Prior probability is calculated from epidemiological info.. Posterior probability combines the epidemiological background info.
with the evidence in the individual case This method allows stimulated assessment of Multiple causes eg: Australian Method, BARDI

BARDI (Bayesian adverse Reactions Diagnostic

Instrument) ot It is a method used to calculate odds in favourn of a particular drug causing an adverse event •compared with alternatives cause. (posterior odds) The posterior odds factor is calculated by consideri ng Six assessment & subsets: one deals with the background epidemiological or clinical trials info. (prior odds pro) and the other si deals with. case specific Info: (likelihood ratios).... The 5 likelihood ratios (LR) are :

1. patient History (Hi)
2. Timing of AF with respect to drug administrat" (Ti)
3. characteristics of AE (CH)
4. Drug dechallange (De)
5. Drug Rechallange (Re)

Pharmacovigilance Programme of India (PVPI)

Directorate General of Health Services, Central Drugs Standard Control Organization (CDSCO), under the guidance of Ministry of Health & Family Welfare, Government of India in collaboration with Indian Pharmacopeia commission, Ghaziabad initiated a nation-wide Pharmacovigilance Programmed (PVPI) for the protection of f patient's health by providing safety from the drugs However. Indian Pharmacopeia commission (IPC), Ghaziabad coordinates these Programs as a National Coordinating Centre (NCC).

1. On 14th July 2010 the Government of India started the Pharmacovigilance Programme of
India (PVPI) with All India Institute of Medical Sciences (AIIMS), New Delhi as its first National Coordination Centre (NCC) for monitoring Adverse Drug Reactions (ADRS) in the country for purpose of safety and protection of public health.
2. 22 ADR monitoring centres including AIIMS, New Delhi in the year 2010 were set up under this Programme. 3) However, on 15th April 2011 the National Coordination Centre was later shifted to Indian Pharmacopoeia Commission (IPC), Ghaziabad, Uttar Pradesh from All India

Institute of Medical Sciences (AIIMS. New Delhi) in order to safeguard and protect implementation of this programme in a better way.

July, 2015 onwards Indian Pharmacopoeia Commission- Pharmacovigilance Programme in India (IPC-PVPI) became the National Coordination Centre

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Mission

To protect the health of Indian population by ensuring that the benefits of medicine used overshadow the risks associated with its use.

Vision

To improve patient safety and welfare in Indian population by monitoring the drug safety and thereby reducing the risk associated with use of medicines.

Vaccine Pharmacovigilance

Pharmacovigilance of Vaccines in India.

3. One of the largest manufacturer and exporters of vaccine is India.
4. One of the largest immunisation programs in the world is run by India (Universal Immunisation Program, UIP.)
5. Every year, UIP targets 27 million newborns and 30 million pregnant women.
6. The Government of India in 1986 initiated AEFI (Adverse Events Following Immunisation Program) surveillance program.
7. In 2008 national and state AEFI were set up by the government.
8. In Health and Family Welfare department, national AEFI Secretariat was established.
9. At Lady Harding Medical College. New Delhi, Collaborating Centre was established AEFI Technical
10. The response and Surveillance of AEFI is reported in pharmacovigilance.
11. Auxiliary Nurse Midwife, Medical Officers, Health Workers, District Health Authority.
12. Immediate serious AEFI and monthly routine reporting is done in this.
13. Primary Health Centre. Community Health Centre. District Immunisation Centre are included in vaccine programs under pharmacovigilance.

VACCINATION

A complex biological formulation that gives active acquired immunity to a particular infectious disease is called vaccine. The process of ingestion of antigenic agents to stimulate an individual's immune system to develop adaptive immunity to a pathogen is called vaccination. It is one of the most effected ways The to prevent diseases. According to the CIOMSAVHO Working Group on Vaccine Pharmacovigilance. Vaccine pharmacovigilance is defined as the science and activities relating to the:

1. Detection,
2. Assessment.
3. Understanding,
4. Reporting of adverse events following immunisation and other vaccine- or immunisation related issue. and to avoid the untoward effects of the vaccine or immunisation.
5. The WHO defines an Adverse Event Following Immunisation (AEFI) as. "a medical incident that takes place after an immunisation causes concern, and is believed to be caused by the immunisation."
6. The goal of vaccine PV is "the early detection and timely response to adverse events following immunisation, in order to minimise negative effects to the health of individuals and lessen the potential negative impact on immunisation of population".

Goals

1. Vaccine pharmacovigilance aims to minimise negative effect of adverse events by detecting the risk early and providing appropriate response (risk management) to the problem.
2. To lessen the potential negative impact on immunisation programr is another goals of vaccine programs.

Objectives

1. To promote the safe use of vaccines for its consumer.
2. To detect the adverse event early.
3. To make sure that healthy people usually receive the vaccines.
4. To ensure that infants and children consume most of the vaccines.

Basic Termenology used in Pharmacovigilance

1) Drug Medicine

It is any physiological and pathological change experienced by the beneficiary after having pharmaceutical product. It comprise of complete formulated and registered product, including thepresentation, packaging as well as associated information.

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2) Adverse Event

Adverse event, also known as adverse experience, can be defined as any unexpected/ inappropriate or untoward medical incidence associated with drug use in humans, with or without any relationship to the drug. it can be any unintended or unfavorable sign, symptom, or disease associated temporarily with the use of any drug.

For example: Physical findings (increase in B.P. or temperature), abnormal laboratory values. symptoms (nausea, headache, dizziness etc.) and medical errors (miscalculation. misunderstanding of verbal orders, name confusion in drugs, overdose, route of drug administration etc.). Transfusion reactions, accidental injuries, Surgery.

3) Adverse Drug Reaction

i. It can be defined as "Any unintended, noxious or undesirable effect of drug occurring at doses used normally in humans for the purpose of diagnosis, prophylaxis or therapy of disease, or for any changes to be done in physiological function"

ii. For example: Cough, nausea, vomiting. diarrhea, headaches, skin reactions (redness, rashes, itching), anaphylaxis, anemia, etc.

4) Suspected Adverse Reaction

It occurs when there is a reasonable possibility that the adverse event is caused by the specific drug. Reasonable possibility indicates a causal relationship between the adverse event and drug.

5) Serious Adverse Event or Reaction

It can be defined as any unintended, or untoward medical intervention at any dose resulting in significant disability or life threatening death. A serious adverse needs hospitalization of inpatient or its prolongation.

6) Unexpected Adverse Reaction

It is an adverse reaction in which the nature or severity of drug is not constant that is mentioned in the domestic labeling or market approval or is a known characteristic of the medicine.

7) Side Effect

It is an undesirable physical symptom caused by taking a drug or undergoing medical treatment or therapy. For exampe: Diarrhea, constipation, dermatitis or skin rash, dizziness, dry mouth, headache, drowsiness, insomnia, etc.

8) Drug Alerts

It is an action of informing a large group of people in comparison to the initial information holders of alleged relation between a drug and an adverse reaction. Generally, the term can be used in different contexts that are confusing like an alert may be from a manufacturer to a regulator or from a regulator to the public

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