

REVIEW ARTICLE

Pharmacovigilance: A Review

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ABSTRACT

At an ever-growing scale people are using newer and more effective drugs with various medical conditions which are being manufactured with developing scientific advances. Safety and efficacy are the two major concerns about any drug. Now a day's significance of pharmacovigilance is growing and with the contemporary high-profile drug extractions by the regulatory agencies, consumers and others have become more responsive about the advantage and hazards of remedies.

Key words: Pharmacovigilance, Adverse Drug Reaction, Adverse Events, Pharmacogenomics, Pharmacoenvironmentology, Pharmacoepidemiologists.

INTRODUCTION

The satisfactory reimbursements and hazards possessed by the drug at the time of approval of a new drug are decided on the basis of the recent data available. New information will be generated when drug is marketed which may have an effect on the advantage and disadvantage profile of the product. To ensure safe use of the drug, the thorough assessment of the new evidence generated through pharmacovigilance activity is needed. At the pre-clinical and clinical testing stages of the new product when prescribed to huge inhabitants there is no safety of that product. The impacts of pharmacovigilance on the life cycle of the product is needed to understand, that can be achieved by more and more clinical trials and other clinical research activities being conducted in India^[1]. In new class of all drugs, continuous observing and evaluation is required under the real-world conditions on the side effects and contraindication a strong pharmacovigilance system is required. The products which are already approved and marketed in the delimited markets of Japan, USA, Europe or other countries Indian market has mostly launch only those products. In 1986 a formal adverse drug reaction (ADR) monitoring system consisting of 50 million populations was covered by 12 regional centers, so Pharmacovigilance is not new to India. Uppsala Centre for Adverse Event Monitoring joined by India from 1998, great achievements were made

during this retro, but much more still needs to be done in this field in India. Day by day, the importance of pharmacovigilance is increasing and with recent high-profile drug withdrawals was done from markets the regulatory agencies, consumers and others because the value of pharmacovigilance increased and people become more aware about the advantage and hazards of medicines^[2].

WHO DEFINITION:

WHO define the Pharmacovigilance (PV) as the pharmacological science relating to the detection, evaluation, understanding and prevention of adverse effects, particularly long term and short term side effects of medicines^[3].

In Generally, pharmacovigilance is the knowledge of amassing, observing, examining, assessing and estimating evidence from health care workers and patients on the contrary effects of drugs, natural products, herbal and traditional medicines with a view to:

- Finding new risks associated with remedies.
- Prevention and control of infectious diseases in patients.
- Reporting requirements in special situations.

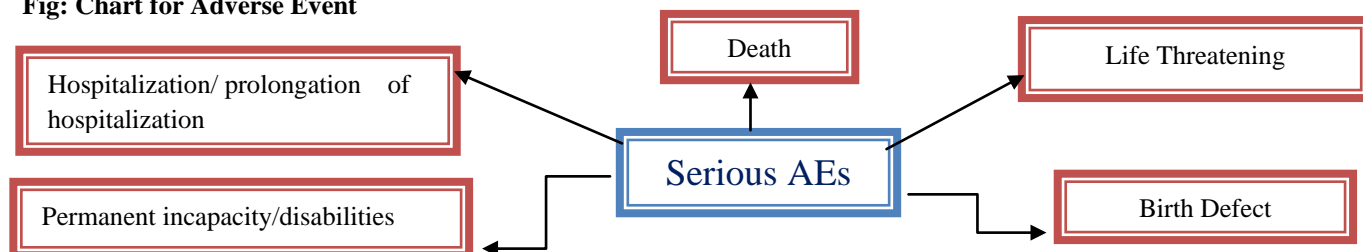
Pharmacovigilance is an important and integral part of clinical research. Both clinical trials safety and post marketing pharmacovigilance are critical throughout the product life cycle^[2].

AIM OF PHARMACOVIGILANCE^[4]:

Expand precaution for patient.

- Increase public protection from the new products.
- To contribute the knowledge of value, detriment, efficiency and hazard of medicines.
- Encourage edification and clinical training.
- Endorse healthy communication to the community.
- To promote rational and safe use of medicines.

Fig: Chart for Adverse Event



ADVERSE DRUG REACTION:

At a normal dose sometimes the given medications may harm the patients which are called as an **adverse drug reaction (ADR)** [5]. Meaning of adverse drug reaction is different from side effect. The evaluation of ADRs is most critical in the field of pharmacovigilance. Concerning marketed remedies, a suitable definition of an adverse drug reaction is as follows:

In patient at normal doses harmful and unpleasant reaction of drug for treatment and medication of disease or for changes of biological utility.

Mainly two types of adverse drug reaction which are as follows:

1. Unlisted / Unexpected Adverse Drug Reaction

An adverse reaction is the nature or harshness of drug which is not reliable with the proper product data which available at the time of the clinical trials [6].

- Company is needed help during investigators brochure for an unapproved drug
- Brief summary of drug data sheet for an official product.

2. Listed / Expected Adverse Drug Reaction

The information about ADR its like nature or severity and specificity of the drug is already recorded [6].

ADVERSE DRUG REACTIONS REPORTING:

When the adverse reaction to drugs is curious, potentially serious or clinically important, all health care workers, including doctors, pharmacists, nurses and other health experts are requested to clarify it. It is necessary to report an adverse drug reaction to the pharmacovigilance

ADVERSE EVENT:

An adverse event is not having any casual relationship with patient treatment but its one of the medical incidence with patient. So an adverse event (AE) can be any critical or Unintentional indication of disease which is temporally related with the use of a medication [5,6] (Fig 1).

program even if you do not have all the facts or you are unsure that the medicine is definitely responsible for causing the adverse reaction.

SPONTANEOUS REPORTING SYSTEMS

- Regionalization.
- Repossession of further data.
- Access to all important pre- and post-marketing information.
- Detailed drug utilization data.
- Standardized Evaluation of causality and significance.
- Encouragement.

LINKING PHARMACOVIGILANCE WITH PUBLIC HEALTH PROGRAMMES USING MEDICINES:

An important arm of patient carries Pharmacovigilance. Treatment or prevention of disease by use of medicines is the main aim of the Pharmacovigilance. Unfortunately some medicine will sometimes harm patient. For avoiding or minimizing harm associate with medicines, good pharmacovigilance will identify the hazard aspects in the short period of time. Public Health Programmers (PHP) are intended to develop the health of target inhabitants by use of medicines, education, environmental modifications, nutrition involvement, behavioral changes and preventive actions such as immunization, hypertension and assessment for breast cancer are the important components of a PHP [7].

The systematized efforts of the public to care for and encourage people's health are known as Public health. Through mutual or community actions can be increase the health of all the people, this can be mainly done by the combination of sciences and skills.

In developing countries, agencies and health workers with a skill and proficiency conducts PHPs. In developed countries, patients have direct contacts with PHPs instead of usually contact with a physician. In developing countries PHPs, without proper instruction and training can lead to higher risks of adverse events, ADRs or medication error. These problems could be related to various syndromes, population characteristics, drugs, health-care providers or the health-care system.

Sometimes use of the substandard products for the formulation of medicines creates many tragic results. By mistake death of more than 500 people, mostly children occurred when diethylene glycol (DEG) when incorporated in pharmaceutical preparations. Federal Food, Medicine & Cosmetic Act passed by United State Congress in 1938, because of the DEG poisoning 105 people died in 1937. Acute renal failure was caused by DEG because it is a highly toxic organic solvent when ingested. Death of many people occurred because it was used as a diluent for sulfonamides.

Before launching new medicines in the market, it should be tested for toxicity. Number of children death occurred in 1998 due to the contaminated-DEG cough syrup in India but still toxicity due to DEG continues to appear^[8].

The risks of adverse reactions, their diagnosis and reporting should be to know by the public health team and the PHP Manager. Serious and/or unexpected adverse reactions have been confidently deal by PHP Manager and should contribute to any subsequent decision-making process.

Due to some reason, pharmacovigilance is not mentioned as a part of public health which is as follows:

- Misunderstanding of the meaning
- Intentions of the discipline;
- Deficiency of services for receipt,
- Administration and exploration of reports
- Absence of a commentary culture.

To develop a complete understanding of the importance of pharmacovigilance, this document will help in encouragement of programme manager.

The aims of pharmacovigilance in PHPs are same as those of the national pharmacovigilance centre. These are:

- Health professionals should be knowledgeable for safe use of medicines;
- Evaluation of the hazards and efficiency of remedies used

- Educating and advising patients.

The control and treatment of tuberculosis, malaria, HIV/AIDS, schistosomiasis and immunization programmes provide by the Phamecovigilance. It is also essential in providing the necessary infrastructure for vital drugs programmes.

PHARMACOGENOMICS- A COMPONENT OF PHARMACOVIGILANCE:

For the treatment of different type of disorders, different classes of medication are available. A major issue in clinical world is that why particular person with particular disease respond to a particular drug or tolerate a drug well and other patient does not respond or can not tolerate the same drug. Due to difference in genetic pattern, patient may respond differently to medication and develop different adverse effects^[9].

Difference in drug response and drug tolerability can be understood by use of Pharmcogenomics and Pharmacogenetics. Many types of assumed ADRs are complex and involve or depend upon several factors which cause disease for examples it include the metabolic syndrome, suicidality, hepatic dysfunction and cardiac abnormalities. Pharmcogenomics and Pharmacogenetics are clinically substantial and are frequently associated with drug therapies, but they cannot be easily or completely recognized to a drug exposure. Individual who are susceptible to ADRs and has a potential to reduce the personal and population costs of drug related morbidity can be helped by Pharmacogenetics.

The most common example of enzyme deficiency is glucose-6-phosphate dehydrogenase (G6PD) deficiency, with many of discrepancies. It is associated with acute haemolysis on exposure to oxidizing drugs such as primaquine, sulfonamides and sulfones. For G6PD deficiency phenotypic tests are recommended before using drugs such as primaquine, but it is not known how often this is carried out.

Although promising, the eventual impact of pharmacogenomics profiling for identification of ADR susceptibility among individuals would depend upon incidence of drug toxicity, prevalence of variants severity of consequence and also the availability of rapid, reliable and cost effective assays. Several researchers have proposed the integration of genomic information with the pharmacovigilance database, which can not only enhance signal detection but also aid in determining whether genotypic examination should be performed prior to initiation of drug therapy. However, several key operational, regulatory, ethical and legal issues need to be

addressed before the potential role of pharmacogenomics in ADR detection and prevention can be realized.

LINKING

PHARMACOENVIRONMENTOLOGY WITH PHARMACOVIGILANCE:

When drug administered orally in human or animal through the gastrointestinal tract drug may either be fully or poorly absorbed and along with through the feces unabsorbed drug will pass into the surroundings. When route of administration is parenteral or oral the drug may be metabolized to some amount and expelled into the surrounding areas (including through respired air) as main drug or its metabolites, or as a mixture of both. So if once they are inserted into the environment, they enter food chains and concentrate as they move to other life cycles^[9]. Insertion of elements or remedies into the environment through anyway and at any attentiveness disturbing the balance of environmental science is called as Ecopharmacology (Ecosystem + pharmacology). If these drugs enter through living organisms via elimination subsequent to pharmacotherapy, it should be a specific field of pharmacology and not of environmental studies. This domain may be referred as Pharmacoenvironmentology^[10].

Before proposing a new drug to market, it must be evaluated for the risk assessment and concentrations in the environment by FDA. The drug is assumed to cause acceptable risks when the risk valuation determines that the concentration will be less than billion. FDA has never turned down a proposed new drug based on estimated environmental concentrations, and no actual testing is conducted after a drug is marketed to see if the environmental concentration was estimated correctly. At given therapeutic doses of particular drugs, it is possible to find the adverse effects on environment. Same as clinical trials, we can also estimate drugs on environs is accomplished elaborately. Pharmacovigilance concerns to the undertakings adverse effects of medication at therapeutic doses on human and animal. At the therapeutic concentrations of given drugs, the frame work of Pharmacoenvironmentology may be an enlargement of Pharmacovigilance which is allocating with the possessions related to the surrounding areas and ecosystem. Pharmacologists having this particular expertise (pharmacoenvironmentologist) may be is a compulsory component of the team assessing different aspects of drug safety. We need to monitor the effects of drugs not only as a good

medical practice, but also to safe guard our environment.

BUILDING A NETWORK OF PHARMACOVIGILANCE AND PHARMACOPEIDEMIOLOGISTS:

Pharmacovigilance and pharmacoepidemiology is relatively new fields in India, it is absolutely essential for a group of experts to come together to formulate guidelines for the set-up and implementation of relevant processes within pharmacovigilance. A core group will need to be formed which will have representatives from Indian pharmaceutical companies and personnel's from the regulatory authority. Epidemiologists, pharmacists and other people can also contribute to the development of the system^[11].

LINKING PHARMACOVIGILANCE WITH ACADEMICS:

Good pharmacovigilance programmes needed for every country. In many developed countries pharmacovigilance is being taught in theory, but they should move toward the practical area. Pharmacovigilance should ideally be taught to small groups of medical students, interns, postgraduates etc. Teaching of PV should be problem-based, activity-based and linked to the rational use of medicines. Students should be trained during their internship and residency and problem-based learning serve as hesitant blocks for the success of the concept. Pharmacovigilance can be taught at the under graduate course. Awareness of pharmacovigilance among doctors in their specialties and extending their support in teaching the subject should be created by Pharmacologists^[12].

The clinicians and other healthcare workers should participate in spontaneous ADR reporting, during post-marketing observation from drug use in public. The knowledge and training of the clinicians will generate the quality of reports. Teaching pharmacovigilance to medical students makes them realize that all medicines can cause ADRs and their responsibility to participate in the national pharmacovigilance system.

A major source for pharmacovigilance to get information about drug is spontaneous reporting. Pharmacovigilance must be linked to component on the rational use of medicines (RUM). Pharmacovigilance course for pharmacologists and other healthcare personnel has been suggested by Uppsala Monitoring Centre (UMC) and the international collaborating centre for ADR.

The UMC's training programme is a good starting point for a thorough knowledge of pharmacovigilance to postgraduate (PG) students

and pharmacology. They should be active members of pharmacovigilance programmes in their medical colleges or teaching hospitals.

PG students should also be made aware of the need and importance of reporting ADRs and the reporting procedure.

Doctors (general practitioners and specialists) are important in reporting ADRs to the pharmacovigilance programme. Educated doctors in the community will increase the effectiveness of the reporting programme. Pharmacologists have an important role in creating awareness among doctors working in the community. Training programmes for doctors should be problem-based, activity-based and carried out in small groups. In Wales, a distance-learning programme in pharmacovigilance, linked to educational credits, was found to significantly improve the rate and quality of ADR reporting by general practitioners and pharmacists.

PHARMACOVIGILANCE OF HERBAL MEDICINES:

Now a days herbal medicine are very popular in general public but the safety of these remedies are major issue for population of nation and national health committee [13]. The use of herbs in Traditional medicines continues to expand rapidly across the world. In various national health-care settings for the health of the patients now they are taking herbal medicines or herbal products. However, mass media reports of adverse events tend to be sensational and give a negative impression regarding the use of Herbal medicines in general rather than identifying the causes of these events, which may relate to a variety of issues [14].

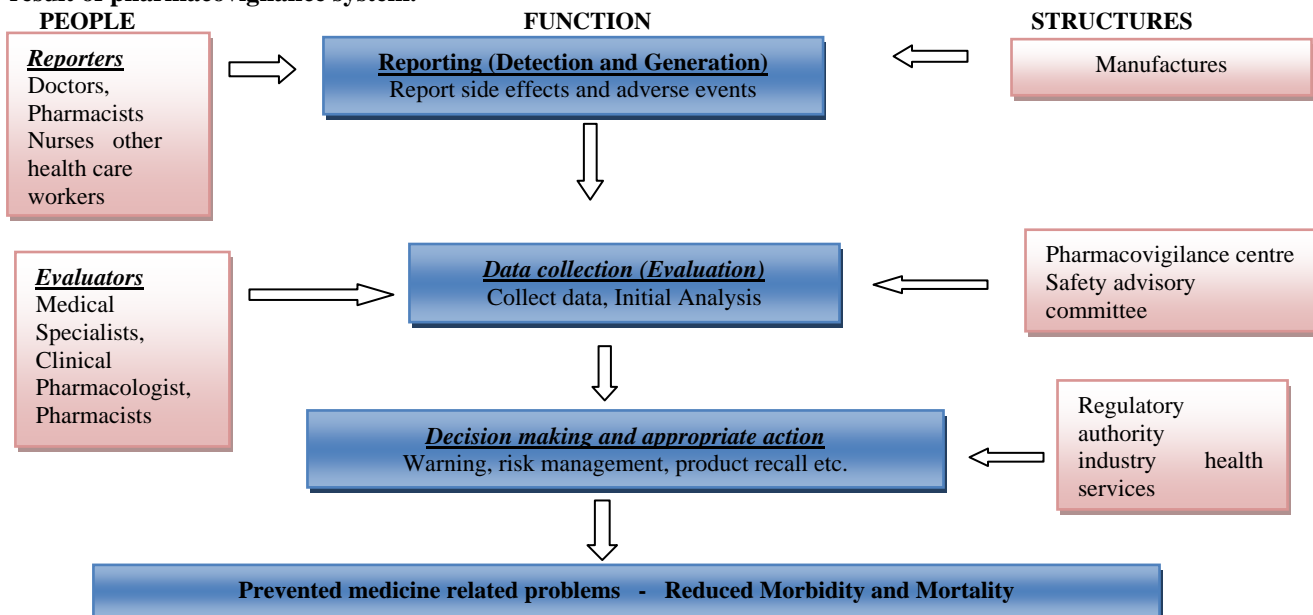
PHARMACOVIGILANCE PROGRAMME IN INDIA:

The Central Drugs Standard Control Organization (CDSCO) under the aegis of Ministry of Health & Family Welfare, Government of India in collaboration with Department of Pharmacology, All India Institute of Medical Science (AIIMS), New Delhi has initiated a nation-wide pharmacovigilance programme for protecting the health of the patients by assuring drug safety which will include data for drugs, biological, vaccines, diagnostics and medical devices from public and private sector. The comprehensive national programme is coordinated by the Department of Pharmacology at AIIMS as a national coordinating centre [15].

FRAMEWORK FOR PHARMACOVIGILANCE IN INDIA:

The National Pharmacovigilance Program established in January 2005, New Delhi and the performance of various Zonal, Regional and Peripheral Centers will be supervise by the National Pharmacovigilance Advisory Committee (NPAC) and will perform the functions of “Review Committee” for this program. A country-wide Pharmacovigilance programmed is initiating by the Central Drugs Standard Control Organization (CDSCO) under the guidance of Ministry of Health & Family Welfare and Government of India. The National Pharmacovigilance Centre shall coordinate the program at CDSCO. The National Centre will operate under the supervision of the National Pharmacovigilance Advisory Committee to recommend procedures and guidelines for regulatory services [16] (Fig 2).

Fig 2: illustrates the constant pharmacovigilance system describing the people, functions, structures of a pharmacovigilance and medicine system. Medicine-related problems, morbidity and mortality should be decreased as a result of pharmacovigilance system.



INTERNATIONAL COLLABORATIONS:

To record and report adverse effects of drugs in different country patients is the main principal basis for the WHO International Drug Monitoring Program, through which over 90 member countries had send their reports to the Uppsala Monitoring Centre where they are processed, evaluated and entered into the WHO International Database^[15].

The **Uppsala Monitoring Centre** (the UMC), located in Uppsala, Sweden, is the field name for the World Health Organization Collaborating Centre for International Drug Monitoring. The UMC works by collecting, assessing and communicating information from member countries national pharmacovigilance programs in regards to the benefits, harm, effectiveness and risks of drugs.

EUROPE:

The national competent authorities (NCAs) coordinate and conduct the European Medicines Agency (EMA). The pharmacovigilance database of human and animals consisting of all suspected serious adverse reactions are maintained and developed by the EMA in the European Community and the system is called EudraVigilance.

JAPAN:

Pharmaceuticals and Medical Devices Agency (PMDA) and Ministry of Health, Labour and Welfare (MHLW) regulate the pharmacovigilance in Japan.

UNITED STATES:

Three primary branches of pharmacovigilance in the U.S. include the FDA, the pharmaceutical manufacturers, and the academic/non-profit organizations.

SERBIAN:

To achieve the optimum number of 2000 spontaneous reports/year, regular contact with healthcare professionals, and finally Good Pharmacovigilance Practice is the final goal of the Serbian Pharmacovigilance System^[17].

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