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A Review of Pharmacovigilance Emergence and its Scope in India

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INTRODUCTION

The World Health Organization has defined adverse drug reactions (ADRs) as "a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the modification of physiological function"[1]. There are 2 traditional pharmacologic classifications. Type A, generally referred to as "side effects," are dose-dependent and predictable reactions that account for 85–90% of all ADRs. Type B reactions, generally referred to as "idiosyncratic" or "allergies," are not dose dependent and are unpredictable and account for approximately 10–15% of all ADRs. Patients sometimes misapprehend some side effects as allergies (e.g., diarrhea with amoxicillin/clavulanate), which may be maintained through the patient's medical record.

Adverse drug reaction [ADR] is an unwanted or harmful reaction experienced following the administration of a drug or combination of drugs under normal conditions of use and is supposed to be related to the drug. An ADR usually require the drug to be stopped or the dose reduced.

Meanwhile 2012, the definition applies to reactions occurring as a result of error, misuse ,or abuse, and to suspected reactions to medicines that are unrestricted or being used off-label in addition to the approved use of a medicinal product in normal doses. Medicines that are associated in ADR related hospital issues include antiplatelets, anticoagulants, cytotoxics, immunosuppressants, diuretics, antidiabetics and antibiotics[2].

DIAGNOSIS

The diagnosis of an adverse drug reaction is seldom questionable, the clinical appearances often being similar, if not identical, to a number of primary dermatoses and infectious conditions (particularly viral exanthems) and, in the situation of transplantation patients, graft-versus-host disease (GVHD). The histologic diagnosis can also be awfully difficult, as drug reactions can demonstrate several inflammatory histologic patterns that mimic other dermatoses (i.e., spongiotic, psoriasiform, lichenoid, pityriasiform)[4].

The problem is increased in the immunologically compromised patient. In human medication the most common symptoms of ADRs (e.g. nausea/vomiting, diarrhea, abdominal pain, rash, pruritus, drowsiness, headache) are also reported in 80% of healthy patients on no medication. A corresponding situation may also exist in veterinary medicine. An investigation of the US Center for Veterinary Medicine Freedom of Information summaries for seven NSAIDs reveals that simultaneous placebo-treated dogs display similar incidences of the most encountered adverse signs: vomiting, diarrhoea/soft stool and in appetence. In addition, lethargy, dermatitis, pyrexia, abdominal pain and even death were reported in the placebo group. A recent UK study of ill health following vaccination of dogs (Edwards et al 2004) revealed a similar incidence of reported signs of ill health in newly vaccinated and unvaccinated dogs. Surprisingly, the reported incidence of signs of ill health was 19% and 25% in the 2-week period prior to questionnaire completion for recently vaccinated and unvaccinated dogs respectively. Placebo administration in humans causes an surge in the percentage of patients with symptoms and the number of symptoms per patient. Although a true placebo effect apparently does not exist in animals, veterinarians are reliant on the explanations of owners who may be subject to various conscious or subconscious factors that may influence their understanding of their pet's behaviour. The problem is further compounded by the diversity of different that any one particular drug may induce. Inversely, a given clinical appearance may be caused by a large number of dissimilar drugs.

The incidence of adverse drug reactions (ADRs) in the general as well as paediatric populations remains unknown, although data from

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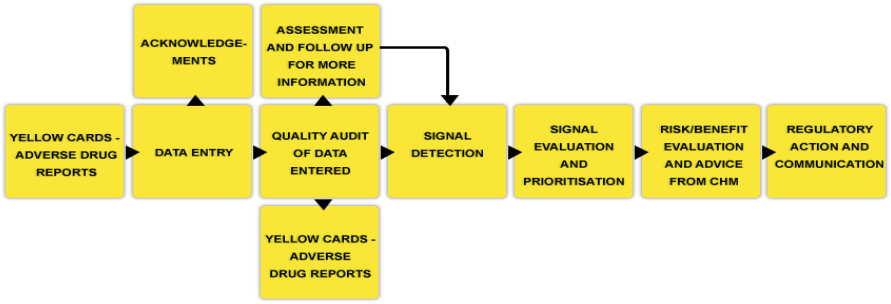
hospitalized patients show it to be 6.7%, with a 0.32% incidence of fatal ADRs. Databases such as the U.S. Food and Drug Administration (FDA) MedWatch program (http://www.fda.gov/medwatch/index.html) likely suffer from underreporting. Cutaneous reactions are the most common form of ADRs, with ampicillin, amoxicillin, penicillin, and trimethoprim/sulfamethoxazole (TMP/SMX) being the most frequently implicated drugs (Tables 177.1 and177.2). Although the majority of ADRs do not appear to be allergic in nature, 6–10% can be attributed to an allergic or Adverse drug reactions can occur if the drug is wrongly administered to a patient. . Over the past 2 decades, NHS England (the National Patient Safety Agency [NPSA]) and the Institute of Medicine in the United States have both compiled massive data eminence that this is a serious and widespread issue in hospitals and drug administration errors are the single most preventable cause of patient harm. Although the majority of these reported errors lead to minimal or no harm, in anaesthesia they have the potential to cause irresistible effects. A U.K. study of 12,606 reported incidents showed medication errors occurred in 1,120 patients.5 Of these, only 15 (1.3%) resulted in severe harm or even death. A further 6-month examination of reports to the NPSA regarding drug errors in intensive care showed of the 2428 incidents reported, 355 different drugs were involved, with morphine, gentamicin, and norepinephrine the most common.6 A review of anesthetic drug errors states that an error can happen as often as every 133 anesthetics.7 Much work is being done to prevent administration errors and recent evidence suggests that double-checking of drugs with a second person may reduce errors.8,9munologic mechanism. Importantly, given the high probability of recurrence of allergic reactions, these reactions should be preventable, and information technology–based involvements may be especially useful to reduce risk of exposure [3,5].

Despite the limitations associated with determining the incidence of ADRs in children, it is estimated that their occurrence in patients 0-4 yr of age (3.8%) is more than double that seen at any other time during childhood or adolescence. In the outpatient setting, children age 0-4 yr accounted for 43% of clinic and emergency department visits for ADRs. One study reported that 60% of the ADRs occurred in those <1 yr. The reasons for this are not currently known but may involve developmental differences in pharmacokinetics and pharmacodynamics (i.e., altered dose-concentration-effect relationship), age-associated differences in physiologic "systems" that modulate drug- and metabolite-mediated cellular injury (e.g., immune system), and therapeutic use of drugs known to have a relatively high incidence of producing ADRs (e.g., delayed hypersensitivity reactions associated with β-lactam antibiotics). Also, it is important to recognize that infants can experience ADRs from drugs that are not directly administered to them therapeutically, but rather from maternal drug exposure (transplacental, breastfeeding). Examples include neonatal abstinence syndrome associated with maternal opiate use, production of a hyperserotonergic state in neonates born to mothers who received selective serotonin reuptake inhibitors during pregnancy, and opiate toxicity in breastfed infants whose mothers were taking codeine for pain management. In these cases, drug accumulation caused by reduced activity of drug-metabolizing enzymes linked with development and, potentially, pharmacogenetically determined phenotypical changes, which in concert can produce a level of systemic drug exposure capable of producing an extravagant response or frank toxicity.



PHARMACOVIGILANCE

Medicines and vaccines have renovated the prevention and treatment of diseases. In

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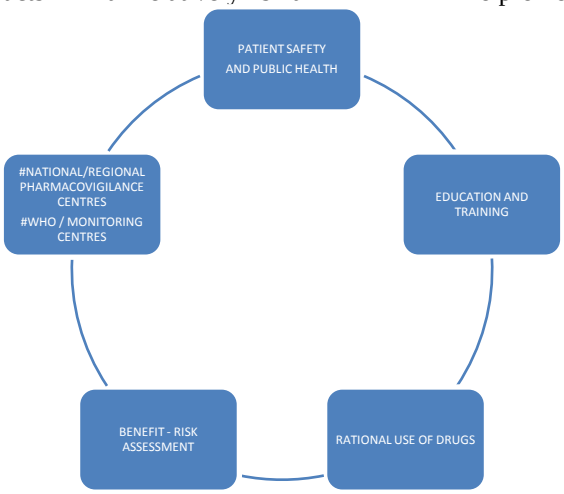
addition to their benefits, medicinal products may also have side effects, some of which may be undesirable and / or unexpected.

Definition: "Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine/vaccine related problem".

All medicines and vaccines undergo laborious testing for safety and efficacy through clinical trials before they are authorized for use. However, the clinical trial process involves studying these products in a relatively small number of selected individuals for a short period of time. Certain side effects may only emerge once these products have been used by a heterogeneous population, including people with concomitant diseases, and over a long period of time.

AIMS

- To improve patient care and safety
- To improve public health and safety
- To contribute to the assessment of benefit , harm, effectiveness and risk of medicines
- To promote education and clinical training
- To promote rational and safe use of medicines



METHODS OF PHARMACOVIGILANCE

1. Individual case safety reports
2. Clinical review of case reports
3. Cohort event monitoring
4. Longitudinal electronic patient records
5. Spontaneous reporting
6. Periodic safety update reports (PSUR)
7. Expedited report
8. Record linkage

WHO PROGRAM FOR INTERNATIONAL DRUG MONITORING

- Started 1968
- Located in Uppsala ,Sweden
- Collaborating centre for maintaining global ADR database – Vigibase

ROLES OF WHO COLLABORATING CENTRE

- THE UPPSALA MONITORING CENTRE

1. Recognise first warning signals of serious ADR to medicines
2. Evaluate the hazard
3. Undertake research into the mechanisms of action to aid the development of safer and more effective medicines[6].

HISTORY AND DEVELOPMENT OF PHARMACIVIGILANCE

Pharmacovigilance began about 170 years ago, even though it was not yet named as such at that time. Pharmacovigilance began as a reaction to a major and unsuccessful oversight in the testing of a popular pharmaceutical drug. The practice of pharmacovigilance has gained significant momentum since its beginnings in the 1960s. In the end of 2010, the World Health Organization Pharmacovigilance Program listed about 134 countries as members. Today, pharmacovigilance is a standard practice in the development and testing of pharmaceutical drugs[7] .It is a structured activity in the professional health field, it also had important social and commercial implications aimed at monitoring the risk/benefit ratio of drugs, improving patient's safety and the quality of life. The historical phase helps us to understand how pharmacovigilance helped us to achieve such important results for man's health and for pharmacology itself, and to identify the challenges that await Pharmacovigilance in future years[8].

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On Jan 29, 1848, a young girl (Hannah Greener) from England died after receiving chloroform anesthetic before removal of an infected toenail. Sir James Simson discovered that chloroform was a safer and powerful anesthetic and he introduced it in clinical practice. The cause of Hannah's death was investigated to understand what happened to Hannah, but it was impossible to identify the cause of her death. And it was concluded that she died of a lethal arrhythmia or pulmonary aspiration[8].

In 1937, there were more than 100 deaths associated with a sulfanilamide elixir[9]. Essentially, sulfanilamide elixir wasn't the real cause behind those patients's death, but its solvent (diethyl glycol) was the fundamental reason for their death. The pharmaceutical companies were not aware of diethyl glycol's toxicity, which caused this catastrophe. Concerning this event, the Federal Food, Drug, and Cosmetic were founded to guarantee drug safety before its approval and their release to the market[10]. Public outcry lead to the creation of the Food, Drug and Cosmetic Act. Its aim was to modernize the public health system and introduce protections regarding the safety of drugs before their market approval [9].

By 1959 as many as new active substances were being introduced to the market each year. Combined with the emergence of the randomized controlled trial as the basic tool of experimental therapeutics, medicine appeared to have entered a pharmacological paradise. The thalidomide disaster brought this pharmacological paradise to an unforeseen halt. Introduced as an 'a toxic' hypnotic in 1956, thalidomide was marketed in Britain with specific claims for safety in both the elderly and children. Initial reports, in 1961, Dr. McBride, an Australian doctor, witnessed a connection between congenital malformation of babies and thalidomide suggesting that thalidomide might be teratogenic and were quickly confirmed but not before several thousand babies, exposed to the drug in utero, had been afflicted by the characteristic embryopathy. The thalidomide disaster had intense effects on drug development, the pharmaceutical industry, and professional and public attitudes to drug safety. It resulted in the institution of legal controls on pharmaceutical manufacturers throughout the Western world, and it laid to the development of what is now known as 'pharmacovigilance'[11].

In 1963, the Sixteenth World Health Assembly adopted a resolution that endorsed the need for early action regarding reporting adverse drug reactions. This assembly ultimately led to the creation of the World Health Organization (WHO) Pilot Research Project for International Drug Monitoring (World Health Organization, 2002)[7].

In response to this crisis, UK released the Yellow Card Scheme in 1964 to facilitate drug toxicities reporting process. And in 1965, the European legislation was established to regulate the operation of medicinal products.

In 1968, the WHO Program for International Drug Monitoring was formed [9], in 1978 the scientific and technical responsibility of the WHO Program was transferred to Sweden. And it was the start of the first WHO collaborating center, the Uppsala Monitoring Centre in Sweden [10].

In 1992, the European Society of Pharmacovigilance (ESoP) was founded, turned into the International Society of Pharmacovigilance (ISoP). The aim of this society was to promote Pharmacovigilance, and enhance all aspects of the safe and proper use of medicines [8]. In 1995, the European Medicines Agency (EMA) was created [9].

In 2001, EudraVigilance was founded. It is an official European database for managing and analyzing information on suspected adverse reactions to medicines which have been authorized for the market or being studied in European clinical trials[8].

In 2012, major amendments were established in the European Pharmacovigilance, and this was the start of the New European Pharmacovigilance. A new definition for the Adverse Drug Reactions (ADR) is included in the New European Pharmacovigilance: "A response to a medicinal product which is noxious and unintended." Because the new definition of ADR is broad, medication errors, drug misuse, and drug abuse were also included under the umbrella of this definition. It also included strengthening of the EudraVigilance Database [10].

In 2017, the new Eudravigilance was founded. The marketing authorization extended their access to the EudraVigilance Database to fulfill their obligations. The obligations include the continuous monitoring of EudraVigilance data and the statement of validated signals to the Agency and national regulatory authorities, as outlined in Commission Implementing Regulation (EU) N. 520/20121[8].

The origin of pharmacovigilance in India goes back to 1986, with a formal adverse drug reaction (ADR) monitoring system consisting of 12 regional centers, each covering a population of 50

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million, was proposed for India. However, nothing much happened until a decade later when in 1997, India joined the WHO Adverse Drug Reaction Monitoring Programme based in Uppsala, Sweden. This attempt was unsuccessful and hence, from 1 January 2005, the WHO sponsored and World Bank-funded National Pharmacovigilance Program for India was launched [8]. It was renamed as Pharmacovigilance Programme of India (PvPI) in 2010. The PvPI works to safeguard the health of the Indian population by ensuring that the benefit of medicines outweighs the risks associated with their use [12].

SCOPE OF PHARMACOVIGILANCE

The main aim of pharmacovigilance is to give clear information regarding drug safety and its Risk or benefits of drugs to the patients. Patients are the end users of medicine. Patient information leaflet relating to medicine is to be provided to the patient to increase the advantages of the medication and to reduce the risk associated with them. It is crucial for Risk Minimization by making an early detection and preventing the progression of the adverse effects[13]. Recently, the concerns of pharmacovigilance have been widened to include herbal, traditional and complementary medicines, blood products, biological, medical devices and vaccines[14].

1. In Herbal Medicines: There is an increasing awareness at several levels of the need to develop pharmacovigilance practices for herbal medicines. Awareness has arisen not only because of the extensive use of herbal medicines, but also because of their high-profile herbal safety concerns which have had an impact on the public Health[15].
2. In Ecopharmacovigilance: Ecopharmacovigilance refers to drug-related toxic effects within the ecosystem and all effects on humans and other species in the environment. A survey reported disposal of prescription residuals are either thrown to landfills or drains[16]. The potential route of environmental entry of pharmaceutical include excretion of pharmaceutical ingredients from patients, release from the skin, left over medicines, Manufacturing units and hospital, discharge from drug formulations and animal carcass etc[17].
3. In Haemovigilance: Haemovigilance is a process of data collection and analysis of blood transfusion related adverse reaction to investigate and prevent their occurrence or reoccurrence. It is an integral part of quality management in a blood system and preventive action for the improve end of the quality and safety of blood products and the transfusion process[18].
4. In Immunization and Vaccination: The goal of vaccine pharmacovigilance is the early detection and timely response to adverse events following immunization, in order to minimize negative effects to the health of individuals and lessen the potential negative impact on immunization of population. The majority of vaccines are administered to a vulnerable (children) as well as healthy population, a strict safety supervision of vaccines is essential[19]. The vaccine administration route is known to be another important factor influencing safety of a vaccine. Potential implications need to be considered, in particular for alternative routes of administration (e.g. intranasal, oral and intradermal). The impact of adjuvants needs to be explored[20].

IMPORTANCE OF PHARMACOVIGILANCE

WHO defines pharmacovigilance as "the science and activities relating to the detection, assessment, under-standing and prevention of ADRs or any other medicine-related problem"[21]. Whenever a medicinal or pharmaceutical drug is introduced in the market a lot of things that are unknown about the safety of that new drug can be observed. These medicines are used by various patients who must be following different lifestyle and used for different diseases who might be using several other drugs and which may produce adverse impact of medicine in them. In addition, Adverse drug reactions might also occur in patients who take these drugs with traditional and Herbal medicines which should be monitored through pharmacovigilance. . To prevent all intemperate physical, mental and financial suffering of patients, pharmacovigilance proves to be an important monitoring system for the safety of medicines in a country with the support of doctors, and other health care professionals such as pharmacists, nurses and other of the country[22].

The importance of pharmacovigilance is as follows.

- Drug Safety Monitoring

"Drug safety monitoring is a risk mitigation exercise in which the ADRs caused by therapeutic drugs, biologicals or medical devices can identified, prevented or minimized. It is the

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process of identifying expected and unexpected adverse reactions that may resulting from the use of medicines during post-marketing phase"[23]. The current global network of pharmacovigilance centers, coordinated by the Uppsala Monitoring Centre(UMC), would be strengthened by an independent system of review. This would consider contentious and important drug safety issues that have the potential to affect adversely on public health beyond national boundaries. Nowadays, pharmacovigilance has been confined, mainly to detect adverse drug events that were previously either unknown or poorly understood. Pharmacovigilance is considered to be important and integral part of clinical research and these days it is growing vastly in many countries. Currently many pharmacovigilance centers are working for drug safety monitoring in this global pitch, however, at the turn of the millennium pharmacovigilance faces major challenges in aspect of better safety and monitoring of drugs [24].

All the medications that intended for clinical purposes have to undergo several meticulous preclinical and clinical testing for assuring their safety and e Occasionally, adverse events are seen only during usage of products among general population. The process whereby adverse effects are detected through regular monitoring after the release of drug in market is called pharmacovigilance[25].

- Clinical trials regulation

Clinical trials are used to come stumble on a chemical or biological compound's safety and efficacy. Pharmacovigilance in clinical research tries to discover whether the benefits exceed the risks; if they do, drug manufacturers take steps to obtain approval to market that new drug. Trials are strictly monitored by an investigator and the pharmaceutical company who responsible for developing a medicinal product. Phase I, II, and III clinical trials are important before a drug company can apply for a new medicine's market authorization. During clinical trials, the analyst collects and analyzes serious adverse events (SAEs), finding whether the drug in study caused the SAEs. If they come to a conclusion that the adverse side effects were causal, they are categorized as adverse drug reactions (ADRs).If approved, without any ADRs the drug company may conduct Phase IV clinical trials to produce additional data on the efficiency and safety profile. PV in clinical trials is necessary for healthcare professionals and consumers to update the potential risks of medications and to assess risk to benefit ratio. The risk-benefit ratio is improved, monitored, and updated accordingly .

Various approaches can be adopted, such as; drug registries, spontaneous reporting systems, electronic health records. And after when a distinct adverse reaction is recognized, the list of side effects on the label must be updated. At times, PV data can remove a drug from the market (drug recall) due to dangerous side effects[26].

- Drug Regulation

Many drug regulation problems related to the safety and quality of drugs exists in many places. Effective drug regulation is necessary to ensure the safety, efficacy and quality of drugs, and also the accuracy and appropriateness of the drug information available to the public. Regulation of drug encloses a variety of functions like licensing, inspection product assessment and registration, adverse drug reaction (ADR) monitoring, QC, and control of clinical drug trials[27].

- Pharmacoepidemiological studies
- Case reports
- Developing case series
- Analysis of case series
- Use of data mining to identify product -event combination
- Spontaneous reporting
- Safety of traditional medicines, Vaccines, biological medicines

PHARMACOVIGILANCE PROGRAMME OF INDIA

The Pharmacovigilance Programme of India (PvPI) is an Indian government organization which identifies and responds to drug safety problems. Activities of PvPI comprises receiving reports of adverse drug events and taking necessary action to prevent it . The Central Drugs Standard Control Organisation established the program in July 2010 with All India Institute of Medical Sciences, New Delhi as the National Coordination Centre, later shifted to Indian Pharmacopoeia Commission in Ghaziabad on 15 April 2011[28].

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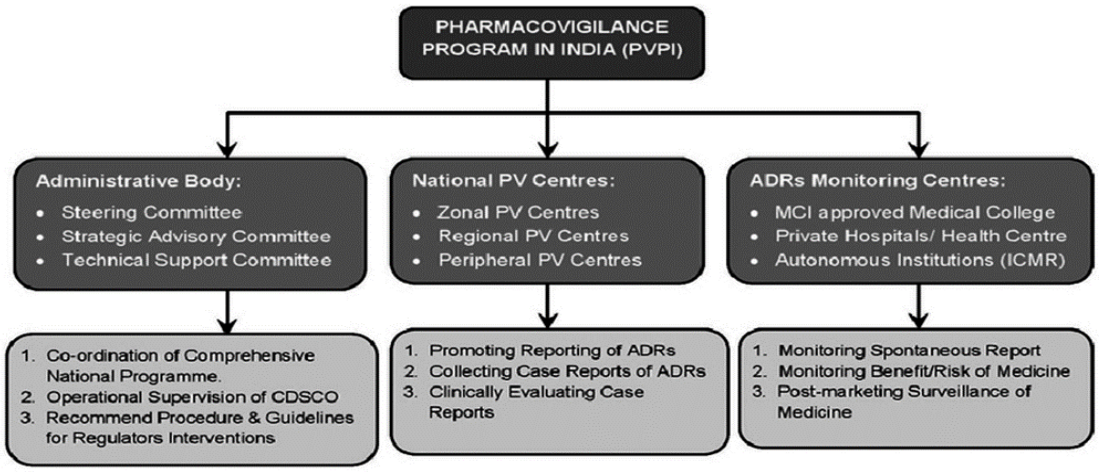

[29] Pharmacovigilance in India was initiated in 1986 with a formal adverse drug reaction (ADR) monitoring system, under supervision of the drug controller of India. World Health Organization (WHO) Programme joined by India for International Drug Monitoring in 1998, but was not successful. Behind, the National Programme of Pharmacovigilance was launched in 2005, and was renamed as the Pharmacovigilance Programme of India (PvPI) in 2010. Numerous steps were taken in consideration of having a robust pharmacovigilance system in India. The National Coordination Centre, New Delhi was shifted to the Indian Pharmacopoeia Commission (IPC) in Ghaziabad. The PvPI works to safeguard the health of the Indian population by ensuring that the benefit of medicines outweighs the risks associated with their use. And as a result he culture of reporting of ADRs has achieved remarkable success, with 250 PvPI-established adverse drug monitoring centres all over India and provision of training to healthcare professionals. The programme is endeavour hard to build trust between the physician and the patient, thereby increasing patient safety and the confidence of people in the country's health system, rather than the detection of substandard medicines and prescribing, dispensing and administration errors. In progression, PC-PvPI has now become a WHO Collaborating Centre for Pharmacovigilance in Public Health Programmes and Regulatory Services. Apart from all these achievements, several challenges are faced by the PvPI, during monitoring of generic drugs, biosimilars, and about disease-specific ADRs of antidiabetic, cardiovascular and antipsychotic drugs and, above all, creating awareness, which is a continual process. Simultaneously, the PvPI is trying to address other challenges like counterfeit drugs, antimicrobial resistance, and surveillance during mass vaccinations and other national programmes[30].

Objectives

The objectives of the PvPI are to:

• Create a wide system nationally for patient-safety by ensuring drug safety

• Identify and study new signals from the reported cases

• Examine the benefit-risk ratio of marketed medications

•Generate evidence-based information on safety of medicines

• Promote rational use of medicinal products

• Hold upregulatory agencies in the decision-making process use of medications

• Communicate safety information about use of medicines to various stakeholders for Preventing/minimizing the risks

• Exchange of information and data Management by collaborating with other national Centers

• Provide training and consultancy support to other National Pharmacovigilance Centres

• Come out as a National Centre of Excellence for Pharmacovigilance Activities[31,32].

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ADR CLASSIFICATION

1. Based on the type of reaction.

Type of reaction	Features	Examples
Type A:Augmented pharmacological effect	• Relatively common • Pharmacologically predictable effect • Dose dependent • Low morbidity • Low mortality	• Bradycardia with beta adrenergic receptor antagonist
Type B:Bizzare effects	• Uncommon • Unpredictable • Not dose dependent • High morbidity • High mortality	• Anaphylaxis associated with a penicillin antibiotic
Type C:Dose related and time related(chemical)	• Uncommon • Related to drug concentration	• Hypothalamic pituitary adrenal axis suppression by corticosteroids
Type D:Time related(delivery)	• Uncommon • Dose dependent • Occurs or becomes apparent sometime after administration of the drug • Improves if medicine is withdrawn or method of delivery changed	• Carcinogenesis
Type E:withdrawal(Exit)	• Uncommon • Occurs when medicine is stopped or dose is reduced	• Opiate withdrawal syndrome
Type F:Unexpexted failure of therapy	• Common • Dose related • Caused by drug interaction	• Failure of oral contraceptive in presence of enzyme inducer[33].

2. Based on onset of event

- Acute(<60 minutes)
- Sub-acute(1-24hrs)
- Latent(>2 days)

3. Based on severity

- Minor ADRs: No therapy, antidote or prolongation of hospitalization is required.
- Moderate ADRs: Requires change in drug therapy, specific treatment or prolongs hospital stay by atleast one day.
- Severe ADRs: Potentially life threatening causes permanent damage or requires intensive medical treatment.
- Lethal: Directly or indirectly contributes to death of the patient[34].

MONITORING OF ADR

Adverse drug reaction (ADR) monitoring involves following steps:

I. Identifying adverse drug reaction (ADR)
II. Assessing causality between drug and suspected reaction
III. Documentation of ADR in patient's medical records
IV. Reporting serious ADRs to pharmacovigilance centres /ADR regulating authorities

I. Identifying adverse drug reaction (ADR)

The WHO definition is internationally accepted and most widely used. According to WHO ADR is defined as "A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the modification of physiological function". This definition excludes therapeutic failures, intentional and accidental poisonings, drug abuse, adverse events due to errors in drug administration or noncompliance.

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ADRs are identified in the pre-marketing studies and in the post-marketing surveillance studies. Disadvantages of the pre-marketing studies are that they lack adequate knowledge to extrapolate information collected from animal studies directly into risks in humans and few number of subjects are exposed to the new drug prior to the general release of product into market. A major disadvantage is that clinical trials cannot be conducted in rare group of subjects like children, elderly and pregnant women. Clinical trials often have short duration which means they cannot generate information about long term adverse effects. Therefore, only type A adverse reactions are known at the time of general marketing of a new drug. Thus, all other types of ADRs can only be identified in post marketing surveillance.

Post marketing surveillance can be done by different methods:

1. Anecdotal reporting: Anecdotal reports are collected by individual doctors when a patient has suffered some peculiar effect. The report is verified by further studies and these sometimes fail to confirm the problem.

2. Intensive monitoring studies: This study provide systematic and detailed collection of data from well defined groups of inpatients .The surveillance was done by specially trained health care professionals. Example for this methodology is Boston collaborative drug surveillance program

Strengths:

a. It derives incidence rates
b. Analyses factors that contribute to reactions
c. Helps to identify drug interactions
d. To generate and test hypothesis
F. Under reporting can be reduced

Weakness:

a. Need great expense of resources
b. Short period of observation results in non-identification of delayed reaction
c. Small proportion of population size results in non-identification of rare reactions
d. Lack of follow up and outcome information

3. Spontaneous reporting system (SRS): It is used for monitoring the safety of marketed drugs. In UK, USA, India and Australia, the ADR monitoring programs are based on spontaneous reporting systems. In this system, clinicians are encouraged to report any or all reactions that believe may be related with drug use. Normally, attention is focused on new drugs and serious ADRs. The basis for SRS is to generate signals of potential drug problems, to identify rare ADRs and to monitor constantly all drugs used in a variety of real conditions from the time they are first marketed.

Strengths:

a. It is simple, effective, inexpensive and continuous
b. ADRs that are rare to be demonstrated by other methods may be detected
c. Drugs that are rarely used may be monitored

Weakness:

a. Under reporting is common
b. Reporting rates for each agent may vary with time.
c. Clinical information obtained is often limited.

4. Cohort studies (Prospective studies): In this study, patients taking a particular drug are identified and events are recorded. The weakness of this method is that relatively small number of patients is likely to be studied, and lack of suitable control group to assess the incidence of any adverse events. Such studies are expensive and difficult to justify and organize such a study for every newly marketed drug.

5. Case control studies (retrospective studies): Patients who have symptoms or an illness due to an adverse drug reaction are screened to see if they have taken the drug. It is then compared with a reference population who do not have the symptoms or illness. Thus this study is suitable for determining whether the drug causes a given adverse event once there is some initial indication that it might. However, it is not a method for detecting completely new adverse reactions.

6. Case cohort studies: The case cohort study is a hybrid of prospective cohort study and retrospective case control study, Patients with symptoms or an illness that could be due to an adverse drug reaction are screened to see if they have taken the drug. Then the results are compared with the incidence of the symptoms or an illness in a prospective cohort of patients who are taking the drug.

7. Record linkage: The idea is to bring together a variety of patient records like general practice records of illness and general records of prescriptions. It is possible to match illness events with drugs prescribed.

8. Meta-analysis: Meta-analysis is a quantitative analysis of 2 or more independent studies for the determination of an overall effect and to describe reasons for variation in study results, is another potential tool for identifying ADRs and assessing drug safety.

9. Use of population statistics: Birth defect registers and cancer registers can be used If drug induced

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event is highly significant or frequent. If uncertainties are aroused then case control and observational cohort studies will be initiated.

II. Assessing causality between drug and suspected reaction:

Causality assessment is a method by which the extent of relationship between a drug and a suspected reaction is established. There are three methodologies to asses causality. These include

a) Opinion of an individual expert
b) Opinion of a panel of experts
c) Formal algorithms

In the first methodology, an individual who is an expert in the area of ADRs would evaluate the case. In the process of evaluation, he or she may critically evaluate all the data obtained to assess whether the drug has caused a particular reaction. A panel of experts adopts a similar procedure to arrive at a mutual opinion. Using formal algorithms, collected data is subjected and assessed by using one or more standard algorithms. Some of the important algorithms used are Naranjo, WHO, European ABO system, Kramer, Bayesian, Karch and lasanga and French imputation method.

III. Documentation of ADRs in patient's medical records

This aids as a reference for alerting clinicians and other health care professionals to the probability of a particular drug causing suspected reaction.

IV. Reporting serious ADRs to pharmacovigilance center / ADR regulating authorities

According to FDA, a serious reaction is classified as one which is fatal, life threatening, prolonging hospitalisation, and causing a significant persistent disability, resulting in a congenital anomaly and requiring intervention to prevent permanent damage or resulting in death.

Karch and Lasanga classified severity into minor, moderate, severe and lethal. In minor severity, there is no need of antidote, therapy and prolongation of hospitalisation. In moderate severity, a change in drug therapy, specific treatment or an increase in hospitalization by at least one day is necessary. Severe class includes potentially life threatening reactions that cause permanent damage or require intensive medical care. Lethal reactions directly or indirectly contribute to death of the patient.

Different ADR regulatory authorities are - Committee on safety of medicine (CSM), Adverse drug reaction advisory committee (ADRAC), MEDWATCH, Vaccine Adverse Event Reporting System. WHO-UMC international database maintains all the data of ADRs.

In India, national pharmacovigilance programme was officially inaugurated on 23rd November 2004. It has one national pharmacovigilance center located at CDSCO in Delhi, two zonal, five regional and twenty four peripheral centers. National pharmcovigillance center communicates all the reported ADR data to WHO –UMC international database[35].

MANAGEMENT

The management of adverse drug reactions requisite inversion of the acute manifestations of anaphylaxis as well as identification and removal of the offending allergen and development of a program of long –term prophylaxis. Of primary prominence in the management of adverse drug reactions is the early recognition and prompt treatment of anaphylaxis. This life-threatening reaction is usually explosive in onset and is the most arising allergic catastrophe. Symptoms may extend from mild itching to irreversible hypotension and/or fatal pulmonary insufficiency resulting from laryngeal edema. These clinical manifestations are consequent to vascular and smooth muscle changes induced by the release of biologically active chemical mediators from the mast cell. Release may be induced by antigen as a result of sensitization of these cells with specific IgE.

Anaphylaxis, however, may also result from the administration or formation of immune complexes. In an unconventional complication of administration of blood, serum, blood, serum, or immunoglobulin, such reactions may result from the transfusion of donor IgE directed against an antigen to which the recipient is revealed at the time of transfusion. Conversely, the transfusion of a soluble antigen into a host sensitized to this antigen can uniformly precipitate IgE-induced adverse reactions. Occasionally, such transfusion reactions are consequent to immune complex formation with the activation of complement; the resulting generation of anaphylatoxin causes mast cell mediator release, with subsequent vascular and smooth muscle variations. Patients deficient in IgA may influence IgG antibodies to IgA, particularly if they have been recipients of multiple transfusions. These antibodies can form complexes with IgA and activate the classic complement pathway. IgA comprises 0.5% to 4% of commercial IgG preparations, so that anti-IgA responses may also occur in people acquiring immunoglobulin replacement therapy.

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SYSTEMIC REACTION MANAGEMENT WITH SPECIFlC MEASURES

Mild wheezing. pruritus, and transient urtlcaria can usually be managed as described for the local reactions. However, the potential for rapidly progressive bronchospasm and severe hypotension necessitates close monitoring of respiratory rate and blood pressure.

Delayed absorption of antigen

1.Epinephrine hydrochloride (adrenalin), 1:10OO. 0.3 ml(300µg) injected into the injection site

2.Tourniquet applied proximal to the injection site

Enhanced oxygenation

1.Epinephrine hydrochloride, I: 1000, 0.5 ml(500µg) administered subcutaneously into a nonoccluded extremity.

3. Controlled flow or intermittent positive pressure breathing with a β-agonist [i.e., isoproterenol (Isu . prel), I :2,000, 0.5 ml] and saline solution, 1.5ml

Reversal of hypotension

1. Rapid restoration of intravascular volume with isotonic saline solution is essential; colloidal solution may be desirable.

2. Infusion of u-agonist may be needed to maintain blood pressure [levarterenol bitartrate (Levophed) at 4 ml 0.2% solution to 1000 ml 5% dextrose solution, each milliliter of the solution containing 4 kg base]. Administer it intravenously in a plastic catheter at a flow rate of 2 ml/min, adjusting the rate to obtain low to normal blood pressure; dopamine may be useful in the presence of cardiac failure.

3. Corticosteroids have not been proved in controlled studies to be of immediate value, but when given at this stage they may prevent delayed reactions (100 mg hydrocortisone sodium succinate administered as an intravenous push and 100 mg added to an intravenous infusion of 2.50 ml 5% dextrose in saline solution).

4. AddItional measures such as glucagon, atropine, and isoproterenol may be needed for protracted hypotension in the patient who has received β-blocking agents.

LOCAL REACTION MANAGEMENT

The well-defined local reaction occurring at the site of parenterally administered drugs requires specific therapy for the prevention of discomfort and systemic manifestations. Local reactivity is invariably indicative of subsequent systemic sensitization. Therefore, future therapy with the specific or cross-reacting drugs should be avoided. Specific therapy includes the following:

1. A tourniquet applied proximal to the site of the reaction if an extremity is involved, with relaxation of the occlusion for 1 minute every 3 minutes

2. Epinephrine hydrochloride, 1: 1000, 0.2 ml administered subcutaneously into the reaction site

3. Epinephrine hydrochloride, 1: 1000, 0.3 ml administered subcutaneously into the nonoccluded extremity

4. Diphenhydramine hydrochloride, 50 mg by mouth or intramuscularly, depending on the severity of the local reaction

5. Theophylline, or P,-agonist tablet 6. Observation of the patient until the reaction begins to subside. (usually 30 to 60 minutes)[36].

CAUSALITY ASSESSMENT SCALE

Causality assessment can be defined as the determination of chance, whether a selected intervention is the root cause of the adverse event observed. The causality assessment is the liability of either a single expert or an established committee. As it is a common phenomenon of variable estimation of knowledge and experience by each expert, there is a high possibility of disagreement and inter-individual variability on assessment. Establishing a relationship of causality between the medications received and the events occurred utilizing causality assessment scale is much needed to lower the incidence of Adverse Drug Reactions (ADRs) and to prevent exposure of patients towards additional drug hazards.

Informal causality assessment of ADRs is in general practice by healthcare professionals to conclude decisions concerning therapy management. Algorithms should supply more objective decision on causality rather than theoretical explanation in identifying adverse events during therapy. The four basic principles underlying the objective causal assessment include- 1) temporal eligibility, 2) dechallenge and outcome, 3) rechallenge and outcome, and 4) confounding factors.

Methods of causality assessment

To characterize ADRs, research workers identified various causality assessment methods based on different criteria such as analogous scales, theorems, probability scales, algorithms, etc. however, inter-rater and intra-rater variability are wide as there is no predefined diagnostic criteria or classifications. Until now, not a single causality assessment scale has been accepted and affected universally due to variability and inconsistency in reproducibility and validity. A High occurence of ADRs arises during the treatment at tertiary care

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hospitals. Hence causality assessment at such instances contributes to i) early identification of ADRs and minimization of further complications ii) Optimized therapy ; iii) new strategical treatment to avoid recurrence iv) Cost minimization by reducing prolonged hospitalization.

World Health Organization (WHO)–Uppsala Monitoring Centre (UMC) causality assessment criteria

WHO causality assessment scale is majorly used scale for the assessment of the causal relationship of case reports and has been developed during the International Drug Monitoring Programme in discussion with national centers.

This scale has been categorized into 6 groups considering the basic criteria of 4 requirements in each category. These 4 criteria include a) temporal relationship b) plausibility and absence of other factors c) laboratory findings and d) de-challenge and re-challenge. Unclassified is applicable when additional information is necessary to evaluate the relationship.

Naranjo scale: Naranjo scale assesses the causality using the traditional categories of definite, probable, possible and doubtful. A ten elemental questionnaire with yes, no and unknown replies are developed. Based on the replies, the score has been determined into categories. Drawback: The Naranjo Scale does not address the points needed in the assessment of the causality of possible drug interactions.

Drug interaction probability scale (DIPS): Horn et al. proposed a DIPS scale to evaluate ADRs caused due to drug interactions. To determine the drug interactions, DIPS adopted ten questions with 'yes' or 'no' answers yielding a score. It covers the information on pharmacological resources of the drug, patient profile and impact of other drugs through the questions. Drawback: Assessment of this scale can be done only by experts who have sound knowledge in pharmacological and pharmacokinetic profiles of involved drugs.

Causality assessment of vaccine-related adverse events

Vaccines require a high degree of safety and efficacy strategies as these are administered in healthy individuals, particularly in neonates and infants for beneficiary outcomes. Though most of the adverse events due to vaccines are unpreventable, causality assessment has to be given utmost preference. Advisory Committee on Causality Assessment (ACCA) in Canada developed a method for vaccine-related events. ACCA reviews every individual case in a methodological and systematic way to evaluate causal association on a form using specialists from various clinical and medical departments. This form consists of seven sections that focus on different parameters related to the importance of adverse reactions due to vaccine and its impact for further evaluation[37].

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Conflict of interest

There is no conflicts of interests.