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PHARMACOVIGILANCE AND ADVERSE DRUG REACTION REPORTING-A REVIEW

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ABSTRACT

Pharmacovigilance is an activity related to the detection, assessment, understanding, management and prevention of adverse drug reaction (ADR) in an individual patient and launched to ensure the safety of the marketed drug products. In India, tuberculosis and HIV infection have a high prevalence rate and the pharmacotherapy drugs are related to multiple drug adverse effects. Both the National Tuberculosis Control Program and National AIDS Control Organization accepted to collaborate with the Pharmacovigilance Programme of India (PVPI) in order to monitor the treatment of tuberculosis and HIV infection. National Coordinator Center (NCC) started a mobile phone application for stakeholders to improve ADR reporting. Many countries do not allow the patients to do ADR reporting, so PVPI created the source for ADR reporting by patients. In this review article, we provide an overview of the PVPI and created the awareness about the ADR reporting to minimize the morbidity and mortality caused due to ADR, which in turn decreases the occurrence of ADR and brings effective therapeutic management to the patients.

KEYWORDS: Pharmacovigilance; Adverse Drug Reaction; Pharmacovigilance Programme of India; Reporting; Drug Safety.

Pharmacovigilance

As per World Health Organization (WHO), Pharmacovigilance is a concerted activity related to the detection, assessment, understanding, management and prevention of adverse drug reaction in order to prevent or to reduce the harm in patients.[1] It was first proposed in 1986 with 12 regional centers of formal adverse drug reaction monitoring system. In 1997, India joined the WHO in the international drug monitoring programme. The Pharmacovigilance Programme of India (PVPI) was launched on a national foothold under the ministry of health and family welfare by the year 2010.[2] This was started to safeguard the Indian population health status by validating the safety of marketed drug products.[3] Uppsala monitoring center (UMC), the WHO collaborating center for international drug monitoring in Sweden, supports PVPI through the tools such as, vigiflow, vigimine, vigimed, vigisearch, vigilyze and vigiaccess. India's total contribution in the ADR monitoring is more than 280,000 individual case safety report (ICSR) to vigibase.[2] India's contribution in the year 2013 was about 2% in ADR monitoring of WHO-UMC global drug safety database-vigibase and it was in the 7th position among the 10 countries who are contributing to global drug safety database.[4]

Aims of pharmacovigilance[5]

- Severe and unexpected ADR detection to establish drugs and even the minor ADR ones to newer drugs.
- Identifying the risk factors associate with the ADR and its mechanism.
- Estimation of prevalence, incidence and risk factor of ADRs.
- Estimation of pharmacoeconomic data of ADR.
- Ensuring both the safety and efficacy of the drugs.
- Estimation of prescribing pattern of drug.

Pharmacovigilance programme of india

To improve the ADR monitoring system, an extensively revised ADR monitoring programme called PVPI was launched on 14th July 2010, under the guidance of health ministry. PVPI was introduced with all Indian Institute of Medical Science (AIIMS), New Delhi for monitoring ADRs to safeguard the public health.[6] To screen this programme in a potential way, the National Coordinator Center (NCC) was transferred from AIIMS, New Delhi to the Indian Pharmacopeia Commission, Ghaziabad and Uttar Pradesh on 15th April 2011 [1]. Dr G.N. Singh, scientific director of IPC was delegated as National Coordinator for ADR monitoring 17th July 2017.[7]

Functioning of NCC PVPI

Under PVPI, ADR monitoring center plays an important role in collecting, enforcing and reporting of ADR reports from the health care professionals. These ADRs are collected in the developed suspected ADR reporting form, which contains the following information: patient's information, suspected ADR, suspected medication(s) and reporter's information from healthcare professionals.[8] ISCRs were then reported to the ADR monitoring center or central drug standard control organization (CDSCO) zonal or sub-zonal office. Then they are communicated to the national coordinating center. Finally, it reviewed and submitted to the WHO UMC-Sweden.[6]

Pecking order of pharmacovigilance centers under PVPI

The PVPI has four tier configurations[9]

1. Peripheral pharmacovigilance center
2. Regional pharmacovigilance center
3. Zonal pharmacovigilance center

National pharmacovigilance center

The National Pharmacovigilance Programme consists of 24 peripheral Pharmacovigilance centers, reporting their data at 5 regional Pharmacovigilance centers, which it was communicated to the 2 zonal Pharmacovigilance centers.[10] Five regional pharmacovigilance centers are IPGMR-SSKM hospital- Kolkata, TN Medical College and BYL Nair charitable hospital- Mumbai, Indira Gandhi medical college- Nagpur, Lady Harding medical college- New Delhi, and JIPMER-Pondicherry. Two Zonal Pharmacovigilance centers are KEM Hospital-Mumbai and All India Institute of Medical Science- New Delhi.[11] The teaching and non-teaching hospitals, clinics and pharmacies in each and every state and union territory include the Peripheral Pharmacovigilance centers and, it records and forwards the ADR information to its respective Regional Pharmacovigilance Center.[9] Initially, there were 22 ADR monitoring centers. In India, at present, there are 150 ADR monitoring centers. In the forthcoming year, 350 ADR monitoring centers will be there all over the world to make the largest Pharmacovigilance Programme around the world.[2] The Regional Pharmacovigilance Centers report to the Zonal Pharmacovigilance Centers after assessment of causality of the reported adverse drug event/reaction. The Zonal Pharmacovigilance centers undertake the basic activities of Pharmacovigilance like data collection and analysis regarding the adverse drug event/reaction. They communicate it to the National Pharmacovigilance center.[12]

Recent development associated with pvp

In India, tuberculosis and HIV infection have a high prevalence rate and the pharmacotherapy drugs are related to multiple drug adverse effects. There was a scarcity in the data related to the ADR reporting and this led to the collaboration between the revised National Tuberculosis Control Program in monitoring the treatment of tuberculosis and PVPI on 11th October 2013. Similarly, the National AIDS Control Organization accepted to collaborate with PVPI on 15th September 2014.[13] The NCC has launched a toll-free helpline number (1800 180 3024) for stakeholders to report the ADR in an effective way. NCC-PVPI thought of utilizing the mobile phone to help in increasing the ADR reporting in the country. NCC started a mobile phone application on 22nd May 2015 for stakeholders, in collaboration with NSCB medical college in Jabalpur to improve or to promote the ADR reporting.[6] There are many countries which will not allow the patients to do ADR reporting by them. On 1st August 2014, PVPI started the process of ADR reporting by patients.[4] The patients can report ADR in the following way:

1. Using helpline number (1800 180 3024)
2. Using email (pvpi.compat@gmail.com)
3. Using ADR reporting blue form in nearest ADR monitoring centers which will be available in IPC official website, and this form is available in 10 local Indian languages (Hindi, Marathi, Bengali, Kannada, Assamese, Odiya, Telugu, Tamil Malayalam And Gujarati Languages)[6]

Impact of pharmacovigilance

The NCC worked hard in the last 5 years to enhance the knowledge of health care personnel regarding ADR reporting. Until December 2015, more than 149000 ADRs were reported to CDCSO.[14] In Jan 2017, 5523 ICSRs were reported to PVPI from different ADR monitoring center. Currently, 3% of the WHO global ICSR database was contributed by India.[15]

International collaboration

PVPI collaborates with multiple international authorities and organization. The main collaboration is with;

1. WHO- World Health Organization
2. UMC- Uppsala Monitoring Center- Sweden
3. The Council For International Organization Of Medical Sciences (CIOMS)

The WHOs International Drug Monitoring Program is based on data sharing by the member states. At present, there are more than 100 countries participating in the program.[16] UMC is used by the WHO for International Drug Monitoring. The collection, assessment and communication of ADR reporting information from member countries are carried out by UMC.[26] During the years 2001-02, UMC received about 1,62,336 ADR reports, which was rapidly increasing about 2.85 million over the year 2002.[17] CIOMS provide guidance on drug safety issues.

ADR

As per WHO, ADR is defined as any response of a drug that is noxious and unintended, that occurs at doses normally used in human for the prophylaxis, diagnosis, and treatment of disease, or for modification of physiological function purposely excludes therapeutic

failures, overdoes, drug abuse, non-compliance, and medication errors.[18]

Adverse event
Any untoward occurrence that may occur during the treatment with pharmaceutical product/drug but does not have a causal relationship to the treatment.

Serious adverse effect
Any untoward medical occurrence at any dose results in the requirement of hospitalization, prolongation of hospital stay, death, required intervention to prevent permanent impairment/damage, disability/incapacity or life-threatening.[19]

Side effects
It is defined as an expected and known effect of a drug, which is unrelated to the therapeutic action.

Classification of ADRS[20]
It is classified as more common and less common ADRs which "more common ADRs" include type A and type B reaction and "less common ADRs" include type C, D and E reaction.

Type a: Augmented reactions
These types of ADRs were dose-dependent and predictable from the pharmacology of the drug. These are dose-related actions, and the reactions may improve both partially or completely when there is a reduction in drug dose or withdrawal of the offending drug. They are augmented with the pharmacological effect of the drug. The reactions are the frequent ADR, which can be observed in as many as 25-45% of patients. 80% of hospital stays or causing hospital admission is due to type A ADRs. Eg: Bradycardia caused by beta-blockers.

Type b: Bizarre reactions
It is rare, genetically determined and it can be classified as non-immunological ADRs, and further categorized into predictable and unpredictable. These are due to a collective effect, slow toxicity, intolerance, teratogenicity, and metabolic modification, aggravation of disease; drug-induced chromosomal disturbance and drug interaction. The immunological ADRs are unpredictable and occur because of immunoglobulin E-dependent drug reaction, immune complex dependent reactions, cytotoxic drug-induced reactions, and cell-mediated reactions. Idiosyncratic drug reactions are an uncommon response to the drug. Eg: broad-spectrum antibiotics causing oral thrush.

Type c: Chemical reactions
The ADR depends upon the chemical nature or structure of the drug. It is associated with long-term therapy. It can be anticipated and it is not pharmacologically predictable. It may be irreversible and unexpected. Eg; gastrointestinal mucosa damage caused by a local irritant action and tardive dyskinesia caused by antipsychotic agents.

Type d: Delivery reactions
This type of ADRs occurs due to the physical nature of the drug formulation and/or method of administration. These ADRs are heterogeneous because when the methods of delivery differ, the specific nature of the reactions should also differ. Once the method of delivering change, the specific nature of the reaction will not occur or stop to occur. Eg: corneal opacities after thioridazine.

Type e: Exit reactions
This type of ADRs is known as a withdrawal reaction. It occurs typically after stopping the administration of a drug or at the time of dose reduction. Eg: withdrawal seizure- due to phenytoin withdrawal.[21]

The drug classes which are responsible for ADR in an adult are adrenal corticosteroids, antibiotics, anticoagulants, antineoplastic, immunosuppressive drugs, nonsteroidal anti-inflammatory drugs and opiates. The drug classes which are responsible for ADR in children are anti-infective drugs, respiratory drugs and vaccines.[22]

Reasons for the increase in ADR number[23]

- The number of drugs prescribed is high
- Increased number of drugs in the market and,
- Lack of ADR monitoring system among healthcare professional, doctors, nurses and pharmacist.

Mechanisms of ADR
The mechanism of ADR can be divided into direct toxicity studies and hypersensitivity reactions that occur due to the pharmacokinetics and pharmacodynamics alterations of the drug products.[24] Direct toxicity reactions may be related to the toxic effects of a compound or its metabolites which are clear in various organ systems, inducing noxious chemical reactions, physiological dysfunction, DNA damage or injury to cellular structures and tissues.[25] Hypersensitivity reactions could be determined after the immune system of the individual shows an exaggerated response to a drug or its metabolites, which include allergic and anaphylactic reactions.[26]

Susceptibility factors to ADR[27-29]
Drug-Related Factors

1. Drug dose, frequency and Time of Administration: Administering underdose or overdose of medication, increasing or decreasing frequency of administration, changing the proper time of the day to administer the medication can affect the patient health and can causes ADR.
2. Poly-pharmacy: It causes ADRs due to the drug additive effect, synergism, duplication, drug interactions, discontinuation of treatment and physiological antagonism.

Patient-Related Factors

1. **Age:** Geriatric patients with multiple disease conditions, decreased elimination process of drug and past history of allergy reaction is more susceptible to ADRs. Paediatric patients have a low capacity to metabolize drug hence they are more open to ADRs.

2. **Sex:** Menstruation, pregnancy and menopause are more common in the woman; this may significantly affect the drug action. Men's are differing from women in having higher body weight, internal organ size and glomerular filtration, but has a lesser difference in body fat; these factors affect both the drug pharmacokinetics and pharmacodynamics.

3. **Pregnancy:** It causes several physiological changes that may affect drug pharmacokinetics and pharmacodynamics, which include cardiovascular changes; increase in cardiac output due to the increase in heart rate and increase in stroke volume; increase in blood volume; increase in renal drug excretion due to increase in renal blood flow, increase in GFR and decrease in serum protein.

Disease-Related Factors

Drugs which are used to treat one disease are harmful in others. NSAIDs usage can exacerbate a peptic ulcer. Patients with diseases like diabetes, hypertension or hypotension, ulcer, glaucoma, an enlarged prostate, poor bladder control should be monitored carefully because the patients with these conditions are more prone to drug-disease interaction and ADRs.

Social Factors

1. **Smoking:** Smoking causes interaction with theophylline, thiothixene, insulin, oral contraceptives, and H2 blockers. On clinical investigation, the results prove that on average, an insulin-dependent diabetic smoker required 15-20% more insulin than non-smokers and up to 30% more for heavy smokers.

2. **Alcohol:** It affects drug metabolism and promotes the development of ADRs. Alcohol causes hepatitis and liver cirrhosis that probably affect the drug metabolism rate. Ingestion of alcohol with some drugs led to many ADRs like nausea, vomiting, headache, drowsiness, fainting, and hypotension.

3. **Race:** Patient from East-Asia has3 times more risk of developing a cough with ACE inhibitors than white patients. Some research has proven that black people had a higher risk of intracranial haemorrhage compared to non-black people.

Steps involved in ADR monitoring[30]

1. Identifying ADR
2. Assessment of the causality of ADR (between drug and suspected reaction) using various algorithms.
3. Filing or documentation of ADR in the patient's medical records.
4. Reporting of ADRs to pharmacovigilance centers or to ADR regulating authorities.

Reporting of ADRS[27]

The National Pharmacovigilance Programme encourages the reporting of all suspected ADR, which include the suspected ADR caused by the usage of herbal, traditional and alternative medicines. The programmes particularly request the reports of the following:

1. All suspected ADR caused by new drugs and 'drugs of current interest'.
2. All suspected drug interactions and
3. Suspected ADRs caused by other drugs are probably affecting a patient's management, including death, life-threatening conditions, initial or prolonged hospitalization, significant, persistent or permanent disability and congenital anomaly.

Regulatory authorities for reporting of ADR[27]

1. Committee on Safety of Medicine,
2. Adverse Drug Reactions Advisory Committee,
3. MedWatch and Vaccine Adverse Event Reporting System.
4. WHO–UMC international database in Sweden maintains all information on ADRs.
5. In India, National Pharmacovigilance Programme located at the CDSCO, in New Delhi

Utilization of PVPI data[6]

Data collected from pharmacovigilance are used in various ways:

Signal generation and strengthening: early detection of signal related to possible ADR is the main aim of the Pharmacovigilance. Various methods have been used to detect the signals using spontaneous reporting data. WHO-UMC uses the Bayesian Confidence Propagation Neural Network methodology whereas the US FDA uses the Multi-Item Gamma Poisson Shrinker. Other analysis methods like Reporting Odds Ratio and Proportional Reporting Ratio are engaged by drug safety research units and some national ADR reporting authorities.

Risk management: risk management is a global activity. Aim of risk management is to ensure the benefits of drugs/medical products run over the risk by the certain achievable margin for the single patient or for the target population. The risk management of drugs/medical product may vary due to difference in prevalence, severity and population genetics.

Drug regulation: After approval of a medical product/drug, all the safety information is regularly monitored by the CDSCO. Pharmacovigilance data are useful in reviewing the product safety information and implementation which required changes in the prescribing information/pack label.

Education: PVPI data regarding the ADR are more useful in improving or upgrading the knowledge or medical product information to the healthcare professionals.

CONCLUSION

Pharmacovigilance plays an important role in ensuring the safety of medical products, and also many new drugs are being introduced every year so that all the healthcare professionals should have the knowledge about the ADR monitoring and reporting to the Pharmacovigilance. The main aim of the PVPI is to find the drug-related ADR and create awareness about the existing ADR's to the medical professionals to minimize the morbidity and mortality caused due to ADR. As a part of the medical profession, all students under clinical pharmacy along with other healthcare professionals should be aware of ADR and it reporting, so that it decreases the occurrence of ADR and brings effective therapeutic management to the patients.

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