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Review Article

Introduction and evaluation of pharmacovigilance for beginners

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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 sulfanilamide 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 15-20% 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.

Keywords: Pharmacovigilance, Adverse drug reaction, Adverse Event, ICSR

INTRODUCTION

The history and evolution of pharmacovigilance

The history of pharmacovigilance (PV) begun with the German toxicologist Louis Lewin, who published the first book devoted to adverse drug effects in 1881, Die Nebenwirkungen der Arzneimittel [1]. In USA, concern about adulterated and misbranded foods and drugs in the start of the 12th century culminated in the publication of 11 articles by Samuel Hopkins Adams in Collier's Weekly in 1905, titled "The Great American Fraud," in which he exposed many of the false claims made about patent medicines. This leads directly to the 1906 Pure Food and Drugs Act, which was established the forerunner of the Food and Drug Administration (FDA) [2]. In 1951 Leopold Meyler published a 192-page book in Dutch, titled Schadelijke Nevenwerkingen van Geneesmiddelen, which was entirely devoted to descriptions of adverse reactions to drugs.[3] The WHO Programme for International Drug Monitoring came into effect in 1968, after thalidomide disaster in the 1961 and at that time thousands of congenitally deformed infants were born as the result of exposure in utero to medicine use by pregnant mothers.[4,5] The WHO programme was started as a pilot project with 10 participating countries, it now comprises 134 member countries.[6,7] In 2000, there were 5 African countries with 'Good Pharmacovigilance' capacity; this figure has now reached 34 in 2010.[7] The adverse drug reactions (ADRs) are estimated to be between fourth and sixth leading cause of death in USA and more than 10% of ADRs lead to hospitalization.[8] The Institute of Medicine (IOM) reports that at least 1.5 million preventable adverse drug events (ADEs) occur annually in the United States.[9] About 10%–20% ADRs reported are from hospitalized patients which leads to prolongation of a stay.[10] Worldwide more than 50% of all medicines are prescribed, dispensed or sold

inappropriately, and 50% of patients fail to take them correctly and 30% of the total health budget accounts for use of medicines in many countries[11]

In late 4000 BC Sumeria find out euphoric effect of the poppy, in late 1600s Friedrich Hoffman described ergot adverse effects, in 1839 first observation of anaphylaxis in rabbits by Magenta, in 1881, the first book on Adverse Drug Reactions was published. In 1938 Aspirin noted to be a cause of gastric haemorrhage, 39 years after its first use published in untoward effects of drugs a pharmacological and clinical manual.[12] In 1960s Oral it was observed that contraceptives lead to thromboembolic episodes in young women.[13] In 1961 Thalidomide disaster: Dr. Widukind Lenz played an important part in the identification of thalidomide's adverse effects. The U.S. Kefauver Harris Amendment or "Drug Efficacy Amendment" is a 1962 amendment to the Federal Food, Drug, and Cosmetic Act.[14] It introduced a requirement for drug manufacturers to provide proof of the effectiveness and safety of their drugs before approval, required drug advertising to disclose information about side effects, and stopped cheap generic drugs being marketed as expensive drugs under new trade names as new "breakthrough" medications.

INITIATION OF MONITORING DRUG SAFETY

In1960 FDA begin to collect reports of adverse reactions, in 1964 Yellow Card Scheme started in the UK, in 1967 WHO International System of Monitoring ADRs established, in 1952 First edition of Meyler's Side Effects of Drugs published and in Beginning of the 19th Century early example of a systemic collection of adverse drug reactions occurred in the when reactions were reported during a smallpox vaccination campaign in the Netherlands

Appropriate and effective monitoring of ADRs, i.e. pharmacovigilance, is the only best way to safeguard the public health. Spontaneous reporting system (SRS) is the most widely used method to report ADRs.

It is enable to early detection of new, rear and serious ADRs due to less safety related data available. Based on already reported cases new signal is generated. Signal is new possible causal link between a suspected ADR and drug; which is previously unknown or incompletely documented. Disproportionality analysis is most commonly used method of data interrogation to figure out the causality between drug and ADR of interest. The severity of under-reporting of ADRs is very high; it estimates that only 6% of ADRs are reported. There are many factors associated with under reporting of ADRs; categorized as personnel and professional characteristics of healthcare professional and their knowledge and attitude to ADR reporting. In terms of ADR reporting knowledge and attitudes of health professionals is strongly related. Under-reporting of safety related data can be significantly improved by appropriate educational intervention. In year 2002, more than 65 countries have their own pharmacovigilance departments.[15] Membership of the WHO Programmed for International Drug Monitoring is coordinated by the WHO Collaborating Centre for International Drug Monitoring, known as the Uppsala Monitoring Centre (UMC).[4]

We all know that; all drugs have some beneficial along with some adverse effects. ADRs are the very widespread problem of all drugs. Hence, to minimize ADR, PV came in a focus for appropriate and effective monitoring of ADR which can safeguard the public health.[16]

Importance of PV

Once a new medicine is launched without any known long-term safety studies may not claim to be the therapeutically safe and effective and may show harmful or life-threatening effect in population after use. Few years ago, in India, the safety evaluation of drug was based on the chronic use of that drug, but this practice was inaccurate and failed to claim complete safety.[17] Considering fact, many companies or CRO started investing in individual drug research and launching newer product in market. Once new product is developed a new information tends to be generated which may be beneficial or harmful and may impact on risk-benefit profile of that medicinal product. Complete safety and efficacy study or assessment of newly generated information with the help of PV system is needed to safeguard the public health. The adverse effects of drugs could result in morbidity or mortality and study of which is essential to minimize risks and maximize benefits. Due to recent high-profile drug withdrawal, the pharmaceutical company and regulatory authorities are strictly focusing on safety of drug in market i.e PV.[18]

DEFINITIONS OF PHARMACOVIGILANCE

The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.[4,7] It focuses on investigating and monitoring adverse drug reactions after medicinal products are licensed.[19]

The term "pharmacovigilance" first appeared in French in the late 1960s, when the terms "pharmacovigilance intensive" and "pharmacovigilance spontanee" were contrasted.[20]

Detection: In case of clinical trial, it's the investigator or in case of post marketing trial, it's either the physician or the prescriber or the patient himself who reports the adverse event or any drug related problem.

Assessment: The investigator or the health care professional (HCP) would be assessing if the adverse event or drug related problem is due to the drug or is it due to some other reason.

Understanding: The reporter and safety specialist is involved in the understanding the adverse event or drug related problem.

Prevention: By pro-actively reporting the adverse event or drug related problem to the regulatory authority and taking precautionary actions would help in preventing the adverse event in future.

Pharmacovigilance is a branch of pharmacoepidemiology but is restricted to the study, on an epidemiological scale, of drug events or adverse reactions. Pharmacovigilance is equal to drug Monitoring. It is the process of monitoring, evaluating and improving the safety of medicines in use.

PV is the science of collecting, monitoring, researching, assessing and evaluating information from health-care providers and patients on the adverse effects of medications, biological products, blood products, herbals, vaccines, medical device, traditional and complementary medicines with a view to identifying new information about hazards associated with products and preventing harm to patients. The challenge of maximizing drug safety and maintaining public confidence has become increasingly complex. Pharmaceutical companies not only monitor, but also proactively estimate and manage drug risk throughout a product's lifecycle, from development to post-market.[4]

THE AIMS OF PHARMACOVIGILANCE ARE IDENTIFICATION AND QUANTIFICATION OF PREVIOUSLY UNRECOGNIZED ADVERSE EFFECTS AND REACTIONS

Identification of subgroups of patients at particular risk of adverse reactions; continued surveillance of a product throughout the duration of its use, to ensure that the balance of its benefits and harms are and remain acceptable; the description of the comparative adverse reactions profile of products within the same therapeutic class; detection of inappropriate prescription and administration; the further elucidation of a product's pharmacological and toxicological properties and the mechanism(s) by which it produces adverse effects; the detection of clinically important drug–drug, drug–herb/herbal medicine, drug–food, and drug–device interactions; communication of appropriate information to healthcare professionals; the confirmation or refutation of false-positive signals that arise, whether in the professional or lay media, or from spontaneous reports.[21]

WHY PHARMACOVIGILANCE IS IMPORTANT

Pharmaco-vigilance is important for monitoring and surveillance of drug; alleviating human sufferings; to reduce disease related economical loss; identifying new information about hazards associated with medicines; proactive monitoring and reporting on the quality, safety and efficacy of drugs; assessment of the risks and benefits of marketed medicines; providing information to consumers, practitioners and regulators on the effective use of drugs; designing programs and procedures for collecting and analysing reports from patients and clinicians; early detection of safety problems and increases in frequency of adverse drug reactions (ADRs); identification of risk factors for ADRs; risks analysis and mitigation and finally the most important is the patient safety.

WHO WILL REPORT THE ADVERSE EVENTS

Adverse events can be reported by Physicians, Hospitals, Pharmaceutical manufacturers through Medical Representatives etc.. pharmacists, nurse. Not only Patients but also their friends, relatives can report the adverse events. In short, anybody either the person consuming the drug or the person knowing the patient or observing the event can report the adverse event.

WHAT SHOULD BE REPORTED

For the new drugs, all suspected reactions including the minor or mild in severity adverse events should be reported. For established or well-known drugs, all serious, unexpected, unusual ADRs. If there is a change in the frequency of given reaction, i.e. increase in frequency of event of vomiting for a particular drug. All suspected drug-drug, drug-food, drug-food supplement interactions. Statement highlighting marine source of supplements such as glucosamine so that can be avoided by those with allergy to sea food. ADRs associated with drug withdrawals. ADRs due to medication errors like overdose, under dose, misuse, abuse and off label use. ADRs due to lack of efficacy or suspected pharmaceutical defects – for example: the drug was showing the effects but suddenly the new batch of drug failed to show any efficacy.

WHAT ARE THE VARIOUS SOURCES OF REPORTS

Adverse event reports can be reported in two ways:

Unsolicited sources: Report which is not asked for reporting unsolicited sources include reports from spontaneous report, literature, internet and other sources like fax, email and social media.

Solicited: Report which is mandatory reports to be submitted to authority Solicited sources include reports from clinical trials: pre-marketing (Phase I, II and III).

Entire process of pharmacovigilance

Pharmacovigilance starts with case processing: this involve safety data collection and coding, case management reporting and submission. Then, comes risk assessment aggregate reporting, signal identification and evaluation which involves reviewing the cumulative safety information from a wide range of sources, on a

periodic basis and submitting the findings to regulators worldwide.

Finally, is the risk Management which is monitoring any reported AE of the product (investigational or marketed) on a patient or patient population and to seek methods or rationales to minimize or remove such AE from such patient or a specific patient population.

REPORTING REQUIREMENTS AND SUBMISSION TIMELINES OF ICSRS

For EMA

Spontaneous ICSRs

Submit the valid ICSR (EEA and non-EEA serious within 15 days, and EEA non-serious ICSR within 90 days to Eudra Vigilance (EV)). Non-serious non-EEA ICSRs should not be submitted to EV.[22]

Clinical ICSRs

The sponsor shall ensure that all relevant information about suspected serious unexpected adverse reactions that are fatal or life-threatening is recorded and reported as soon as possible to the competent authorities in all the Member States concerned, and to the Ethics Committee, and in any case no later than seven days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days.

All other suspected serious unexpected adverse reactions shall be reported to the competent authorities concerned and to the Ethics Committee concerned as soon as possible but within a maximum of 15 days of first knowledge by the sponsor.[23]

For USFDA

Spontaneous ICSRs

Must report adverse drug experience that is both serious and unexpected, whether foreign or domestic, as soon as possible but no later than 15 calendar days from initial receipt of the information and must submit follow-up reports within 15 calendar days of receipt of new information by the applicant.

The applicant must report each adverse drug experience involving serious listed, non-serious unlisted and listed events at quarterly intervals, for 3 years from the date of approval of the application, and then at annual intervals. The applicant must submit each quarterly report within 30 days of the close of the quarter (the first quarter beginning on the date of approval of the application) and each annual report within 60 days of the anniversary date of approval of the application. Follow-up information to adverse drug experiences submitted in a periodic report may be submitted in the next periodic report.[24]

Clinical ICSRs

The sponsor must also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

The sponsor must notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days.[25]

For PvPI

Spontaneous ICSRs

All serious unexpected adverse reactions must be reported to licensing authority within 15 days receipt of information by applicant.

All serious AEs/ADR must be reported to regulatory authority/NCA-PvPI, IPC within 15 days receipt of information by MAHs.

All non-serious AEs/ADR must be reported to NCA-PvPI, IPC within 30 days receipt of information by MAHs.[26]

Clinical ICSRs

All serious adverse events must be submitted to DCGI within 14 calendar days receipt of information by applicant.

BASIC TERMINOLOGY USED IN PHARMACOVIGILANCE

Pharmacovigilance

The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problem.[6] Pharmacovigilance is the science of collecting, monitoring, researching, assessing and evaluating information from healthcare providers and patients on the adverse effects of medications, biological products, herbalism and traditional medicines.

What is the minimum criterion required for a valid case?

The options are an identifiable reporter, an identifiable patient, a suspect product, an adverse drug events.[22]

What is an ADE?

Any untoward medical occurrence that may appear during treatment with a pharmaceutical product, but which does not necessarily have a causal relationship with the treatment.[22]

What is an ADR?

An adverse drug reaction is a "response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function."[19] Note that there is a causal link between a drug and an adverse drug reaction. In sum, an adverse drug reaction is harm directly caused by the drug at normal doses, during normal use.

What is the difference between an ADE and ADR?

There may not be a causal relationship between a drug and an ADE, whereas, there is a causal link between a drug and an adverse drug reaction.

Unexpected adverse reaction

An adverse reaction, the nature or severity of which is not consistent with domestic labelling or market authorization or expected from characteristics of the drug.[4]

When do you consider an event to be serious?

If an event is associated with any one of the following, it is considered to be serious: death, life threatening, hospitalization or prolongation of hospitalization, congenital anomaly, disability, other: medically significant or important medical events.[22]

When do you consider a case to be medically confirmed?

A case is considered to be medically confirmed if it contains at least one event confirmed or reported by an HCP (health care professional). Note: HCP can be a physician, nurse, pharmacist, coroner or psychologist.[22]

What do you mean by causality?

In pharmacovigilance, causality assessment is a method of finding the relationship between drugs exposed and reported Adverse drug reactions (ADR). It includes, finding the temporal relationship between drugs and reported ADR, dechallenge, rechallenge, clinical and pathological characteristics of the events.

Name some data elements in ICSR?

Patient demographic are age, gender and race.

Suspect product details are drug, dose, dosage form, therapy dates, therapy duration and indication.

Adverse event details are event, event onset date, seriousness criterion, event end date and latency.

What should a narrative consist of?

A narrative should consist of precise and concise information about the source of report, patient demographics, patient's medical history, concomitant medications, suspect product details and adverse event details, action taken in a chronological manner.

What do you mean by MedDRA?

Medical dictionary for regulatory activities. MedDRA used to code disease, symptoms, drug indication, medial history and currents conditions.

The MedDRA dictionary is organized by System Organ Class (SOC), divided into High-Level Group Terms (HLGT), High-Level Terms (HLT), Preferred Terms (PT) and finally into Lowest Level Terms (LLT).

Individual cases are usually coded for data entry at the most specific (LLT) level, and outputs of counts or cases are usually provided at the PT level. The higher levels (HLT, HLGT and SOC) as well as SMQ are used for searching and for organization and sub totalling of outputs.[27] MedDRA is managed by the Maintenance and Support Services Organization (MSSO). The March release is the main annual release and contains changes at the HLT level and above along with LLT and PT changes. The September release typically contains changes only at the LLT and PT level.

Signal

Information arising from one or multiple sources, including observations and experiments, which suggests a new potentially causal association, or a new aspect of a known association between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.[28]

Day zero

It is the first day when a notified competent authority or marketing authorization holder gets knowledge of a valid ICSR. Day 0 (zero) is defined as the date when any employee or representative (including contractors, distributors and designee/third party vendors) of MAH first becomes aware of adverse event that meets valid ICSR criteria, also known as Clock Start Date. This includes both verbal and written communication and is classed as Day 0 (zero) of the regulatory reporting process.[28]

Expectedness

All AEs that are previously unobserved or undocumented are referred to as "unexpected," (e.g., approved professional package insert or product label). Determination of expectedness is made by the sponsor on a case-by-case basis. Expected events typically do not require expedited reporting to the regulatory authorities.[29]

Relatedness

Relatedness is a term intended to indicate that a determination has been made that the event had a reasonable possibility of being related to exposure to the product. This assessment of causality may be based on factors such as biological plausibility, prior experience with the product, and temporal relationship between product exposure and onset of the event, as well as dechallenge (discontinuation of the product to determine if the AE resolves) and rechallenge (reintroduction of the product to determine if the AE recurs).[30]

Overdose

This refers to the administration of a quantity of a medicinal product given per administration or cumulatively, which is above the maximum recommended dose according to the authorized product information. Clinical judgement should always be applied.[22]

Off-label use

This relates to situations where the medicinal product is intentionally used for a medical purpose not in accordance with the terms of the marketing authorization.[22]

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the marketing authorization.[22]

Abuse

This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.[22]

Occupational exposure

This refers to the exposure to a medicinal product as a result of one's professional or non-professional occupation. It does not include the exposure to one of the ingredients during the manufacturing process before the release as finished product.[22]

Medication error

This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.[22]

Lack of efficacy

Unexpected failure of a drug to produce the intended effect as determined by previous scientific investigation.[4]

Dechallenge and rechallenge

Challenge-In our pharmacovigilance world, this refers to the giving of the drug to the patient during the AE or treatment in question. That is, a patient is started today on, say, ampicillin orally. This is the "challenge".

Dechallenge

This refers to the stopping of the drug, usually after an adverse event (AE) or at the end of a planned treatment (e.g. a two-week course of ampicillin). Dechallenges may be complete or partial. That is, the drug is fully stopped or decreased in dose and the AE may fully disappear or only partially decrease. The results of the dechallenge can be confusing.

A positive dechallenge: this refers to the AE disappearing after the stopping of the drug.

A negative dechallenge: this refers to the AE not disappearing after the stopping of the drug.

Rechallenge

This refers to the restarting of the same drug after having stopped it, usually for an AE. Rechallenges may also be complete or partial. Thus, the patient may have restarted ampicillin a week later after having stopped it.

A positive rechallenge: This refers to the AE recurring after restarting the drug.

A negative rechallenge: This is the case where the AE does not recur after the drug is restarted. Note the confusion here: With a positive dechallenge the AE disappears but with a positive rechallenge the AE comes back and vice versa.[31]

CONCLUSION

The numerous published articles available explaining history of pharmacovigilance. Present article gives brief overview of history and terminology use in daily pharmacovigilance activities. It will useful for the industry personnel as well as students wish to start carrier in pharmacovigilance and risk management.

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