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Review Article

PHARMACOVIGILANCE: A REVIEW ARTICLE

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ABSTRACT

Pharmacovigilance (PV) is an important area for the safety and ensuring that the patients are safe in every aspect of the drugs being taken or injected. India is still in its nascent stage; there is a lot to be done and to learn, in the field of PV, in ensuring that the safe implementation of the activities and work done is achieved. The major problem in India is the under-reporting of adverse drug reaction (ADR). There is an increasing number of hospitalization of patients owing to adverse effects of drugs and it becomes a challenge to find out the exact cause the ADRs when a patient in treated with multiple drugs simultaneously. In the review, we will explore the different types of assessment scale to do the ADR assessment and to find its causative agents.

Keywords: Pharmacovigilance, Adverse drug reactions, ADR assessment.

INTRODUCTION

Pharmacovigilance (PV), also known as drug safety, is the pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, particularly long term, and short term side effects of medicines [1]. PV is an important and integral part of clinical research [2]. The under-reporting of adverse drug reactions (ADRs) is the major setback worldwide which may be attributed to the lack of time and report forms. It has been known that the world health organization (WHO) has initiated the program of reporting all adverse reactions possessed by the drugs [3]. Moreover, its concerns have been widened to include the herbal drug products, traditional and complementary medicines, blood products, biologicals, medical devices, and vaccines. In addition, PV possesses various roles such as identification, quantification, and documentation of drug-related problems which are responsible for drug-related injuries [4-5]. Further, national PV programmes have been introduced which occupies a prime role in increasing the public awareness about drug safety [6-7]. This review article explains the need and importance of PV in daily lives of doctors and patients and the pharmaceutical industry.

Importance of PV

It is the science which deals with the complex process of the understanding and explaining the nature of ADR occurred in a patient taking either oral or parenteral or intravenous (I.V) drugs for an ailment. The drugs being marketed worldwide underwent a whole array of tests and also underwent clinical trials in animals and human subjects to assess the safety of the drug for a particular disease and to know the exact side effects associated with it. Still there is a major part of it goes undetected and some of the ADR are detected in post marketing surveillance. It is estimated that there is significant amount of ADRs which decreases the quality of life, increase hospitalization stay and increases the mortality. A landmark study by Lazarou in 1998 described, ADRs to be the fourth to sixth leading cause of death in the US and ADRs are estimated to cause 3-7% of all hospital admissions [8].

Aims of PV

PV has an important role in the assessment of side effects caused by the drugs whether it is caused by oral drugs; parenteral drugs or I.V. drugs. These drugs are pretested for ADRs before it is being marketed worldwide. PV has a key role in assessment, detection and identification of drugs which caused a particular ADRs and the mechanism by which it caused the injury. But to fulfill these requirements of finding and eliminating, a side effect is the responsibility of the doctors involved in the case; nurses, health workers, residents and proper guidance of the patients themselves help it to alleviate the root cause of ADR.

Methods used in PV

Many researchers developed different methods of causality assessment of ADRs by utilizing different criteria like chronological relationship between the administration of the drug and the occurrence of the ADR, screening for non-drug related causes, confirmation of the reaction by *in vivo* or *in vitro* tests, and antecedent information on homogeneous events attributed to the suspect drug or to its therapeutic class, etc., to define ADRs in different categories [9]. Currently, there is no universally accepted method for assessing causality of ADRs [10]. Currently, there are many algorithmic methods of causality assessment but no single algorithm is accepted as the gold standard because of the shortcomings and discordances that subsist between them [11]. We would explicate them in short as listed below.

Dangaumou's French method [12]

This rule of thumb has been used by the French government agency since 1977. The way of doing thing separates an intrinsic imputability (possible case between abused substance and dispassionate event) from an extrinsic imputability (bibliographical data) by the agency of seven criteria (three connected and four semiological) in two different tables. The criteria are (i) drug challenge, (ii) dechallenge, and (iii) rechallenge by the overall score of four possible categories. The semiological criteria are (i) semiology (clinical signs) using per se (suggestive or other), (ii) favoring component, (iii) arbitrary non-drug-related (none or possible), and (iv) laboratory tests show with three possible outcomes (positive, negative or no test for the event-drug pair). Scores are grouped as possible and dubious.

Kramer *et al.* method [13]

This method applies when the offending drug is administered and a single adverse drug event has taken place. Each adverse event is assessed independently and assessment is prepared. One of the advantages of this algorithm is its transparency. However, certain levels of experience, expertise, and time are required to use this method effectively.

Naranjo *et al.* method (Naranjo scale) [14]

It is utilized to verify causality in a variety of clinical situations utilizing the categories and definitions of definite, probable, possible, and doubtful. It consists of ten questions which are answered as yes, no and unknown. The event is assigned to a probability category predicated on the total score after totaling. A total score of ≥9 is definite, probable is 5-8, possible is 1-4 and doubtful ≥0. This scale is more powerful when the adverse event is associated with only one drug, but when multiple drugs are involved or there is any interactions between drugs, this scale fails to identify the offending agent.

Balanced assessment method [15]

This method evaluates a case report on various visual analog scale (VAS) models that each criterion is fulfilled individually. It has an added advantage that it considers an alternative causative factor as a possibility and not just as a separate factor. Each case is assessed independently by different assessors and the evaluation depends on the assessor's skills knowledge.

Ciba-Geigy method [16]

Expert consensus meetings have resulted in Ciba-Geigy method. Experts used their clinical judgment to assess adverse drug events and assign causality on a VAS. This method uses a checklist which is composed of 23 questions, which is split into three sections: (i) History of present adverse reaction, (ii) patient's past adverse-reaction history, and (iii) monitoring-physician's experience. This updated method was found to have a high degree of agreement (62%) when compared with evaluator's assessments.

Loupi *et al.* method [17]

This method developed to assess the teratogenic potential of drug. The first sections of the algorithm sanction for the drug to be omitted if not implicated in the inception of the abnormality. The second section weighs the bibliographical data. The three questions consider alternative etiological candidates other than the drug; chronology of the suspect drug and other bibliographical data, to arrive at a conclusion on causality.

Roussel Uclaf causality assessment method [9]

This method is used in disease states such as liver and dermatological problems. A retrospect assessment of the reproducibility of this method among four experts had showed a 37-99% agreement rate.

Australian method [18]

Australian method involves the evidence which helps in to draw the conclusion, such as timing, and laboratory information from case reports presented and the antecedent cognizance on the suspect drug profile is deliberately omitted in the assessment.

Probabilistic or Bayesian approaches

It utilizes concrete findings in a case to transform a prior into a posterior probability of drug causation [19]. The prior probability is calculated from epidemiological information and the posterior probability cumulates this background information with the evidence in the individual case. It is open-ended approach with no circumscription to the amount of case details that can be assessed utilizing this method. Simultaneous assessment of multiple causes can be assessed [20].

WHO-Uppsala monitoring centre (UMC) causality assessment criteria [21]

The WHO-UMC causality assessment method includes the following criteria

- Certain-adverse event and the time relationship associated with it
- Probable/likely-unlikely to attribute the other drugs or diseases
- Possible-this can be explained by the drug intake or another disease
- Unlikely-adverse event can be explained with the time relationship associated with it but its not impossible
- Conditional/unclassified-more data in needed to make a proper assessment
- Unassessable/unclassifiable-an adverse event is suggested but more data are needed to make an assessment.

CONCLUSION

PV remains a dynamic part of the clinicians and the general population. After the appearance of these adverse drugs effects, it is very essential that these are reported timely and analyzed. Not only the doctors should be aware of the PV programme but the patients themselves should be made aware of this so self-reporting is increased and the burden on the clinicians is also reduced. India is still in the growing phase of PV and more reporting is necessary to reach the world's standard of reporting these adverse events to provide effective drug use in children's and pregnant women which is one of the most vulnerable populations of all. The PV programme must be able to identify these adverse events timely in the coming years with the help of clinicians, patients, and the pharmaceutical industry to help shape the safety of patients themselves.

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