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Review Article

ADVERSE DRUG REACTION (ADR) MONITORING AND PHARMACOVIGILANCE

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ABSTRACT: The need for systematic follow up of medicines for adverse drug reactions once they are introduced into general use has been widely recognised today. Even in developing countries like India, national pharmacovigilance programme has been started for monitoring adverse drug reactions. In its first year this program mainly aimed to foster the culture of ADR notification among health care professionals. As a part of health care team every pharmacist must have knowledge about adverse drug reaction monitoring systems and pharmacovigilance.

KEYWORDS: Adverse drug reaction, Pharmacovigilance, Post marketing surveillance

Review Article

INTRODUCTION:

"ANYTHING YOU CAN THINK OF, ANYTHING YOU CAN SEE AND SOME THINGS YOU DON'T EVEN THINK OF CAN BE DUE TO A DRUG"

Every occasion when a patient is exposed to a medical product, is a unique situation and we can never be certain about what might happen. A good example for this is thalidomide tragedy in late 1950s and 1960s.Thalidomide prescribed as a safe hypnotic to many thousands of pregnant women caused severe form of limb abnormality known as phocomelia in many of the babies born to those women. It was a seminal event that led to the development of modern drug regulations aimed to identify, confirm and quantify ADRs. An adverse drug reaction (ADR) is any undesirable effect of a drug beyond anticipated therapeutic effects occurring during clinical use (pirmohamed etal1998). Hence every health care professional who give advice to patients need to know the frequency and magnitude of the risks involved in medical treatment along with its beneficial effects.

Recent epidemiological studies estimated that ADRs are fourth to sixth leading cause of death[1]. It has been estimated that approximately 2.9-5% of all hospital admission are caused by ADRs and as many as 35% of hospitalised patients experience an ADR during their hospital stay[2] . An incidence of fatal ADRs is 0.23%-0.4%[3]. Although many of the ADRs are relatively mild and disappear when drug is stopped or dose is reduced, others are more serious and last longer. Therefore there is a little doubt that ADRs increase not only morbidity and mortality but also add to the overall health care cost[4-6].

Pharmacovigilance is the science and activities relating to detection, assessment, understanding and prevention of adverse effects or any other drug related problems[7]. Pharmacovigilance should however not be limited to the reporting of classical adverse effects. It should also be concerned with identification of product defects, unexpected insufficient therapeutic effects, intoxications and misuse – abuse situations[8]. According to WHO guidelines (2000), functions of pharmacovigilance are the detection and study of ADR's, measurement of risk and effectiveness of drug use, dissemination of this information and education.

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)

Several definitions of ADRs exists, including those of WHO, FDA, Karch and Lasanga.The WHO definition is internationally accepted and most widely used.

WHO technical report no 498(1972) defines ADR 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[9]. This definition excludes therapeutic failures, intentional and accidental poisonings and drug abuse. Also this does not include adverse events due to errors in drug administration or noncompliance (taking more or less of a drug than prescribed amount) [3].

ADRs are mainly identified in the pre-marketing studies and in the post-marketing surveillance studies. Disadvantages of the pre-marketing studies are that they lack sufficient knowledge to extrapolate information collected from animal studies directly into risks in humans and very few number of subjects (not more than 4000) are exposed to the new drug prior to the general release of product into market. Another major disadvantage is that clinical trials can not be done in rare group of subjects like children, elderly and pregnant

women. For cost reasons clinical trials often have short duration which means they can not generate information about long term adverse effects. As a consequence of the above reasons, only type A adverse reactions are known at the time of general marketing of a new drug. So, 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**[10]: The majority of the first reports of ADR come through anecdotal reports from individual doctors when a patient has suffered some peculiar effect. Such anecdotal reports need to be verified by further studies and these sometimes fail to confirm problem.
2. **Intensive monitoring studies**[11,20]: These studies provide systematic and detailed collection of data from well defined groups of inpatients .The surveillance was done by specially trained health care professionals who devote their full time efforts towards recording all the drugs administered and all the events, which might conceivably be drug induced. Subsequently, statistical screening for drug-event association may lead to special studies. Popular example for this methodology is Boston collaborative drug surveillance program

   Strengths:

a. Derives incidence rates
b. Analyses factors which may contribute to reactions
c. Identifies drug interactions
d. Generates and tests hypothesis
F. Under reporting can be minimised

Weakness:

a. They need great expense of resources
b. The relatively short period of observation resulting in non identification of delayed reaction
c. Relatively small proportion of population size resulting in non identification of rare reactions
d. The lack of follow up and outcome information

3. Spontaneous reporting system (SRS)[12]:

   It is the principal method used for monitoring the safety of marketed drugs. In UK, USA, India and Australia, the ADR monitoring programs in use are based on spontaneous reporting systems. In this system, clinicians are encouraged to report any or all reactions that believe may be associated with drug use. Usually, attention is focused on new drugs and serious ADRs. The rationale for SRS is to generate signals of potential drug problems, to identify rare ADRs and theoretically to monitor continuously all drug used in a variety of real conditions from the time they are first marketed.15

Strengths:

a. Simple, effective, inexpensive and continuous
b. The entire population comprising extremes of age, people in hospital and community may be included
c. ADRs that are too rare to be demonstrated by other methods may be detected
d. Drugs that are uncommonly used may be monitored Weakness:

a. Under reporting is almost universal
b. Absence of reliable numerator or denominator precludes the provision of quantitative information
c. Numerous other reporting biases include the novelty factor of new drug and the effect of publicity
d. Reporting rates for each agent or group of agents may vary with time.
e. Clinical information supplied is often limited.

4. Cohort studies (Prospective studies) [11]:

   In these studies, patients taking a particular drug are identified and events are then recorded. The weakness of this method is relatively small number patients likely to be studied, and the lack of suitable control group to assess the background incidence of any adverse events. Such studies are expensive and it

would be difficult to justify and organize such a study for every newly marketed drug.

5. Case control studies (retrospective studies) [10]:

   In these studies, patients who present with symptoms or an illness that could be due to an adverse drug reaction are screened to see if they have taken the drug. The prevalence of drug taking in this group is then compared with the prevalence in a reference population who do not have the symptoms or illness. The case control study is thus 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[10]:

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

7. Record linkage[10]:

   The idea here is to bring together a variety of patient records like general practice records of illness events and general records of prescriptions. In this way it may be possible to match illness events with drugs prescribed. A specific example of the use of record linkage is the so called prescription event monitoring scheme in which all the prescriptions issued by selected parishioners for a particular drug are obtained from the prescription pricing authority. The prescribers are then asked to inform those running scheme of any events in the patients taking the drugs. This scheme is less expensive and time consuming than other surveillance methods

8. Meta analysis[13]:

   Meta analysis is a quantitative analysis of 2 or more independent studies for the purpose of determining an overall effect and of describing reasons for variation in study results, is another potential tool for identifying ADRs and assessing drug safety.

9. Use of population statistics[14]:

Birth defect registers and cancer registers can be used If drug induced event is highly remarkable or very frequent. If suspicions are aroused then case control and observational cohort studies will be initiated.

II. Assessing causality between drug and suspected reaction[15]:

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

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

In the first approach, an individual who is an expert in the area of ADRs would evaluate the case. In the process of evaluation, he or she may consider and critically evaluate all the data obtained to assess whether the drug has caused the particular reaction. A panel of experts adopts a similar procedure to arrive at a collective opinion. Using formal algorithms, collected data is subjected and critically 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. There is no gold standard for causality assessment. The categorisation of causal relationship between a drug and suspected adverse reactions varies with the scale adopted. WHO scale categorises the causality relationship into certain, probable, possible, unassessible/unclassifiable, unlikely, conditional /unclassifiable. The Naranjo's scale

categorises the reaction as definite, probable, possible or unlikely.

In general the following four different basic points can be considered in attributing a clinical adverse event to the drug.

1. Temporal time relationship between suspected reaction and drug.
2. Dechallenge (cessation of drug)
3. Rechallenge (re introducing drugs)
4. Likelihood of other possible causes

Table 1: Causality assessment strengths and limitations

What causality assessment can do	What causality assessment can not do
• Decreases disagreement between assessors • Classify relationship likelihood • Mark individual case reports • Education /improvement of scientific assessment	• Exact quantification measurement of relationship likelihood • Distinguish valid from invalid cases • Prove the connection between drug and event • Quantify the contribution of a drug to the development of an adverse event • Change uncertainty into certainty

III. Documentation of ADRs in patient's medical records

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

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

According to FDA, a serious reaction is classified as one which is fatal, life threatening, prolonging hospitalisation, causing a significant persistent disability, resulting in a congenital anomaly and requiring intervention to prevent permanent damage or resulting in death[16].

Hatwig SC, Seigel J and Schneider PJ categorised ADRs into seven levels as per their severity. Level 1&2 fall under mild category whereas level 3& 4 under moderate and level 5, 6&7 fall under severe category.

Karch and Lasanga classify severity into minor, moderate, severe and lethal. In minor severity, there is no need of antidote, therapy or prolongation of hospitalisation. To classify as moderate severity, a change in drug therapy, specific treatment or an increase in hospitalization by at least one day is required. Severe class includes all potentially life threatening reactions causing permanent damage or requiring intensive medical care. Lethal reactions are the one which directly or indirectly contributes to death of the patient.

Different ADR regulatory authorities are - Committee on safety of medicine (CSM), Adverse drug reaction advisory committee (ADRAC)[17], MEDWATCH,

Vaccine Adverse Event Reporting System[18]. WHO-UMC international database maintains all the data of ADRs.

In India, national pharmacovigilance programme[19] 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.

CONCLUSION: India has more than half a million qualified doctors and 15,000 hospitals having bed strength of 6, 24,000. It is the fourth largest producer of pharmaceuticals in the world. It is emerging as important clinical trial hub in the world. Many new drugs are being introduced every year and so every health care professional must have knowledge about importance of ADR monitoring and pharmacovigilance. Every health care professional should see it as a part of his/her professional duty keeping in mind about Hippocrates admonition" at least do no harm".

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