Review Article

ADVERSE DRUG REACTION-CAUSALITY ASSESSMENT

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INTRODUCTION

Adverse drug reactions (ADRs) are considered as one among the leading causes of morbidity and mortality[1]. The epidemiological importance of ADR is justified by its high prevalence rate – they cause from 3% to 6% of hospital admissions at any age, and up to 24% in the elderly population; they rank fifth among all causes of death and, moreover, they represent from 5 to 10% of hospital costs[2]. and is a great cause of concern to the medical profession. 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[14]. 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[3]. 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[4]. An incidence of fatal ADRs is 0.23%-0.4%. [5] 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 [6, 7].

Adverse drug reaction (ADR)
Definitions of ADRs exist, including those of the World Health Organization (WHO)[8]. Karch and Lasagna[9] and the Food and Drug Administration (FDA)[10].

WHO
Any 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 physiological function.

Karch and Lasagna
Any response to a drug that is noxious and unintended, and that occurs at doses used in humans for prophylaxis, diagnosis, or therapy, excluding failure to accomplish the intended purpose.

FDA
For reporting purposes, FDA categorizes a *serious adverse event* (events relating to drugs or devices) as one in which "the patient outcome is death, life-threatening (real risk of dying), hospitalization (initial or prolonged), disability (significant, persistent, or permanent), congenital anomaly, or required intervention to prevent permanent impairment or damage.

Classification of Adverse Drug Reactions
ADRs can be divided schematically into two major categories:

Type A and Type B (Table 1).

Type A reactions are common, predictable and may occur in any individual. Type B ADRs are uncommon and unpredictable and only occur in susceptible individuals [11].

Type A reactions are the most frequent and can be observed in as many as 25–45% of patients. These represent an exaggeration of the known primary and/or secondary pharmacological actions of the drug, they are dose related and could probably be avoided and/or foreseen[12]. Multi-factorial, involving not only defects at multiple gene loci but also environmental factors such as concomitant infections. Most work has focused on enzyme polymorphism in drug oxidation and conjugation as risk factors for drug toxicity but genes involved in cell repair mechanisms, elaboration of cytokines and immune responsiveness cannot be excluded to predict individual susceptibility to different forms of ADRs[12,14]. Genetic polymorphisms are a source of variation of drug response in the human body. In relation to ADRs, most interest has centred on the involvement of pharmacokinetic factors and, in particular, drug metabolism. However, there is now increasing realization that genetic variation in drug targets (Pharmacodynamic factors) might also predispose to ADRs, although research into this area is in its infancy[15].

Mechanism by which ADR Occurs [16]
ADRs can be classified as either pharmacological reactions representing an augmentation of the known pharmacological actions of the drug or idiosyncratic reactions that are not predictable. Pharmacological reactions are most common, usually dose-related and are due to the primary or secondary pharmacological characteristics of the drug. Factors that predispose to these ADRs include dose, pharmaceutical variation in drug formulation, pharmacokinetic or pharmacodynamic abnormalities, and drug-drug interactions. Pharmacological ADRs occur when drug concentration in plasma or tissue exceeds the "therapeutic window" or when there is increased sensitivity to the drug (even in concentrations considered normal for the general population). Idiosyncratic ADRs are less common, often serious, not dose dependent and show no simple relationship between the dose and the occurrence of toxicity or the severity of the reaction. The toxic reactions may affect many organ systems either in isolation or combination. The mechanism of these is not clear but is thought to include receptor abnormality, abnormality of a biological system that is unmasked by the drug, immunological response, drug-drug interactions, or be multi-factorial.

Adverse drug reaction (ADR) monitoring involves following steps
1. Identifying adverse drug reaction (ADR).
2. Assessing causality between drug and suspected reaction by using various algorithms.
3. Documentation of ADR in patient's medical records.
4. Reporting serious ADRs to pharmacovigilance centres /ADR regulating authorities

Identifying the Adverse Drug Reaction
The ADRs produced by a certain new drug are often recognized when the medication is undergoing its phase three randomized controlled trials. Both in the USA and in the UK there is post marketing surveillance of ADRs. In the UK this involves reporting suspected ADRs to the Commission on Human Medicine using the yellow card system. In this system new or intensively monitored medicines should have all suspected ADRs reported and other medicines should have any suspected serious ADR reported. In spite of these mechanisms ADRs are vastly under reported,[17] and initial reports of adverse reactions to drugs have taken up to seven years for trends to begin to appear in the literature. Under reporting of ADRs is likely to be due to a number of reasons. Reporting is not mandatory to clinicians in the UK and so is likely to be forgotten about amongst the many other work pressures. A clinician may have problems recognizing the scenario as an ADR, because of the background symptoms of the patient's original illness. Clinicians might also be wary of reporting an ADR, because of worries of inducing a complaint, even in this no blame culture NHS. It should be pointed out that the yellow card clearly states you do not need to be sure if it is or is not an ADR before you report it. In recognizing an ADR there are a number of important factors one is identifying those individuals in whom ADRs are most likely to occur. This includes the aged and the premature, those with liver

Post marketing surveillance
Post marketing surveillance can be done by different methods:

Anecdotal reporting [18]
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.

Intensive monitoring studies[19,24]
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.

Spontaneous reporting system (SRS) [20]
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 encourage reporting 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]

Cohort studies (Prospective studies)[19]
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.

Case control studies (retrospective studies)[18]
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.

Case cohort studies[18]
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.

Record linkage[18]
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

Meta analysis [21]
Meta analysis is a quantitative analysis of two 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.

Use of population statistics[22]
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. Causality Assessment Between Drug and Suspected reaction[23]

Causality assessment is the method by which the extent of relationship between a drug and a suspected reaction is established.

It is often difficult to decide if an adverse clinical event is an ADR or due to deterioration in the primary condition. Furthermore, if it is an ADR, which medicine caused it, as many patients are on multiple new medications when ill, particularly if admitted to hospital. In spite of these problems, the decision that a particular drug caused an ADR is usually based on clinical judgment alone. Studies have shown that there is a lot of variation in between rater and within rater decisions on causality of ADRs; this applies both to pharmacologists and physicians[25,26].

There are various approaches 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 algorithms including standardization of methods. Algorithms being structured systems specifically designed for the identification of an ADR, should theoretically make a more objective decision on causality. As such algorithms should have a better between and within rater agreement than clinical judgment. A number of algorithms or decision aids have been published including the Jones' algorithm,[28] the Naranjo algorithm,[27] the Yalealgorithm,[29] the Karch algorithm,[30] the Begaud algorithm,[31] the ADRAC,[32] the WHO-UMC,[33] and a newer quantitative approach Algorithm.34 Each of these algorithms has similarities and differences. And the most commonly used algorithms; the Naranjo algorithm (Fig :1) is shown below

The Naranjo Algorithm is a questionnaire designed by Naranjo et al *for* determining the likelihood of whether an ADR (adverse drug reaction) is actually due to the drug rather than the result of other factors. Probability is assigned via a score termed definite, probable, possible or doubtful. Values obtained from the algorithm are sometimes used in peer reviews to verify the validity of author's conclusions regarding adverse drug reactions. It is also called the Naranjo Scale or Naranjo Score.

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 Centres / 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 [35] 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 .[36](fig:2). 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),[37] MEDWATCH, Vaccine Adverse Event Reporting System[38] WHO-UMC international database maintains all the data of ADRs.

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 does no harm".

Table 1: Characteristics of Type A and Type B Adverse Reactions

Characteristics	Type A	Type B
Dose dependency	Usually shows good relationship	No simple relation ship
Predictable from known pharmacology	Yes	Not usually
Host factors	Genetic factors might be important	Dependent on host factors
Frequency	Common	Uncommon
Severity	Variable but usually mild	Variable, proportionately more severe
Clinical burden	High morbidity and low mortality	High morbidity and mortality
Overall portion of adverse drug reaction	80%	20%
First detection	Phase1-III	Phase IV, occasionally phase III
Animal models	Usually reproducible in animals	No known animal models

Table 2: Hartwig's Severity Assessment Scale

Level 1	An ADR occurred but required no change in treatment with the suspected drug.
Level 2	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. No antidote or other treatment requirement was required. No increase in length of stay (LOS)
Level 3	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. AND/OR An Antidote or other treatment was required. No increase in length of stay (LOS)
Level 4	Any level 3 ADR which increases length of stay by at least 1 day . OR The ADR was the reason for the admission
Level 5	Any level 4 ADR which requires intensive medical care
Level 6	The adverse reaction caused permanent harm to the patient
Level 7	The adverse reaction either directly or indirectly led to the death of the patient

Mild= level 1 and 2, moderate= level 3 and 4, severe= 5, 6 and 7.

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1) Are there previous conclusive reports of this reaction?

If YES = +1, NO = 0, Do not know or not done = 0

2) Did the adverse event appear after the suspected drug was Given?
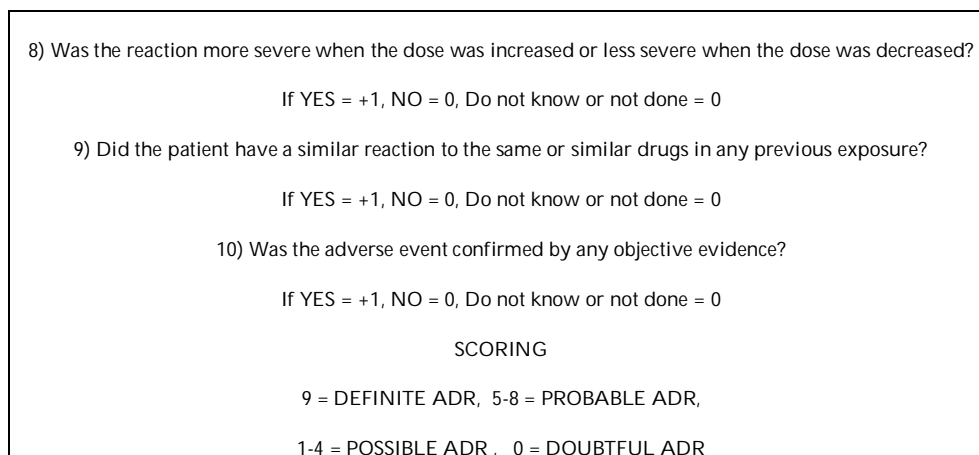
If YES = +2, NO = -1, Do not know or not done = 0

3) Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?

If YES = +1, NO = 0, Do not know or not done = 0

4) Did the adverse reaction appear when the drug was Re-administered?

If YES = +2, NO = -2, Do not know or not done = 0

5) Are there alternative causes that could have caused the reaction?

If YES = -1, NO = +2, Do not know or not done = 0

6) Did the reaction reappear when a placebo was given?

If YES = -1, NO = +1, Do not know or not done = 0

7) Was the drug detected in any body fluid in toxic Concentrations?

If YES = +1, NO = 0, Do not know or not done = 0

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8) Was the reaction more severe when the dose was increased or less severe when the dose was decreased?

If YES = +1, NO = 0, Do not know or not done = 0

9) Did the patient have a similar reaction to the same or similar drugs in any previous exposure?

If YES = +1, NO = 0, Do not know or not done = 0

10) Was the adverse event confirmed by any objective evidence?

If YES = +1, NO = 0, Do not know or not done = 0

SCORING

9 = DEFINITE ADR, 5-8 = PROBABLE ADR,

1-4 = POSSIBLE ADR , 0 = DOUBTFUL ADR

Fig. 1: Naranjo Algorithm.

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