

Mechanisms, Methods of Detection and Causality Assessment of Adverse Drug Reactions

Akshay Sadhotra¹, Anshu Gupta^{2*}, Rani Walia³, Nidhi Sharma⁴

^{1,4}Postgraduate, ²Associate Professor, ³Professor & HOD, Dept. of Pharmacology, MMIMSR, Ambala

***Corresponding Author:**

E-mail: anshudmc@gmail.com

Abstract

Adverse Drug Reactions are very common cause of hospital morbidity.

Keywords: ADRs, Augmented, Bizzare, Continuous, Delayed, Causality Assessment

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Introduction

Thalidomide tragedy of 1960s and many other recent drug withdrawals from the market has led to adverse drug reactions (ADR) being recognised as one of the leading causes of morbidity and mortality by health professionals and the public since the last decade.¹ This problem is further supplemented by limited availability of ADR data & lack of proper drug regulations in developing countries.²

3% to 6% of hospital admissions at any age (up to 24% in the elderly population) has been attributed to ADRs and approximately 35% of hospitalised patients during their stay experience an ADR. Incidence of fatal ADRs is 0.23%-0.4% and rank fifth among all causes of death. Moreover, they represent from 5 to 10% of hospital costs and are a great cause of concern to the

medical profession. Therefore every health care professional needs to know the frequency and magnitude of the risks involved in medical treatment along with its beneficial effects.³

Adverse drug reaction-definition, types & mechanisms of action

An adverse drug reaction is defined by World Health Organization (WHO) as “any noxious, unintended, and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis or therapy.” This definition excludes therapeutic failures, intentional and accidental poisoning (i.e. overdose), drug abuse and adverse events due to errors in drug administration or noncompliance.¹

The term “adverse reaction” must be distinguished from “adverse event”. An adverse effect is an adverse outcome that can be attributed to some action of a drug whereas an adverse event is an adverse outcome that occurs while a patient is taking a drug, but is not or not necessarily attributable to it.⁴

Adverse drug reactions are type A (pharmacological) or type B (idiosyncratic) [Table 1].⁵

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
Clinical burden	High morbidity and low mortality	High morbidity and mortality
Overall portion of adverse drug reaction	80%	20%

Type A ADR

There are two subclasses:

- **Exaggerated Desired Effect-** The undesirable exaggeration of a desired pharmacologic effect after a normal dose in a susceptible subject or after a higher than normal dose. This results from the excess stimulation of targeted receptors by the therapeutic agent. Orthostatic hypotension with an antihypertensive, daytime somnolence after a sedative-hypnotic taken for sleep, and hypoglycemic shock after insulin is examples of this phenomenon.
- **Undesired Effect-** The appearance of an undesired pharmacologic effect, known as lateral or parallel stimulation, can be seen after a normal dose or a higher than normal dose in a susceptible subject; it is due to the stimulation of untargeted receptors by the therapeutic agent. Examples include constipation due to morphine, gastrointestinal irritation with non-steroidal anti-inflammatory drugs (NSAIDs), hair loss from chemotherapy, and loss of libido with antidepressants.

Type B ADR

There are two subclasses:

- **Immunologic-** An allergic or hypersensitivity reaction occurs as a result of an immunologic mechanism. A pseudoallergy or anaphylactoid reaction is the result of a mechanism involving the release of the same mediators released during an immunologic reaction due to immunoglobulin E (IgE). Such reactions can occur with radio contrast agents, NSAIDs.
- **Idiosyncratic-** The term idiosyncratic is often used in a broad sense to designate qualitatively abnormal adverse reactions that occur in a given individual and whose mechanism is not yet understood. These reactions are usually quite rare and in some cases may be due to a genetic or acquired enzyme abnormality with the formation of toxic metabolites. This is also known as primary toxicity. Congenital enzyme abnormalities may produce adverse reactions such as the hemolytic anemia due to glucose-6-phosphate dehydrogenase (G6PD) deficiency.⁵

Some of the ADRs could not be explained by the mechanism of either type A or B reactions which led to ABCDEF classification:⁴

1. Dose-related (Augmented)
2. Non-dose-related (Bizarre)
3. Dose-related and time-related (Chronic)
4. Time-related (Delayed)
5. Withdrawal (End of use)
6. Failure of therapy (Failure)

Recently a three-dimensional classification system based on dose relatedness, to timing and patient susceptibility (DoTS) has been proposed which takes into account the properties of the ADR (time course of its appearance & its severity) and properties of the individual like genetics, pathological & other biological differences that confer the individual susceptibility.⁶

Adverse drug reactions affect patients' quality of life and are also responsible for patients loss of confidence in their doctors, increasing cost of patient care, precluding use of drug in most patients although they may occur in only a few as well as they may mimic disease, resulting in unnecessary investigations as well as treatment delay.⁷

Adverse drug reactions-Methods of Detection

The pharmaco-epidemiological methods are used now days to detect new signals of possible adverse drug reactions (ADRs) and these methods can either be 'hypothesis generating' where the aim is to detect new & previously undetected ADRs with a new drug or 'hypothesis testing' where these methods aim to prove whether any suspicions that may have been raised are justified.

Hypothesis generating methods include

- **Spontaneous ADR Reporting-** which is a system whereby any suspected ADRs are voluntarily notified by health professionals, pharmaceutical companies and other stakeholders to a central authority (Central Drugs Standard Control Organization -CDSCO in India).
- **Prescription Event Monitoring-** represents a method which is hybrid of spontaneous reporting with aspects of formal epidemiological studies.
- **Systematic methods-** public health surveillance data such as death registries are used to identify patterns of reactions that might be associated with drug use.

Hypothesis testing methods include

- **Case-Control Studies-** In case control studies the research compares the exposure rate in the cases with the exposure rate in the control.
- **Cohort Studies-** These studies involve a group of patients (cohort) followed up for a time duration long enough to detect the outcome of interest.
- **Randomized Controlled Trials-** These studies involve patients divided into two groups randomly into exposed and the other not exposed, so that the outcomes can be compared.

Adverse drug reaction-Causality assessment

Causality assessment is the method by which an association is evaluated between a drug and a suspected reaction. It assesses the relationship between a drug treatment and the occurrence of an adverse event and

establishes or negates the same. It is an important tool which is used in pharmacovigilance programmes for evaluating suspected ADR reports for assessing the safety of drugs for use & for regulatory purposes also. This assessment may be undertaken by clinicians, academics, pharmaceutical industry, and regulators.

Causality assessment can be done by treating health professionals as a tool for decision making regarding a drug treatment & by regulators as a help in signal detection and aid in risk-benefit decisions regarding medicines. Algorithms, structured tools specifically designed for the identification of an ADR, should theoretically make a more objective decision on causality. The objective causal assessments are based on four basic principles-temporal eligibility, dechallenge and outcome, rechallenge and outcome, and confounding factors.⁸

It is often difficult to decide if an adverse clinical event is because of therapeutic failure or an ADR and therefore in a patient who is on a drug treatment, the differential diagnosis should include the possibility of an adverse drug reaction.

Immediately after an adverse event it is wise that the first step is to find out whether a patient is taking a medicinal product, including over-the-counter formulations, products that may not be thought of as medicines (such as herbal or traditional remedies, recreational drugs, or drugs of abuse) and long-term treatments that the patient may forget (such as oral contraceptives). The next step is to assess the likelihood of the effect being caused by the medicine and in cases of poly pharmacy it is often a denting task to pinpoint the causative drug. There are many characteristics looked for assigning probability of causation to a suspected adverse drug reaction.

- **Timing-** The time relation between the use of the drug and the occurrence of the reaction should be assessed.
- **Pattern recognition-** The pattern of the adverse effect may match the known pharmacology or allergy pattern of one of the suspected medicines, or of chemically related or pharmacologically related compounds. Some patterns are pathognomonic.
- **Investigations-** It is wise to establish baseline functions like liver function & kidney function tests, allergic tests etc. at the start of therapy in anticipation of an adverse drug reaction.

Next, one should consider the background data related to the frequency of the adverse event and how often it is associated with drugs & finally, rechallenge with the drug should be considered, particularly if the patient is likely to benefit directly from the knowledge gained. At the end of this exercise, it should be possible to attribute causality.⁹

Algorithms are structured tools specifically designed for the identification of an ADR and to make a

more objective decision on causality. A number of algorithms or decision aids have been published including the Jones algorithm, Naranjo algorithm, the Begaud algorithm, the Karch algorithm, the Yale algorithm, the WHO-UMC and a newer quantitative approach algorithm. Each of these algorithms has similarities and differences. WHO-UMC system has been developed in consultation with the National Centers participating in the Program for International Drug Monitoring and is meant as a practical tool for the assessment of case reports. It is basically a combined assessment taking into account the clinical-pharmacological aspects of the case history and the quality of the documentation of the observation.⁸

The most commonly used algorithms is the Naranjo algorithm which 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. The Naranjo criteria classify the probability that an adverse event is related to drug therapy based on a list of weighted questions, which examine factors such as the temporal association of drug administration and event occurrence, alternative causes for the event, drug levels, and previous patient experience with the medication. Probability is assigned via a score termed definite, probable, possible or doubtful. It is also called the Naranjo Scale or Naranjo score.¹⁰ (Table 2).

Conclusion

Even though ADR monitoring (PvPI-Pharmacovigilance Programme of India) is still in its developing stage, it is not new to India. In 1986 a formal adverse drug reaction (ADR) monitoring system consisting of 12 regional centers, each covering a population of 50 million, was proposed for India but nothing much happened until a decade later when in 1997, India joined the World Health Organization (WHO) Adverse Drug Reaction Monitoring Programme based in Uppsala, Sweden. Information about the need to report ADRs and about the functions of these monitoring centres still did not reach the prescribers and there was lack of funding from the government as well. This attempt was again unsuccessful and hence from the 1st of January 2005, the WHO-sponsored and World Bank-funded National Pharmacovigilance Program for India was made operational which is overseen by the National Pharmacovigilance Advisory Committee based in the Central Drugs Standard Control Organization (CDSCO), New Delhi.

Reporting of ADRs after marketing of the drug should be actively encouraged and should involve all those concerned including doctors, pharmacists, nurses, patients and pharmaceutical companies. To enhance and facilitate this, a culture of learning about pharmacovigilance should start early in the professional training of healthcare students and also create awareness by giving adequate information to patients at the start of any

treatment about the potential benefits and risks of the therapy.

All stakeholders in the programme including healthcare professionals, consumer groups, NGOs and hospitals should appreciate that there is now a well-

established system in place to collect and analyse adverse event data. They should start reporting adverse events actively and participate in the National Pharmacovigilance Program to help ensure that people in India receive safe drugs.^{11,12}

Table 2: Naranjo Scaling

Question	Yes	No	Don't know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
4. Did the adverse reaction reappear when the drug was re-administered?	+2	-1	0	
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	

To assess the adverse drug reaction, please answer the following questionnaire and give the pertinent score

Probability Score

Definite (9-13) ___ Probable (5-8) ___ Possible (1-4) ___ Doubtful (0)

Source of Support: None

Conflict of Interest: Nil

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