A Review Article of Adverse Drug Reactions

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Abstract- *gilance plays a consequential role in the surveillance of adverse drug reactions, which is provoked by the drugs used to cure diseases. Adverse drug reactions (ADRs) produce detrimental or undesirable effects to the body after administration of drugs. It has been reported that the number of patients dying because of contrary effects of drugs per year increased upto 2.6-fold. Moreover, rates of hospitalization of patients are increasing owing to adverse effects of drugs.*

I. INTRODUCTION

Drug is single energetic chemical entity existing in a remedy that is use for diagnosis,prevention and remedy of diseases. (Mererjone, 2003). The person-to-person variability of drug response is a important hassle in scientific practice and drug improvement (Meyer, 2000). It can lead to therapeutic failure or unfavourable consequences of tablets (ADRs) in folks or subpopulations of patients. Adverse drug response is sudden impact of drug on animal and human being and regarded as one of reasons of morbidity and mortality of hospitalized patients (Ditto,2004)(1)

A productive hospital-based reporting application can be instrumental in offering precious statistics .regarding possible issues of drug utilization in an institution. Through these efforts, issues are recognized and resolved, which effects in non-stop enchancment inpatient Care (Murphy and Frigo, 1993). Spontaneous reporting program, a frequent approach of drug surveillance is succesful of recognizing ADRs in the every day scientific practice even though below reporting and absence of records on variety of human beings absolutely uncovered to the drug are its dangers Safety problems occur every time scientific selections have to be made (Bauer, 2008). ADRs can take place in all settings the place healthcare is provided. Most of the contemporary proof comes from hospitals because the dangers related with health facility cure are higher (Yurdaguel et al., 2008). Many such occasions take place in other healthcare settings such as consulting rooms, nursing homes, pharmacies, neighborhood clinics and patients' properties (Stevenet al., 2008). While the drug manufacturing method has been revolutionized via cutting-edge techniques, drug security assessment stays at the back of and is nonetheless reliant on applied sciences that have been used for countless a long time (Powley et al., 2009). Current conceptual questioning on the protection of sufferers locations the high duty for ADRs on deficiencies in machine design, organization and operation – instead than on character practitioners or products. Berwick and Leape (1999) advocated Cutaneous drug eruptions are one of the most frequent types of adverse reaction to drug therapy, with an common incidence fee of 2–3% in hospitalised patients.1–3 Almost any medication can result in pores and skin reactions, and certain drug classes, such as non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics and antiepileptics, have drug eruption rates approaching 1–5%.4 Although most drug-related pores and skin eruptions are not serious, some are extreme and doubtlessly life-threatening. Serious reactions consist of angio- oedema, erythroderma, Stevens–Johnson syndrome and poisonous epidermal necrolysis. Drug eruptions can additionally appear as section of a spectrum of multiengine involvement, for instance in drug-induced systemic lupus erythematosus (see Chapter 11). As with different sorts of drug reaction, the pathogenesis of these eruptions may additionally be both immunologica (2,3)

Electronic fitness files (EHRs) have emerged as a probably valuable, and complementary, source of facts for pharmacovigilance, which, as a end result of the barriers of scientific trials – in phrases of period and pattern measurement – needs to be carried out during the life-cycle of a drug to inform choices about sustained use. Adverse drug occasions (ADEs), described as undesired harms ensuing from the use or misuse of a drug (Nebeker et al., 2004), are the most common iatrogenic injury, being accountable for around 3.7% of health center admissions global (Howard et al., 2007). The destructive consequences of tablets cause suffering in sufferers and put an financial burden on healthcare – regularly unnecessarily, as ADEs are in many instances preventable (Hakkarainen et al., 2012). A task for pharmacovigilance is that ADEs are closely underreported (Hazell and Shakir, 2006), each in so-called spontaneous reporting systems, whereby reviews of ADE cases are submitted voluntarily by means of sufferers and clinicians, and in EHRs, in which ADEs can be encoded by using a set of analysis codes

In the United Kingdom, almost a quarter of the populace will be aged over sixty five years with the aid of 2034. The most fast extend has been in the numbers of 'oldest old' (those aged eighty five years and over). It is projected that through 2034 there will be a 2.5-fold increase in the numbers of oldest old, who will then represent 5% of the populace [1].

As a consequence, fitness offerings are an increasing number of required to meet the wants of an ageing, frequently multimorbid populace [2, 3].

ADR is described as a response to a drug which is noxious and unintended, and which happens at doses generally used in man for the prophylaxis, diagnosis, or remedy of disease, or for the change of physiological feature (WHO, 1973). It is additionally described as an undesirable effect, fairly related with the use of the drug that might also take place as

Classification of Adverse Drug Reactions

Type 1 Or Non-Immunologic Reactions

In this type of reaction, the qualitative responses are narmal but quantitative response are abnormal. The responses in predictable reactions are less serious, commonly occurring. The reactions include, side effect, toxic effect, withdrawal symptoms etc.

Excessive pharmacological effect.
Side effect.
Toxic effect.
Secondary pharmacological effect.
Rebound response after discontinuation

Excessive pharmacological effect:- it develops in all patients if excessive dosage is given result in excessive pharmacological effect. It is seen in cardioactive agents, CNS depressant, hypoglycemic agents and hypotensive agents. (3,4)
Side effects:- Side effects are some extension of pharmacological effects which produced at therapeutic doses. It is dose related and minor in nature. Side effects result as extention of the same therapeutic effects. For example: atropine produces dry mouth which is used as anti –secretary in preanesthetic medication.

Codeine (antitussive) has constipating side effects which is used in treatment of diarrhea.

Toxic effects:-the effects produce at overdose or prolonged use of the drug .

Atropines cause delirium
Paracetamol causes hepatic necrosis
Barbiturates cause coma
Morphine causes respiratory failure

Secondary pharmacological effect:-some of the drugs having other many pharmacological actions at commonly administered dosage. The effect produced by the drug is different than drug administered initially for prevention or treatment means it is an indirect consequence of a primary drug action(5,6)

Example:- patient receiving antihistamine drug for the prevention of motion sickness or in the allergic skin reaction may become drowsy

Rebound Response after Discontinuation/Drug Withdrawal Reactions:

Use of long term of many medication produce tolerance at cellular level. Sudden withdrawal of such medication may give rise to severe adverse effects. These reactions occur in absence of drug causing it These types of reactions are common with drugs which acting on CNS For example: narcotics; analgesics hypnotics, ethanol, etc. It can also result with some antihypertensive drugs and corticosteroids. The withdrawal effects can be minimizing by gradual withdrawal of drugs.

Following are the examples of drug withdrawal response:

Clonidine is antihypertensive agent which causes severe rebound hypertension if its use discontinues

suddenlyThe long-term use of CNS depressants like, benzodiazepines barbiturates and alcoholin confusion delirium, tachycardia and convulsion.(4,5)after sudden withdrawal Antiepileptic drug withdrawal may increase seizuresThe reaction generally results due to presence of some patient peculiarities For example Allergy Idiosyncrasy. The reaction is based on patient and not on drug action. It is less common and dose independent. If the reactions are more serious then immediate withdrawalof that drag is required.

Following are the types of unpredictable reactions

Idiosyncrasy or Pharmacogenetics
Genetically determined toxicity.
Allergic drug reaction (ypersensitivity reaction).
Super sensitivity
Photosensitivity
Intolerance
Idiosyncrasy or Pharmacogenetics:

Idiosyncrasrefer to inherent peculiarity of individual and it is described as unusual response/abnormal response to drug or highly exaggerated usual response produced by some drugs with usual doses in few individualIt is genetically determined atypical/bizarte effect

Followingare the examples of idiosyncrasy reaction:

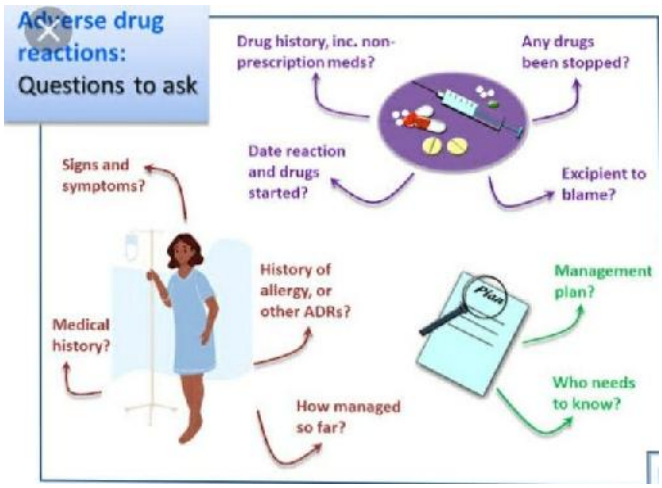
Administration of analgesic drug to patient with renal disease may induce tumors kidney pelves High doses of stilbesterol during pregnancy produce vaginal adenocarcinoma.Long term uses of estrogens produce uterine cancer.

Long term uses of Azathioprine Cyclophosphamide may induce lymphoid tumorsBarbiturate produces excitement and mental confusionQuinine produces cramps, diarrhoea purpura, asthma, vascular collapse Prolonged apnoea caused by pseudocholinesterase deficiencyAspirin produces bronchial asthma.(6,7)

(b) Genetically Determined Toxicity. The reactions occur in patients with special genotype or genetic make up in some literature, this reaction included in idiosyncrasy reaction.Following are examples of genetically determined toxicityHaemolytic anaemia caused exposure with primaquine, sulphonamide, nitrofurantoin,quinine, chloroquine in deficiency of Glucose-6-Phosphate Dehydrogenase (G-6-PD) inRBCs Hereditary deficiencies of plasma cholinesterase are unable to hydrolyze the succinylcholine thus it causes prolonged apnoea for few hours in case of plasma pseudocholinesterase deficient peopleSome of the drugs metabolized by acetylation in the liver by enzyme N-acetyl transferase for example Procainiamede, boniazid and hydralazine. In slow acetylators, there is slow response with enzyme N-acetys transferase for metabolization which results into development of systemic lupus erythematosus with hydralazine and polyneuritis with soniazid While the fast acetylators may show the drug resistance or failure of response.(2,3)

(c) Allergic Drug Reaction (Hypersensitivity Reaction): It includes all the reactions mediated by antigen-antibody reactions involving sensitized lymphocytes Drug acting as aforeign antigen which react with antibody in human body to cause undesirable effects like, skin rashes, bronchospasm, angioedema, anaphylactic shock, vasculitis, etc. These reactions require previous exposure to the drug itself or to a closely related chemical drug. An allergic reaction is not a dose related and it has no correlation with the action of a drug Protein and peptide can act as complete antigen but most drugs are small molecule and do not stimulate antibody production. But they may combine with other carrier macromolecule and function as haptens or partial antigens which stimulate the biosynthesisof antibodies. These are then attached to body tissue and when this drug sensitized person isre exposed to the drug a reaction occurs between the hapten and preformed antibodiesresult into tissue damage leading to signs and symptoms of drug allergy.(3,5)

Anaphylaxis: It is the most serious type of drug allergic reaction. This involves the formation of specific type of antibodies that belong to lgf class. These antibodies present on surface of tissue cell. Upon re exposure of antigen it combines with antibodies on target tissueandresult into liberation of inflammatory mediators like:histamine.



reaction and symptoms. Anaphylaxis may be localized or generalized, in gut it produced diarrhoea and abdominal pain,

it produces asthma when it occurs in bronchi and produce edema when the reactions occur at surface of skin Generalized anaphylaxis is characterized by bronchospasm circulatory colapse with hypotension and sometimes skin rashes. The most serious type of anaphylaxis known as Anaphylactic shock in which there is obstruction of respiratory passage and lowering of blood pressure. If there is complete obstruction for few minutes then it results into death

Following are examples of drugs which produces the allergic reactions
Penicillin dextran, anesthetics and iodine containing compounds produce anaphylaxisreaction.
Sulphonamide, phenylbutazone, thiouracil produces leucopenia
Quinidine, thiazide digoxini produces thrombocytopenia

(d) Super sensitivity

In demonstrated to the increased in the responsiveness to a drug that produced either from denervation or following administration of a drug (a receptor antagonist) for a prolong period. For example, the blocking of dopamine receptor by chlorpromazine may cause super sensitivity by up regulating dopamine receptors(2,3)

(c) Photosensitivity

It consists of phototoxic and photoallergic reaction.Phototoxic reaction: In which the reaction occurs due to drug accumulation in skinwhich absorbs light upon exposure to light results into photochemical reaction. Photobiological or thema or Photoallergic reaction: In this reaction to cause tissue damage eg erythema, edema It is cell mediated immunological response which produces contact dermatitis on coverage to light e.g. sulfonamides, griseofulvin, etc.

F) Intolerance:-It is opposite of tolerance and there is appearance of ADR attherapeutic dose level Following are some examples of intolerance Chloroquine causes vomiting and abdominal pain ataxia [defective movement/gait)Few doses of carbamazepine cause Phenobarbitone may cause excitement and mental confusion. Single exposure of triflupromazine cause muscular dystonia.

Identification OF Adverse Drug Reactions

Case reports By this method, the unpredictable (bizarre) effects i.e. TYPE-B adverse drug reactions are reported.Mostly, all ADR reporting programmes follow this method. Here, the effects are recorded spontaneously. With this method, both unusual and acute ADRs can be focused on and monitored (Naranjo and Busto1981).

Intensive monitoring studies Health care members continuously watch the patients and record all the events observed when a drug or different drugs are administered. In this, defined groups of patients areHncise period of time. Special investigations can be performed if statistical screening is incorporated in this study method (Naranjo and Busto1981; Nebeker and Barach2008).

Contingent studies In these studies, patients administering similar medicines are identified, and their events are recorded. The contingent examinations are too expensive, and these investigations are difficult to perform onCase-control studies (Retrospective Studies)

These patients are then compared with a matched control group that is similar in confounding factors but do not possess the adverse events or illness. event or not. However, by this method, new ADRs cannot be identified (Parthasarathi et al.2007).Case cohort studies These studies includeboth prospective cohort study and retrospective case-control studies; in other words, it is the combination of both the studies (Pearson et al.1994).Record linkage In this method, all therecords such as prescription records, patient records and hospital records arestudied to identify the illness with drugs.(7,8)

Meta analysis :-It is a quantitative examination of two or more independent studies to determine the overall effect and to describe reasons in variation of study results (Prosser and Kamysz 1990).

Utilization of residents statistics:-If a drug induced event is very frequent and if suspicions arise for them, case-control and experimental cohort studies shall be initiated (Rao2010).

Roles of pharmacovigilance in monitoring ADRs

Many incidents happened that triggered the want of legal guidelines and guidelines concerning the secure use of drugs. After rofecoxib withdrawal from the European market, the FDA regulations on post-market surveillance have been criticized and a new gadget of pharmacovigilance used to be delivered that supplied records on recognized dangers (Palaian et al.2006; Rawlins and Thompson1981; (Yadav2008).

Throughout the early post-marketing period, the product might be used in different groups of people from those used in clinical trials and much larger populations might be exposed in a relatively short time. The post-marketing product

is required to develop new information, which can focus on the benefits as well as risks of the product (Arnott et al.2012). Pharmacovigilance produces detailed information of marketed products to ensure their safe use.

The impressive pharmacovigilance planning can reduce the adverse events of drugs in patients. The most important method used in pharmacovigilance is to collect information on a drug when it is in the pre-marketing phase is by conducting a clinical trial.(5,6)

Causalities of Adverse drug reactions

Axis	Scoring of evidence of reaction		
	Favors	Uncertain	Against
History	+1	0	-1
No alternative illness	+2	0	-1
Timing event	+1	0	-2
Drug level	+1	0	-1
Dechallege	+1	0	-1
Rechallege	+1	0	-1
Total score	+7	0	-7

Type A and B Reactions

Table 3 ,Characteristics of Type A and Type B adverse drug reactions

Characteristics	Type A	Type B
Dose dependency	Usually shows a good relationship	No simple relationship
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 severe
Clinical burden	High morbidity and low mortality	High morbidity and mortality
Overall proportion of adverse drug reactions	80%	20%
First detection	Phases I–III	Usually phase IV
Animal models	Usually reproducible in animals	No known animal models

Source: (Giovanni *et al.*, 2003)

Monitoring Of ADRs

monitoring is spelled out as the practice of continuously monitoring the undesirable effects caused using any drug. Pharmacovigilance plays an imperative impersonation in monitoring ADRs (Hall et al.1995; Hornbuckle et al.1999; Juntti and Neuvoren2002).

It is inherent for pharmaceutical regulators to screen their pharmaceutical products in the market and record if any suspected adverse reactions are identified. ADRs can occur by use of various pharmaceutical products, herbal drugs, cosmetics, medical devices, biological, etc. The introducing of this monitoring procedure intends at warranting that patients receive safe and beneficial medicinal products (Karch and Lasagna1997). If any of the adverse events are not stated it may result in noxious and serious effects of remedial products. Thus, properly conducting ADR monitoring programmes will help to reduce the harmful effects of therapeutic products (Kessler1993).

Benefits of ADR monitoring

An ADR monitoring and reportingprogramme can furnish following benefits:

1. It caters information about quality and safety of pharmaceutical products.
2. It initiates risk-management plans.
3. It prevents the predictable adverse effects and helps in measuring ADR incidence 2. It initiates risk-management plans.
4. It instructs health care team, patients, pharmacists and nurses about adverse drug effects and creates awareness regarding ADRs.

The main objective of ADR monitoring is to disclose the risk factors that can cause the adverse reactions (Moore2001; Murphy and(8,9)

II. CONCLUSION

The importance of adverse drug reactions is oftenunderestimated. They are common and can be lifethreatening and unnecessarily expensive. The measuresoutlined in the box above are important to improve thebenefit to risk ratio of drug treatment by reducing theburden of drug toxicity. Because of the wide range ofdrugs available, the manifestations of toxicity may varyand affect any organ system. In fact, adverse reactionshave taken over from syphilis and tuberculosis as thegreat mimics of other diseases. The pattern of toxicity islikely to change with the introduction of newbiotechnology products. It is therefore important forprescribing clinicians to be aware of the toxic profile ofdrugs they prescribe and to be ever vigilant for theoccurrence of unexpected adverse reaction(2,3)

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