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REVIEW ON ADVERSE DRUG REACTIONS

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ABSTRACT

Adverse drug reactions are also known as side effects. Adverse drugs reactions (Adrs) are toxic, unintended, and undesirable impacts which occur as result of drug treatment. adverse drug reactions (ADRs) remain a challenge in modern healthcare, particularly given the increasing complexity of therapeutics, an ageing population and rising multimorbidity. These reactions occur due to self-medication or due to intake of over dose of medicines without prescription. The prescribed drugs may produce undesirable effects along with main effect which leads to adverse drug reactions. Most of the adverse drug reactions are preventable. Hence, in order to avoid adverse drug reactions one should take only properly prescribed drugs.

KEYWORDS: Adverse drug reactions; self-medication; prescribed Drugs.

INTRODUCTION

Adverse drug reaction (ADR) is occurred when combination of two or more drugs. When injury affected and taking a drug, it causes in single dose or continued dose of a drug. It results to cause the side effects. Adverse drug reactions in children square measure a crucial public unhealthiness. Pharmacists in organized health care systems have to develop comprehensive, in progress programs for observance and coverage adverse drug reactions. adverse drug reactions (ADRs) to spontaneous reporting systems and to investigate whether there are differences between different types of ADRs1.[1,2]

An adverse drug reaction (ADR) can be defined as 'an appreciably harmful or unpleasant reaction resulting from an intervention related to the use of a medicinal product; adverse effects usually predict hazard from future administration and warrant prevention, or specific

treatment, or alteration of the dosage regimen, or withdrawal of the produc, Since 2012, the definition has included reactions occurring as a result of error, misuse or abuse, and to suspected reactions to medicines that are unlicensed or being used off-label in addition to the authorised use of a medicinal product in normal doses. While this change potentially alters the reporting and surveillance carried out by manufactures and medicines regulators, in clinical practice it should not affect our approach to managing ADRs.[3]

Some drug reactions could occur in everybody, whereas others occur solely in inclined patients. A drug allergic reaction is associate degree immunologically mediate reaction that exhibits specificity and return on re-exposure to the offensive drug.[4]

Importance of adverse drug reactions[5]

- Account for 5% of all hospital admissions
- Occur in 10-20% of hospital inpatients
- Cause deaths in 0.1% of medical and 0.01% of surgical inpatients
- Adversely affect patients quality of life
- Cause patients to lose confidence in their doctors
- Increase costs of patient care
- Preclude use of drug in most patients, although they may occur in only a few patients.
- May mimic disease, resulting in unnecessary investigations and delay in treatment.

Causes of ADR

- ADR due to improper prescription & dispensing, sometimes improper dose are prescribed without taking patient history.
- Some drugs have very low margin of safety that is therapeutic Index.
- Many Formulations of different companies are therapeutically not equivalent due to differences in bioavailability & thus cause ADRs.
- Some other factors such as presence of disease of liver& kidney may accumulate the drug in the body which can result in ADRs.
- Use of Potent drugs also causes ADR.
- Genetic Factor is also responsible for causing ADRs.[6]

Factors Affecting ADRs

Factors affecting the occurrence of ADRs are subdivided into five groups; Patient related factors, Social factors, Drug related factors, Disease related factors and ADR related factors.

Patient related factors

- **Age**

All drugs can produce ADRs, but not all patients develop the same level and type of ADRs. Age is a very important factor which affects the occurrence of ADRs. Elderly patients with multiple medical problems who are taking multiple drugs, those who have a history of ADRs, and those with a reduced capacity to eliminate drugs are at high risk for ADRs.

- **Gender**

The biological differences of males and females affect the action of many drugs. The anatomical and physiological differences are body weight, body composition, gastrointestinal tract factors, liver metabolism, and renal function. Women in comparison to men have lower bodyweight and organ size, more body fat, different gastric motility and lower glomerular filtration rate. These differences can affect the way the body deals with drugs by altering the pharmacokinetics and pharmacodynamics of the drugs including drug absorption, distribution, metabolism and elimination. Gender plays a role in the effect on ADRs. A study of sex differences in ADRs to antiretroviral drugs indicates potential sex differences in the frequency and severity of ADRs to antiretroviral drugs.

- **Maternity status**

Pregnancy has an impact on drug treatment. Not only are women affected by the drug, but the fetus will also be exposed to ADRs of the drug. There are certain physiologic changes that occur during pregnancy which might affect drug pharmacokinetics and pharmacodynamics, these changes are; total blood.

- **Fetal development**

The fetus, which is exposed to any drugs circulating in maternal blood, is very sensitive to drug effects because it is small, has few plasma proteins that can bind drug molecules and has a weak capacity for metabolizing and excreting drugs. Once drug molecules reach the fetus, they may cause teratogenicity (anatomic malformations) or other ADRs.

- **Allergy**

Drug independent cross-reactive antigens can induce sensitizations, which can manifest as a drug allergy. The existence of such cross-reactivity is supported by medical literature. After primary sensitization to a causative drug, a second exposure causes affected T cells and antibodies to enter the elicitation phase, corresponding to the type I to IV immune reactions (Gell and Coombs Classification). Most of the drug allergies observed are type I or IV reactions; type II and III reactions are only encountered infrequently.

- **Body weight and fat distribution**

In the body, drugs are distributed to and from the blood and various tissues of the body (for example, fat, muscle, and brain tissue). After a drug is absorbed into the bloodstream, it rapidly circulates through the body. As the blood recirculates, the drug moves from the bloodstream into the body's tissues. Once absorbed, most drugs do not spread evenly throughout the body. Some drugs dissolve in water (water-soluble drugs), such as the antihypertensive drug atenolol. Some drugs tend to stay within the blood and the fluid that surrounds cells (interstitial space). Drugs that dissolve in fat (fat-soluble drugs), such as the anesthetic drug halothane, tend to concentrate in fatty tissues. Other drugs concentrate mainly in only one small part of the body (for example, iodine concentrates mainly in the thyroid gland), because tissues have a special attraction for (affinity) and ability to retain the drug.

Social factors

- **Alcohol drinking**

Alcohol affects the metabolism of many drugs and it facilitates the development of ADRs. Alcohol drug interaction refers to the possibility that alcohol may change the intensity of the development of ADRs making it more toxic or harmful to the patient either in a pharmacokinetic or pharmacodynamic manner. Taking alcohol with certain drugs can cause many ADRs like nausea, vomiting, headaches, drowsiness, fainting, loss of coordination, hypotension and many other ADRs.

Race and ethnicity factors Evidences suggest that ethnicity exerts a substantial influence on drug response and action. Drug action varies greatly between individuals. Ethnic background is controlled by genetic factors, which makes the inter-individual differences due to polymorphisms in genes encoding drug metabolizing enzymes, drug transporters, and receptors.

- **Smoking**

Smoking is one of the risk factors of many diseases like peptic ulcer, cancer and cardiovascular diseases. It also affects the metabolic process by affecting liver enzymes acting as a potent inducer of the hepatic cytochrome P-450 (CYP) isoenzymes 1A1, 1A2, and, possibly, 2E. Many drugs are substrates for hepatic CYP1A2, and their metabolism can be induced in smokers, resulting in a clinically significant decrease in pharmacologic effects.

Drug related factors

- **Polypharmacy**

Taking several drugs, whether prescription or over-the-counter, contributes to the risk of having an ADR. The number and severity of ADRs increases disproportionately as the number of drugs taken increases. Many definitions are applied for polypharmacy. It is different from scholar to scholar but the basic concept of taking more medications at the same time than are clinically appropriate remains constant (Bushardt et al., 2008). It implies to the prescription of too many medications for a particular patient, with a possibility of increased risk of ADRs.

Disease related factors

Concomitant patient's disease may also influence susceptibility to ADRs. For example; increases of the frequency of idiosyncratic toxicity with anti-infective drugs such as trimethomprim-sulphamethoxazole. Multiple diseases make patients more vulnerable to ADRs due to the presence of many diseases and the use of many drugs. If hypertension is accompanied with other diseases, these diseases might have an impact on the response of the body to antihypertensive drugs since the metabolic processes of the body will be affected negatively. In patients with renal failure, the effect of drugs on the kidneys is lessened because of the loss of the site of action for these drugs. This leads to increasing the dose which in turn leads to more ADRs.[7]

ADR most common in Women, Elderly (>60 y old), Very young (1-4 y), Patients taking more than one drug (Figure 1)

Figure 1: Adverse drug reaction.

Classification of ADR

- Type A: Augmented pharmacologic effects
- Type B: Bizarre effects
- Type C: chronic Reactions
- Type D: delayed Reactions

Type A

Maximum it is the dose dependent and predictable, Related to pharmacological action of drug. Extensions of the principal pharmacological action of the drug. Toxic reactions linked to excess dose or impaired excretion, or to both .These are three types Predictable, Common, Dose-dependent. Predictable is relatively easily predicted by preclinical and clinical pharmacological studies. Common Type A reactions is not serious and it is usually dose dependent. The toxicity of Drug overdose caused by excessive dosing.

Type B

It is dose independent and unpredictable and Drug Intolerance, Lower threshold to normal pharmacological action of a drug, Undesirable pharmacological effect at recommended doses and single average dose of aspirin. Immune mediated response to a drug agent in sensitized patient eg. Anaphylaxis with penicillin. Idiosyncratic drug reactions are uncommon response to drug.

Type C

It is biological characteristics can be rationalized from chemical structure and associated with long-term drug therapy. It is well known and can be anticipated.

Type D

it is the delayed effects and Carcinogenic, teratogenic effects. Carcinogenic leads to cancer.

Severity of Adverse Drug Reaction

- **MINOR**

No therapy, antidote or prolongation of hospitalization is required.

- **MODERATE**

It requires change in drug therapy, specific treatment or prolongs hospital stay by at least one day.

- **SEVERE**

It is life threatening, cause permanent damage or requires intensive medical treatment.

- **LETHAL**

It directly or indirectly contributes to death of the patient.

Some ADRs are due to a lack of patient confidence surrounding the efficacy of the medications prescribed, and the potential for medication non-compliance. When providers know how an individual patient may positively or negatively respond to a drug treatment plan, patient confidence increases resulting in greater medical adherence.The combination of increased compliance and individualized care plans reduces the chance of ADRs from taking place.[8]

Categories of adverse drug effect

1. Side effects
2. Secondary effects
3. Intolerance
4. Idiosyncrasy
5. Drug allergy
6. Photosensitivity
7. Drug dependence
8. Drug withdrawal reactions
9. Mutagenicity & Carcinogenicity
10. Drug induced diseases
11. Teratogenicity

1. Side effects

- These are unwanted but often unavoidable pharmacodynamic effects that occur at therapeutic doses.
- A side effect may be based on the same action as the therapeutic effect.

e.g.

a) *Atropine* is used in preanaesthetic medication for its antisecretory action , the same action produces dryness of mouth as a side effect.

b) *Acetazolamide* acts as diuretic by promoting bicarbonate excretion acidosis occur as side effect.[9]

2. Secondary effects

- An effect may be therapeutic in one context but side effect in another context.
- E.g.

a) *Codeine* used for cough produces constipation as a side effect but the latter is its therapeutic effect in travellers diarrhoea.

b) Depression of A-V conduction is the desired effect of *Digoxin* in atrial fibrillation, but the same effect is undesirable in CHF.[10]

3. Intolerance

- It is the appearance of characteristic toxic effects of a drug in an individual at therapeutic doses.
- It indicates a low threshold of the individual to the action of a drug.
- These are individuals who fall on the extreme left side of the *Gaussian frequency distribution curve* for sensitivity to the drug.
- E.g.

a) A single dose of *trifluprom*azine induces muscular dystonias in some individuals specially children.

b) Only few doses of *carbamazepine* may cause ataxia in some people.

c) One tablet of *chloroquine* may cause vomiting & abdominal pain.[11]

4. Drug allergy

- It is an immunologically mediated reaction producing serotype symptoms which are unrelated to the pharmacodynamics profile of the drug, this is also called Drug hypersensitivity.

- Generally occurs even with much smaller doses and have a different time course of onset and duration.
- Prior sensatization is needed and a latent period of atleast 1-2 week is requires after the first exposure.
- The drug or its metabolites acts as a antigen or hapten and induced production of antibodies (also called as sensitized lymphosite).
- Chemically Related drugs often show cross sensitivity one drug can produce different type of allergic reaction and different individuals.
- While widely different drugs can produce the same reaction.
- the course of drug allergy is variable an individual previously sensitive to a drug may subsequently tolerated without a reaction and vice versa.

Mechanism & type of allergic reactions

1) ON BASIS OF HUMORAL RESPONCE- there are three types of reactions

a) Type-I anaphylatic reactions

b) Type-II cytolytic reaction

c) Type-III retarded arthus reaction

2) ON BASIS OF CELL MEDIATED RESPONCE-

c) type-IV delayed hypersensitivity.

a) Type-I anaphylatic reactions

- In this reaction reaginic antibodies (IgE) are produced which get fixed to the mast cell.
- On exposure to the drug antigen : antibody reaction take place on the mast cell surface.
- Which leads to releasing mediators like histamine, 5HT, leukotrienes specially LT-C4 and D4,prostaglandin,PAF.
- Resulting in urticaria, itching, angioedema, broncospasm, rhinitis or anapylactic shock.

b) Type-II cytolytic reaction

- Drug+ component of a specific tissue cell act as AG. the resulting antibodies (IgG, IgM) bind to the target cells, on reexposure AG:AB reaction takes place on the surface of these cells, complement is activated and cytolysis occurs .

E.g thrombocytopenia, agranulocytosis, aplastic anemia, haemolysis, organ damage(liver, kidney, muscle),systemic lupus erthematous.

c) Type-III retarded arthus reaction

- These are mediated by circulating antibodies (predominantly IgG or moping antibody)

antigen antibody complex bind complement and precipitate on vascular endothelium giving rise to a destructive inflammatory response manifastations are rashes, serum sickness, polyartiritis nodusa ,stevens jonson syndrome.

d) Type-IV delayed hypersensitivity

- These reactions are mediated through production of senstized T-lymphocyte carring receptor for antigen.
- On contact with antigen these T-cell produce lymphokines which attract granulocytes and generate an inflammatory response.

Eg. -contact dermatitis, rashes, fever, photosenstization.

These reactions generally takes more than 12 hours to develop.

Treatment of drug allergy

- Most mild reaction like skin rashes subside by themselves and do not required specific treatment.
- Antihistimines(H1) are benbificial in some type 1 reaction & some skin rashes.
- In case of anaphylactic shock and angioedema of larynxs the resuscitation council of UK has recommended the following measures.

i) put the patient in reclining position ,administer oxygen at high flow rate and perform cardiopulmonary resuscitation if required.

ii) inject adrenaline 0.5mg IM repeat every 5-10 min in case patient does not improve, this is the only life saving measure.

iii) Adrenaline should not be inject IV (can itself be fatal)unless shock is immediately life threatning, if adrenalin inject i.v. (can itself be fatal) unless shock is immediately life threatening. I should be diluted to 1:10,000 or 1:100,000 & slowely with constant monitoring.[12,13,14]

5. Photosensiitivity

It is a coetaneous reaction resulting from drug induced senstization of skin to uv radiation.

The reaction is of two types-

A) Phototoxic

B) Photo allergic

A) Phototoxic

Drug and its metabolites accumulates in the skin, absorbs light and undergo a photochemical reaction followed by a photobiological reaction resulting in local tissue damage (sunburn like) , i.e. erythema, edema, blistering, hyperpigmentation and desqumation.

B) Photo allergic

- Drug involve in active phototoxic reactions are tetracylines(specially demeclocycline) and tar product.
- Drug causing cronic and low grade sensitization are naliedixsic acid, fluoroquinolones, sulfones, sulphonamide, thiazides, aminodaron.
- This type of reaction is more common than photoallergic reaction.[15]

6. Drug dependence

It is a state in which use of drugs for personal satisfaction is accorded a higher priority than other basic needs.

Drug dependence has following aspects:

a. Psychological dependence
b. Physical dependence
c. Drug abuse
d. Drug addiction
e. Drug habituation

a. Psychological Dependence

- In Psychological dependence an individual has personal belives that optimal stage of well being only through the action off drug.
- Psychological dependence accompaines all patterns of self medication.

b. Physical Dependence

- It is an altered physiological state produced by repeated administration of drug to maintain physiological equilibrium.
- In presence of drug the nervous system functions normally it is known as neuroadaptation.

  Drugs which produce physical dependence are

  Alcohol, Benzodiazipines, Barbiturates etc.[16,17]

c. Drug Abuse

- Drug abuse refers to use of a drug by self medication in a manner and amount that deviates from the approved medical & social pattern in a given culture at a given time.
- The terms have a huge range of definitions related to taking a psychoactive drug or performance enhancing drug for a non-therapeutic or non-medical effect.

Some of the drugs most often associated with this term include alcohol, amphetamines, barbiturates, benzodiazepines (particularly temazepam, nimetazepam, and flunitrazepam, cocaine, methaqualone, and opioids.[18]

d. Drug addiction

It is a pattern of compulsive use of drug characterized by overwhelming involvement with use of drug.

Is defined as a drug user's compulsive need to use drug in order to function normally. When such drugs are unobtainable, the user suffers from drug withdrawal.

Examples: cannabis, LSD, amphetamine e.t.c.[19,20]

e. Drug habituation

- It denotes less intensive involvement with the drug so that its withdrawal produces only mild discomfort.
- Consumption of tea coffee, tobacco, social drinking are regarded habituating.
- In it physical dependence is absent.
- Basically habituation & addiction imply different degree of psychological dependence; it may be difficult to draw a clear cut line between these two.

7. Drug withdrawal reaction.[21,22]

- Stopping or discontinuing any drug that was taken from long time can leads to appearance of many adverse symptoms,which are called drug withdrawal reaction of drug.
- Withdrawal from many drugs can bring symptoms such as agitation, sweating, an inability to sleep, and high blood pressure.
- Opiate and narcotic withdrawal symptoms can be among the most difficult.
- Opiates and narcotics are classes of drugs that include heroin, codeine, Demerol (meperidine), and Oxycontin (oxycodone), which are taken to achieve a sense of euphoria.

- Other substances that tend to cause more severe withdrawal symptoms, and potentially life-threatening symptoms, are barbiturates, alcohol, and benzodiazepines.

EXAMPLES

Acute adrenal insufficiency may be precipitated by abrupt cessation of corticoid therapy.

Severe hypertension, restlessness, sympathetic over activity may occur shortly after discontinuing Clonidine. Worsening of angina pectoris, precipitation of M.I may result from stoppage of beta produced.

8. Teratogenicity

- It refers to capacity of a drug to cause abnormalities when administered to the pregnant mother.
- The placenta does not strictly constitute a barrier and any drug can cross it to a greater or lesser extent.
- The embryo is one of the most dynamic biological systems and in contrast to adults, drug effects are often irreversible.[23,24]

DRUGS CAN EFFECT THE FOETUS AT THREE STAGES

1) Fertilization & implantation:

Conception to 17 days: failure of pregnancy which often get unnoticed.

2) Organogenesis:

18 to 55 days of gestation: most vulnerable period, deformities are produced.

3) GROWTH & DEVELOPMENT

56 days onwards: development & functional abnormalities can occur.

Examples

ACE inhibitors- can cause hypoplasia of organs , specially lungs & kidneys.

NSAIDs- may induce premature closure of ductus arteriosus.

The type of malformation depends on the drug as well as the stage of exposure to the teratogen.[25]

PREVENTION FROM ADVERSE EFFECT OF DRUG

Adverse effect of drug can be minimized by observing following practice:-

- Avoid all inappropriate use of drugs in the contex of clinical condition of patient.

- Use appropriate dose, route and frequency of drug administration based on specific variables.
- Elicit and take into consideration previous history of drug reaction.
- Rule out possibility of drug interactions when more than one drug is prescribed.
- Adopt correct drug administration technique
- Carry out appropriate laboratory monitoring.[26]

Role of Pharmacist in ADR.

- Pharmacist is an important link between patients & physicals as he dispenses actual medicaments.
- Pharmacist should give important information about the drugs to the patient regarding drug selection & administration.
- Pharmacist should record the ADRs cases in hospital & should analyze them.
- Pharmacist can educate the public for safe & effective use of medications through verbal communication as well as written material, Computers etc.
- Pharmacist is also expected to participate in post marketing surveillance programs & to monitor for & prevent drug induces disease.
- Pharmacist should do patient counseling so the possibilities of ADRs may be reduced.

CONCLUSION

Here in we have discussed the identification, management and reporting of ADRs. We have described how modern expertise is changing the way that ADRs are predicted, prevented, detected and managed, and how we continue to try to improve these processes with technological advances. The importance of adverse drug reactions is often underestimated. They are common and can be life threatening and unnecessarily expensive. The measures outlined in the box above are important to improve the benefit to risk ratio of drug treatment by reducing the burden of drug toxicity. Because of the wide range of drugs available, the manifestations of toxicity may vary and affect any organ system.Individualized therapy is becoming more of a possibility as not just pharmacogenetics but other phenotypic information can be combined to generate patient-specific advice to prescribers. Such regulatory science at national and international level can help achieve a positive benefit-to-harm ratio throughout the lifecycle of a medicinal product. For individual clinicians, achieving the best outcomes from therapies remains a key goal because avoiding or mitigating the risk of ADRs continues to challenge our everyday clinical practice.

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