Adverse effects of drugs

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Introduction

- It is harmful or seriously unpleasant effects at doses intended for therapeutic effect and which call for reduction of doses or withdrawal of the drug and or forecast hazard from future administration.
- The term *adverse drug reaction* has been defined as ' any noxious change which is suspected to be due to a drugs, occurs at doses normally used in man, requires treatment or decreases in dose or indicates caution in the future use of the same drug'.

  (excludes trivial or expected side effects and poisonings or overdose)
- WHO defination: "**An adverse drug reaction is defined as" any response to a drug that is noxious and unintended and that occurs at doses used in human for prophylaxis, diagnosis or therapy"**
- Adverse effects may develop promptly or only after prolonged medication or even after stoppage of the drug.
- It is estimated that about 10-20%of hospitalized patient suffers from adverse effects.

- Adverse effects have been classified in many ways. One may divide them into:

❖ Type A (predictable or augmented) reactions:

- These are based on the pharmacological properties of the drug.
- Means they are augmented but qualitatively normal response to the drug.
- Include side effects, toxic effects and consequences of drug withdrawal.
- More common (80%), dose related and mostly preventable and reversible.
- Bleeding due to anticoagulants, hypoglycemia due to insulin and sedation due to antihistamines.

❖ Type B (unpredictable or Bizarre) reactions:

- These are based on peculiarities of the patient and not on drug's known action; include allergy and idiosyncrasy.
- Less common, often non-dose related, generally more serious and require withdrawal of the drug.
- Carry much higher risk of mortality.
- Agranulocytosis due to chloramphenicol, malignant-hyperthermia due to halothane are examples

Severity of adverse affects:

- Minor reactions:
  - ❖ Minor reaction:
    - ✓ No need of therapy, antidote or prolongation of hospitalization is required
  - ❖ Moderate reaction:
    - ✓ Requires change in drug therapy
    - ✓ Specific treatment or prolongs hospital stay by at least one day
  - ❖ Severe reaction:
    - ✓ Potentially life-threatening, causes permanent damage or requires intensive medical treatment.
  - ❖ Lethal reaction
    - ✓ Directly or indirectly contributes to death of the patient.

Pharmacovigilance

- According to WHO:"*it is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems*".
- The information generated by pharmacovigilance is useful in educating doctors about ADRs and in the official regulation of drug used.
- It has an important role in rational use medicines, as it provides the basis for assessing safety of medicines.

Prevention of ADRs

ADRs can be minimized by observing the following practices:

i. Prescribe the minimum no. of drugs as required to patients
ii. Avoid all inappropriate use of drugs in the context of patient's clinical condition.
iii. Use appropriate drug to right patient in right dose
iv. Elicit and take into consideration previous history of drug reaction and allergic diseases; exercise caution.
v. Rule out possibility of drug interaction when more than one drug is prescribed.
vi. Choose correct route of drug administration
vii. Carry out appropriate laboratory monitoring of drug level in plasma
viii. Prescribe new drugs with caution.

Adverse drug effects may be categorized into

- **Side effects :**
  - These are unwanted but often unavoidable pharmacodynamic effects that occur at therapeutical doses.
  - They can be predicted from the pharmacological profile of a drug and are known to occur in a given percentage of drug recipients.
  - Reduction in dose generally ameliorates the symptoms.
  - A side effects may be based on the same action as the therapeutic effect,
  - Eg:
    - atropine used in preanaesthetic medication for its antisecretory action. The same action produces dryness of mouth as a side effect.
    - Acetazolamide acts as a diuretic by promoting bicarbonate excretion. Acidosis occurs as a side effect due to bicarbonate loss.

- Side effect may also based on a different facet of action,
  - eg promethazine produces sedation which is unrelated to its anti-allergic action;
  - Estrogen cause nausea which is unrelated in their anti-ovulatory action.
- An effect may be therapeutic in one context but side effect in another context
  - Codiene used for cough produces constipation as a side effect but latter is its therapeutic effect in traveller's diarrhoe.
  - Depression of AV conduction is the desired effect of digoxin in atrial fibrillation, but the same may be undesirable when it is used for CHF.

- Secondary effects:

These are indirect consequences of primary action of the drugs, eg:

  - Suppression of bacterial flora by tetracyclines paves the way for superinfections.
  - Corticosteriods weaken host defense mechanisms so that latent tuberculosis gets activated.

- Toxic effects:
  - These are the result of excessive pharmacological action of the drug due to overdosage or prolonged use.
  - Overdosage may be absolute(accidental, homicidal, suicidal) or relative(i.e usual dose of gentamicin in presence of renal failure).
  - The effects are predictable and dose related.
  - They result from functional alteration (high dose of atropine causing delirium) or drug induced tissue damaged (hepatic necrosis from paracetamol overdosage.
  - Toxicity may result from extension of the therapeutic eg; coma by barbiturates, complete AV block by digoxin, bleeding due to heparin.

- Another action may be responsible for toxicity

Eg: Morphine (analgesic) causes respiratory failure in overdosage

Imipramine (antidepressant) overdosage causes cardiac arrhythmia.

streptomycin(anti-tubercular) causes vestibular damage on prolonged use.

❖ Intolerance:

- It is the appearance of characteristics toxic effects of a drug in an individual at therapeutic doses.
- Intolerance means a low threshold to the normal pharmacodynamic action of drug.
- Eg: single dose of trifluprομazine induces muscular dystonias in some individuals, specially children.
- Only few doses of carbamazepines may cause ataxia in some people.
- One tablet of chloroquine may cause vomiting and abdominal pain in an occasional patient.

- **Idiosyncrasy:**
  - ✓it is genetically determined abnormal reactivity to a chemical.
  - ✓The drug interacts with some unique feature of the individual , not found in majority of subjects, and produces the uncharacteristic reaction.
  - ✓Some idiosyncratic reaction are:
    - ✓Barbiturates causes excitement and mental confusion some individuals.
    - ✓Quinine/quinidine causes cramps, diarrhoea,purpura, asthma and vascular collapse in some patients.
    - ✓Chloramphenicol produces nondose-related serious aplastic anaemia in rare individuals.

- **Drug allergy**:
  - it is an immunologically mediated reaction producing stereotype symptoms which are unrelated to the pharmacodynamic profile of the drug.
  - Generally occurs even with much smaller doses and have a different time course of onset and duration.
  - This is also called drug hypersensitivity.
  - Occurs only in a small proportion of the population exposed to the drug.
  - The drug or its metabolite acts as antigen or more commonly hapten and produces antibodies/sensitized lymphocytes.
  - One drug can produce different types of allergic reactions in different individuals, while widely different drugs can produce the same reaction.

- **Photosensitivity**: Cutaneous reaction resulting from drug induced sensitization of the skin to UV radiation.
- The reactions are of two types:
  a. Phototoxic :drug and its metabolites accumulates in skin and bring phototoxic reaction. Eg: tetracycline, thiazides, sulfonamides, nalidixic acid etc
  b. Photoallergic: drug or its metabolites induces a cell mediated immune response which on exposure to light.eg: sulfonylureas, chloroquine, sulfonamides, chlorpromazine.

Teratogenicity

- It refers to capacity of a drug to cause foetal abnormalities when administered to the pregnant mother.
- Placental barrier unable to inhibit the passage of some drugs
- Drugs can affect the foetus at 3 stages:
  - Fertilization and implantation : conception to implantation
  - Organogenesis: 18- 55 days (most vulnerable)
  - Growth and development: 56 days onwards eg:ACE inhibitors can cause hypoplasia of organs, especially lungs and NSAIDS may induce premature closure of ductus arteriosus, methotrexate , warfarin, thalidomide etc

Drug induced diseases

- Also called **iatrogenic** (physician induced) diseases.
- Functional disturbances caused by drugs which persist even after the offending drug has been withdrawn and largely eliminated.
- Eg: peptic ulcer by salicylates and corticosteroid, parkinson's by phenothiazines and other antipsychotics, hepatitis by isoniazide.

pharmacodynamics

- What the drugs does to the body?
- Basic type of drug action can be broadly classifies as:
  - Stimulants
  - Depression
  - Irritation
  - Replacement
  - Cytotoxic action
- Mechanism of drug action

  The fundamental mechanism of drug action can be distinguished into four categories.

  I. Physical action
  II. Chemical action
  III. Through enzymes
  IV. Through receptors

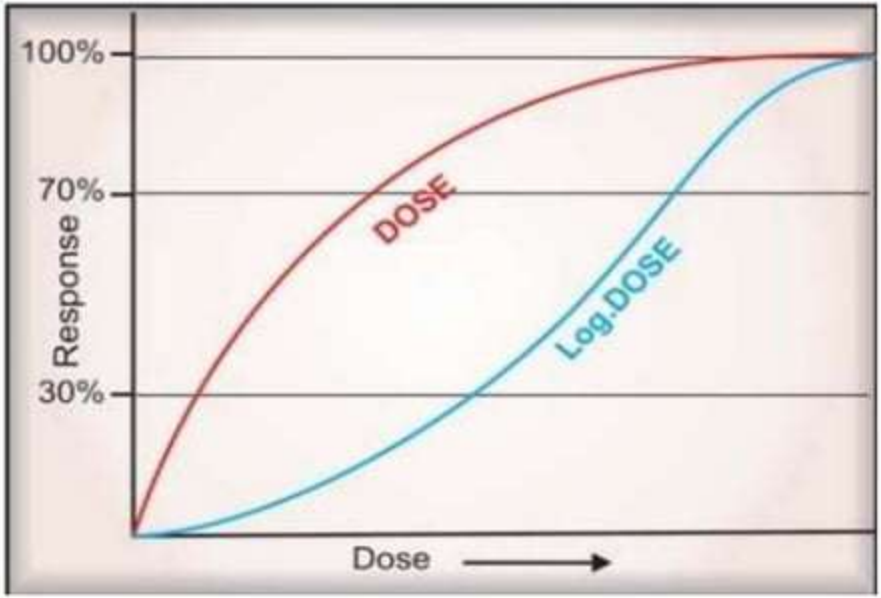
Drug –response relationship:

- When a drug is administered systemically, the dose response relationship has two component:
  i. Dose-plasma concentration relationship
  ii. Plasma concentration –response relationship
- The first one is determined by pharmacokinetic considerations and ordinarily descriptions of dose-response relationship refers to the latter one.
- Generally, the intensity of response increase with increase in dose and dose-response curve is a rectangular hyperbola

This is because drug receptor interaction obeys law of mass action, accordingly-

$$E = \frac{E_{max} \times [D]}{K_D [D]}$$

Where E= observed effect at a dose[D] of the drug
E_{max}= maximal response
K_D =dissociation constant of the drug- receptor complex which is equal to the dose of drug at which half maximal response is produced.



Advantages of plotting log dose-response curve

- A wide range of drug doses can be easily displayed on a graph
- Comparison between agonist and study of antagonists becomes easier.

- Drug potency= it refers to the amount of drug needed to produce a certain response.
  - ✓Relative potency is often more meaningful than absolute potency.
  - ✓Eg: if 10 mg of morphine= 100 mg of pethidine, morphine is 10 times more potent than pethidine
- Drug efficacy: it refers to the maximal response that can be elicited by the drug.

  eg: morphine produces a degree of analgesia not obtained with any dose of aspirin. Morphine is more efficacious than aspirin.

COMBINED EFFECT OF DRUGS

- **Synergism:**
  - ❖ when the action of one drug is facilitated or increased by the other, they are said to be synergism.
  - ❖ In a synergistic pair both the drugs can have action in the same direction or given alone one may be inactive but still enhance the action of the other when given together.
  - ❖ Synergism can be:
    - i. Additive : The effects of the two drugs are in the same direction and simply add up.

      Effect of drug A+B = effect of drug A + effect of drug B
    - ii. Supradditive(potentiation). The effect of combination is greater than the individual effects of the components:

      effect of drug A+ B>effect of drug A + effect of drug B.

- Additive synergism:

Aspirin + paracetamol	As analgesic/antipyretic
Nitrous oxide + halothane	As general anaesthetic
Amlodipine +atenolol	As antihypertensive
Glibenclamide+ metformin	As hypoglycaemia
Ephedrine + theophylline	As bronchodilator

- Supradditive synergism:

Acetylcholine + physostigmine	Inhibition of break down
Levodopa + carbidopa/benserazide	Inhibition of peripheral metabolism
Adrenaline + cocaine/desipramine	Inhibition of neuronal uptake
Enalapril + hydrochlorothiazide (anti-hypertensive)	Tackling two contributory factors
Sulfamethoxazole + trimethoprim	Sequential blockade

ANTOGONISM:

- When one drug decreases or abolishes the action of another, they are said to antagonistic.
- On the basis of mechanism ,antagonistic may be :

1. Physical antagonism:

- Based on the physical properties of drug.
- Eg: charcoal adsorbs alkaloids and can prevent their absorption- used in alkaloid poisonings.

2. Chemical antagonism:

one chemical reacts with others forming inactive complex products.

- KMn04 oxidizes alkaloids- used for gastric lavage in poisoning
- Tannins + alkaloids – insoluble alkaloidal tannate is formed.
- Chelating agents (BAL, EDTA,Cal. Disod. edetate) complex toxic metals (As, Pb).
- Nitrates form methaemoglobin which reacts with cyanide radical.

3. Physiological / functional antagonism:

the two drugs acts by the different receptor or way but shows just opposite pharmacological action in same physiological aspect.

- Histamine and adrenaline in bronchus muscle and BP
- Thiazides and triameterene in K+ excretion.
- Glucagon and insulin in blood sugar level.

4. Receptor antagonism:

one drug(antagonist) blocks the receptor action of the other (agonist)

- Ach ----atropine
- Morphine----naloxone
- Diazepam----bicuculline

Therapeutic index

- The therapeutic index of a drug is the ratio of the dose that produces toxicity to the dose that produces a clinically desired or effective response in a population of individuals.
- Therapeutic index= toxic dose/effective dose
- The therapeutic index is thus a measure of the drug's safety since a large value indicates that there is a wide margin between doses that are elective and doses that are toxic.