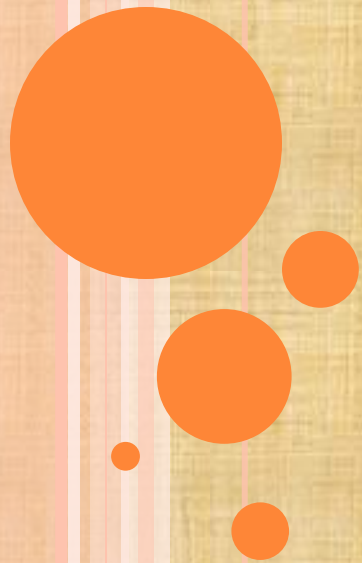
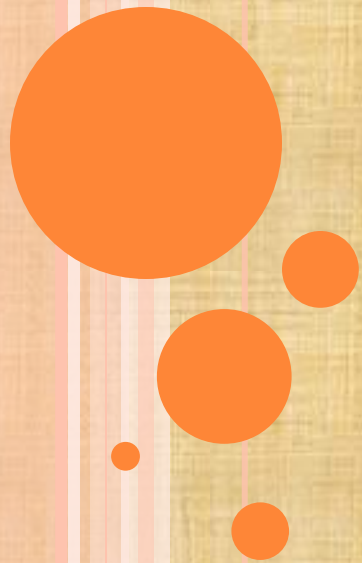


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ADVERSE DRUG REACTIONS



ADVERSE DRUG REACTIONS (ADE)

- **Definition**
- Any response to a drug which is harmful, unintended, undesired & which occurs at doses in man for prophylaxis, diagnosis or treatment.



- Incidence of ADR more
 - Polypharmacy
 - Elderly
 - Children
 - Patient with multiple diseases
 - Pregnancy
 - Malnourished
 - Immunosuppression
 - Drug Abusers and addicts
- Develop
 - Immediately
 - or
 - Prolonged medication
 - or
 - After stopping.



CLASSIFICATIONS OF ADR

- **A (Augmented)**
- **B (Bizarre)**
- **C (Continuous)**
- **D (Delayed)**
- **E (Ending Use)**
- **F (Failure of Efficacy)**

Broadly

Type- A (Predictable)- Based on pharmacological properties

Type- B (Non-predictable) – Based on Immunological response
and genetic makeup of person

TYPE A- AUGMENTED

- These are based on the pharmacological properties of the drug so can be predicted.
- They are common and account for 75% of ADRs
- Dose related and preventable mostly reversible.

Examples:-

- Anticoagulants (e.g., warfarin, heparin) – bleeding
- Anti-hypertensives (e.g., α 1-antagonists) – hypotension
- Anti-diabetics (e.g. insulin) - hypoglycemia



Predictable

TYPE B- BIZZARE OR UNPREDICTABLE

- Have **no direct relationship** to the dose of the drug or the pharmacological mechanism of drug action.
- Develop on the basis of:
 - Immunological reaction on a drug (**Allergy**)
 - Genetic predisposition (**Idiosyncratic reactions**)
- More serious clinical outcomes with higher mortality and morbidity.
- Mostly require immediate withdrawal of the drug.



Un-predictable

TYPE C – CHRONIC (CONTINUOUS) USE

- They are mostly associated with **cumulative-long term** exposure

Example:-

Analgesic (NSAID)– interstitial nephritis, papillary sclerosis, necrosis



Predictable

TYPE D – DELAYED

- They manifest themselves with significant delay
 - **Teratogenesis** -Thalidomide – Phocomelia (flipper-like fore limbs)
 - **Mutagenesis/Cancerogenesis**

Others:

Tardive dyskinesia – during L-DOPA Parkinson disease treatment



Predictable


TYPE E – END OF USE

- Drug withdrawal syndromes and rebound phenomena
 - Example – sudden withdrawal of long term therapy with β -blockers can induce rebound tachycardia and hypertension



Predictable

PREVENTION OF ADVERSE EFFECTS TO DRUGS

- **A**void inappropriate use of drugs .
 - **A**ppropriate drug administration (**R**ational **T**herapeutics)
 - Dose
 - Dosage form
 - Duration
 - Route
 - Frequency
 - Technique
 - **A**sk for previous history of drug reactions and allergies
 - **A**lways suspect ADR when new symptom arises after initiation of treatment.
 - **A**sk for laboratory findings like serum creatinine etc.
- 

Categorized into:

- Side effects-
- Secondary effects
- Toxic effects
- Intolerance
- Idiosyncrasy
- Drug allergy
- Photosensitivity
- Drug dependence
- Drug withdrawal reactions
- Teratogenicity
- Mutagenicity and Carcinogenicity
- Drug induced diseases (Iatrogenic disorders or Iatrogenicity)

Beware of – Iatrogenic, Idiosyncrasy, Idiopathic, Intolerance

SIDE EFFECTS

- Unwanted often unavoidable Pharmacodynamic effects(not harmful).
- Occur at therapeutic doses.
- Predictable

Examples.

-H1 Anti-histaminics- Sedation

-Depression of A-V conduction is the desired effect of **digoxin** in atrial fibrillation, but the same may be undesirable when it is used for CHF.



TOXIC EFFECTS (Poisonous effect)


- An adverse effect of a drug produced by an exaggeration of the effect that produce the therapeutic response.
- **Predictable**
 - Dose dependent
- **Unpredictable**
 - Allergy
 - Idiosyncrasy
- Over dose or prolonged use.
- The CNS, CVS, kidney, liver, lung, skin and bone marrow are most commonly involved in drug toxicity.



- Toxicity may result from extension of the therapeutic effect itself, e.g. complete A-V block by digoxin, bleeding due to heparin.
- **Poisoning:** Poison is a substance which endangers life by severely affecting one or more vital functions.



Predictable toxic effects

- □ Dose dependent adverse effect may be:
 - □ **Direct damaging effect to tissue:** Paracetamol overdose leads to hepatotoxicity ,Aminoglycoside (Gentamicin)causes nephrotoxicity.
 - □ **Rebound response:** abrupt withdrawal after chronic use. Glucocorticoid withdrawal leads to acute adrenal insufficiency.
 - **Excess pharmacological effect:**
 - Result of excessive pharmacological action of the drug due to overdose or prolonged use.
 - □ Excess insulin-hypoglycemia even death from hypoglycemics hock
 - □ Antihypertensive-hypotension
 - □ Anticoagulant-severe bleeding.
- 

Unpredictable toxic effects

- □ **Dose independent:**
- □ Less than the therapeutic dose may lead to toxic effect



○ Tolerance

- □ ↓ pharmacological effect on repeated administration of the drug.
- □ **Pharmacokinetic Tolerance:** ↑ the enzymes responsible for metabolizing the drug.
- e.g. Phenobarbitone induces metabolism of its own by increasing its own metabolic enzyme.
- □ **Pharmacodynamic Tolerance:** Cellular tolerance, due to down-regulation of receptors.



INTOLERANCE

- It is the appearance of characteristic toxic effects of a drug in an individual at therapeutic doses
- **Intolerance**
- □ Converse of tolerance
- □ Indicates a low threshold of the individual
- □ **E.g.**
- □ Chloroquine (single tablet) □ Vomiting and abdominal pain in some individuals



Un-Predictable

Tachyphylaxis:

- □ When responsiveness diminishes rapidly after administration of a drug, the response is said to be subject to tachyphylaxis.
- □ Tachyphylaxis to the Action of Topically Applied Corticosteroids
- **Difference between Tachyphylaxis and Tolerance**
- □ Tachyphylaxis is the result of frequent doses over a short period of time and tolerance is the result of chronic administration over a long. A typical example of tachyphylaxis is epinephrine's action on vessels(bloodpressure). Repetitive stimulus over a short time causes the depletion of a vasoconstricting substance.



IDIOSYNCRASY

- It is **abnormal reaction to a drug due to genetic abnormality.**

Example :-

-Succinylcholine can produce **apnea** in people with abnormal serum cholinesterase. Their cholinesterase is incapable of degrading the succinylcholine, thus sustained NMB results.

-Chloramphenicol produces non dose-related serious aplastic anaemia in rare individuals.



DRUG ALLERGY

It is abnormal reaction to a drug due to antigen-antibody reaction.

- Acquired, altered reaction of the body to drug.
- □ Immunologically mediated reaction.
- □ occur even with much smaller doses
- □ Also called Drug hypersensitivity
- □ Not genetic, not occurred in all
- □ Occurs on reexposure
- □ E.g. penicillin → 1st time → stimulate antibody → Ag-Ab reaction → allergy
- □ Chief organ: Skin, respiratory tract, GIT, Blood & blood vessels



Un-Predictable

- Allergic reactions occur only in a **small proportion of the population** exposed to the drug .
- The drug or its metabolite acts as antigen (AG) or more commonly **hapten** (incomplete antigen) and induce production of antibody (AB)/sensitized lymphocytes.



- **Grading system for hypersensitivity reactions**
- 1-Mild
- Cutaneous and subcutaneous only
- Generalized erythema, periorbital edema, urticaria.
- 2-Moderate
- Cardiovascular, respiratory, or gastrointestinal involvement
- Dyspnea, stridor, wheeze, nausea, vomiting, dizziness, diaphoresis, chest or throat tightness, or abdominal pain

- 3-Severe
- Hypoxia, hypotension, or neurologic compromise , confusion, collapse, loss of consciousness, or incontinence Cyanosis.



PHOTOSENSITIVITY

- It is a cutaneous reaction resulting from drug induced sensitization of the skin to **UV radiation**.
- The reactions are of two types:
 - a) **Photo-toxic :- (T-S)**
 - a) Drug or its metabolite **Accumulates** in the skin,
 - b) absorbs light and undergoes a **Photochemical reaction** followed by
 - c) **Photobiological reaction** resulting in
 - d) Tissue damage (sunburn-like),
 - a) i.e. erythema, edema, blistering , hyper pigmentation, desquamation.



(b) Photo-allergic: (A-L)

Drug or its metabolites induce a cell mediated immune response which on exposure to

Light of **longer wave lengths (320-400 nm, UV -A)**

Produces a papular or eczematous contact dermatitis.

Drugs involved are sulfonamides, sulfonylureas, griseofulvin, chloroquine, chlorpromazine



DRUG DEPENDENCE

- Use of drugs for personal satisfaction

Physical dependence It is an altered physiological state produced by repeated administration of a drug which necessitates the continued presence of the drug to maintain physiological equilibrium.

- Discontinuation of the drug results in a characteristic **withdrawal (abstinence) syndrome.**
- Drugs producing physical dependence are opioids, barbiturates and other depressants including alcohol and benzodiazepines



○ **Drug abuse :**

- It is an illegal use of drug for non medical purposes despite physical, social or psychological problems that may result from that use.

○ **Drug addiction**

It is a pattern of compulsive drug use characterized by overwhelming involvement with the use of a drug. Procuring the drug and using it takes precedence over other activities



○ Drug habituation (Psychological dependence)

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, physical dependence is absent



DRUG WITHDRAWAL REACTIONS

- Sudden interruption of therapy with certain other drugs results in adverse consequences, mostly in the form of worsening of the clinical condition for which the drug was being used
- **Example:** Acute adrenal insufficiency may be precipitated by abrupt cessation of corticosteroid therapy.



TERATOGENICITY (Teratos- Monster)

- Drug to cause foetal abnormalities when administered to the pregnant mother.
- Drugs can affect the foetus at 3 stages-
 - (i) Fertilization and implantation(1-14 days):all or none.**
 - (ii) Organogenesis- 18 to 55 days(3-12 weeks)** of gestation most vulnerable period, deformities are produced.
 - (iii) Growth and development-56 days(12-38 weeks)** onwards developmental and functional abnormalities can occur, e.g. ACE inhibitors , Thalidomide, Warfarin, Barbiturates,.....



Drugs known to be teratogenic

- □ Oral anticoagulants—bony abnormality, mental retardation.
- □ Oral hypoglycemic agents-multiple deformity.
- □ Tetracycline—inhibit bony growth.
- □ Diethylstilbestrol-Oral contraceptive is no longer used because it causes reproductive cancers in daughters born to mother taking the drug.
- □ Aminoglycosides, Chloroquine—Deafness



MUTAGENICITY AND CARCINOGENICITY

- Cause genetic defects and cancer respectively.
- Reactive intermediates which affect genes and may cause structural changes in the chromosomes
- Even without interacting directly with DNA.
Examples- anticancer drugs, radioisotopes, estrogens, tobacco.....



DRUG INDUCED DISEASES

- These are also called **iatrogenic (physician induced)** diseases, and are functional disturbances (disease) caused by drugs .
- Hepatitis by isoniazid and Rifampicin
- Peptic ulcer by salicylates and corticosteroids
- **Retinal damage by chloroquine**



INDIVIDUAL VARIATION IN RESPONSE TO DRUG

- A) Alteration in concentration of drug that reaches the receptors
- Variation in concentration of an endogenous receptor ligand–
- C) Alteration in number or function of receptor
- D) Changes in components of response distal to the receptor



THANKS

