ADVERSE DRUG REACTIONS

- Harmful or seriously unpleasant effects occuring at doses intended for therapeutic (prophylactic or diagnostic) effect & which call for reduction of dose or withdrawl of the drug or indicate caution in future use of the same drug.
- PREDICTABLE (TYPE A)
- UNPREDICTABLE (TYPE B)

Side effects

- Unwanted , unavoidable
- Occur at therapeutic doses
- Can be predicted from pharmacological profile.
- Decrease in dose generally ameliorates the symptoms
- Based on same action as therapeutic effect-
- e.g. atropine in preanesthetic medication
- On different facet of action-
- Antihistaminics produce sedation

S/Es

- **Therapeutic in one context , S/E in another-**
- **Codeine for cough produces constipation, can be used as a therapeutic effect in traveller dirrhoea.**

Secondary Effects

- **Indirect consequences of a primary drug action.**
- **Opportunistic infections due to broad spectrum of antibiotic use , due to alteration of normal flora.**

Toxicity

Direct action of the drug , at high dose , damaging the cells – e.g.

- **Liver damage from Paracetamol overdose.**

Intolerance

Low threshold to the normal pharmacodynamic action of the drug.

Appearance of characteristic toxic effects of a drug in an individual at therapeutic doses.

Idiosyncrasy

- **Genetically determined abnormal reactivity to a chemical e.g.**
- **Barbiturates- excitement & mental confusion in some.**

Classification of ADRs

- **Type A – Augmented**
- **Type B - Bizarre**
- **Type C – Chronic**
- **Type D – Delayed**
- **Type E – Ending of use**

Type A

- Occurs in everyone if enough of dose is given.
- Due to excess of normal , predictable, dose related pharmacodynamic effects
- Common
- e.g. postural hypotension due to alpha blockers
- Hypoglycemia due to insulin

Type B

- In some people
- Not as a part of normal pharmcology of drug
- Not dose related
- Unpredictable for the individual
- Idiosyncrasy , drug allergy

Type C

- Long term exposure
- Analgesic nephropathy

Type D

- Delayed effects following prolonged exposure
- e.g. carcinogenesis or
- short term exposure at critical time

  e.g. teratogenesis

Type E

- **Abrupt discontinuation of chronic therapy**
- **e.g. adrenal steroid**

Drug abuse

- **Drugs are abused (used in the ways that are not medically approved) because they cause strong feelings of euphoria or altered perception.**
- **Repetitive exposure induces widespread adaptive changes in the brain. As a consequence drug use may become compulsive : Addiction.**

Drug Addiction

- **Compulsive drug use characterised by the overwhelming involvement with the use of a drug.**
- **Amphetamines, cocaine, cannabis, LSD.**

Drug Habituation

- **Less intensive involvement with the drug .**
- **Withdrawl leads to mild discomfort.**
- **Tea , coffee , tobacco , social drinking**

Teratogenecity

- **Capacity of a drug to cause foetal abnormalities when given in a pregnant mother.**

- **Drug can affect the foetus at three stages-**
- **Fertilization & Implantation – Conception (17 days) - failure of pregnancy**
- **Organogenesis – (18-55 days of gestation)**

  Most vulnerable

  Deformitis
- **Growth and development- 56 days onwards**

  Developmental and functional abnormalities.

  ACE inhibitors – hypoplasia of organs

  NSAIDs- premature closure of ductus arteriosus .

- **AVOID IF POSSIBLE**
- **CATEGORIES – A ,B, C, D, X**
- **A,B,C,D – LOOK FOR RISK- BENEFIT RATIO.**
- **X- POTENTIAL RISK OUTWEIGHS THE BENEFIT.**
- **CARCINOGENECITY**

Drug Induced Reactions

- **IATROGENIC** (physician Induced)
- Functional disturbances caused by the drug which persist even after the offending drug has been withdrawn & largely eliminated.
- e.g. peptic ulcer by salicylates & corticosteroids.
- Parkinsonism by phenothizines
- Hepatitis by isoniazid

Drug Allergy

- **Immunologically mediated reaction producing stereotype symptoms which are unrelated to pharmacodynamic profile of the drug and are largely independent of the dosage.**
- **In a small proportion**
- **Prior exposure , sensitization is needed.**
- **A latent period of 1-2 wks after the first exposure.**
- **AG, AB production .**

TYPES OF ALLERGIC REACTIONS

A. HUMORAL

B. CELL MEDIATED

HUMORAL

TYPE- 1. ANAPHYLACTIC REACTION

TYPE –II. CYTOLYTIC REACTION

TYPE- III. ARTHRUS REACTION

CELL-MEDIATED

TYPE –IV. DELAYED HYPERSENSITIVITY

TYPE 1

- **IgE antibodies are produced, get fixed to mast cells.**
- **On exposure to the drug ,**
- **AG: AB reaction on mast cell surface**
- **Release of mediators-**
- **Histamine**
- **5-HT**
- **LT**
- **PGs, PAF**

Type II

- Cytolytic Reactions
- After the drug & component of a specific tissue cell act as AG,
- IgG & IgM produced
- On reexposure AG:AB reaction on surface of these cells
- Complement activated
- CYTOLYSIS

TYPE- III

- **ARTHRUS RECTIONS**
- **CIRCULATING AB - IgG**
- **Ag:Ab complexes bind complement**
- **Precipitation on vascular endothelium**
- **Destructive inflammatory response**
- **Rashes, serum sickness (fever, arthralgia, lymphadenopathy)**
- **PAN**
- **Steven-Johnson Syndrome (erythema multiforme , arthritis, nephritis , myocarditis, mental symptoms)**

DELAYED H/S

- **> 12 HRS TO DEVELOP**
- **Through sensitized T-lymphocytes carrying receptors for antigen**
- **On contact with Antigen-**
- **Lymphokines**
- **Attract granulocytes**
- **Inflammatory response**
- **Contact dermatitis, rashes, fever, photosensitization**

TREATMENT OF DRUG ALLERGY

- **Stop the drug.**
- **For Type 1 - Antihistaminics**
- **For Anaphylactic shock or Angiodema of larynx :**
- **Recline the patient**
- **Give oxygen at high flow rate**
- **Cardiopulmonary resuscitation**
- **Inj. Adrenaline 0.5 mg (0.5 ml of 1 in 1000).**
- **Antihistaminic, Chlorpheniramine 10-20mg i/m or slow i/v.**
- **I/V glucocorticoid , Hydrocortisone 100-200 mg.**

PHOTOSENSITIVITY

- **Drug induced sensitization of skin to uv radiation**
- **PHOTOTOXIC :**
- **Drug accumulates in the skin**
- **Absorbs light**
- **Undergoes a photochemical reaction**
- **Photobiological reaction**
- **Local tissue damage i.e. erythema,edema Followed by Hyperpigmentation and desquamation**

- **Drugs**-

  nalidixic acid, fluoroquinolones, sulfones sulfonamides, phenothiazines, thiazides, amiodarone.

PHOTOALLERGIC

- Drug induces CMI
- On exposure to sunlight – papular or eczematous contact dermatitis
- Drugs – sulphonamide, sulphonylureas, Griseofulvin, chloroquine

Drug Dependence

- **A state arising from repeated , periodic or continuous administration of a drug , that results in harm to the individual and sometimes to the society.**
- **The subject feels a desire , need , or compulsion to continue using the drug and feels if abruptly deprived of it (abstinence or withdrawl syn).**
- **Psychological dependence**
- **Physical dependence**

Psychological dependence

- Person believes that optimal state of wellbeing is achieved only through the actions of the drug.
- Liking – compulsive drug use.
- Desire – craving
- **Reinforcement**- Ability of the drug to produce effects that make the user wish to take it again.

Physical Dependence

- **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 withdrawl (abstinence syndrome)**
- **Drugs - opioids, barbiturates, alcohol, benzodiazepines.**
- **Stimulant drugs – amphetamines, cocaine .**

PHARMACOVIGILANCE

- Science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems.

ADR MONITORING SYSTEMS

- Collecting a new information from reliable scientific sources.
- Classifying & analyzing above information
- Circulating its contents as well as any action taken on specific drug to all health sectors.

ADR REPORTING

4 ELEMENTS-

- PATIENT
- A DRUG
- AN ADVERSE DRUG REACTION
- REPORTER OF THE REPORT

METHODS OF COLLECTING DATA ON ADVERSE DRUG REACTION

- **EXPERIMENTAL STUDIES – FORMAL THERAPEUTIC TRIALS OF PHASES 1-3.**

  DETECT AN INCIDENCE OF UPTO ABOUT 1:200 .
- **OBSERVATIONAL STUDIES- Where the drug is observed , epidemiologically under conditions of normal use in the community i.e. pharmacoepidemiology. Observational cohort & case –control study.**
- **Spontaneous/ voluntary reporting**
- **Prescription event monitoring**
- **Record linkage system**

PHARMACOVIGILANCE CENTERS

- **NATIONAL PHARMACOVIGILANCE CENTRE**

  CENTRAL DRUG STANDARD CONTROL ORGANISATION (CDSCO)

. 2 ZONAL CENTERS

KEM HOSPITAL,MUMBAI

AIIMS ,N.DELHI

. 5 REGIONAL CENTERS

KOLKATA,MUMBAI, NAGPUR, DELHI, JIPMER

. 24 PERIPHERAL

ORISSA,KOLKATA,GUWAHATI, GOA, GUJRAT,AHEMDABAD….