



# Factors Modifying Drug Action and Therapeutic Outcome

Dept. of Pharmacology, GMC  
Amritsar

1

## Subject (Patient) Related Factors

- Age
- Body weight/surface area
- Gender
- Race /species
- Genetic variations
- Psychological / Emotional state
- Physiological state
- Pathological state

Dept. of Pharmacology, GMC  
Amritsar

2

# Drug Related Factors

- Dose of a drug (drug dosage)
- Form of a drug
- Route of drug administration
- Time of drug administration
- Drug combinations
- Drug cumulation (cumulative action)
- Drug tolerance

## Age

- Extremes of age show extreme drug sensitivity
- **Neonates and infants** more sensitive : chloramphenicol, gentamicin, morphine, thyroxine
- Immature drug metabolizing enzymes
- Lower plasma protein binding
- Incomplete development of excretory system
- Smaller tissue mass

## .....Age

- Gray baby syndrome in neonates on chloramphenicol, in large dosage
- **Infants** require smaller amount than children
- **Elderly** require less drug: degenerative changes in kidney, liver, brain, heart

## Body weight / Surface area

- Concentration of drug at site of action depends upon ratio between **body weight or surface area** and amount of drug administered
- Adjust drug dose
- Lean and obese people
- Dehydration ( underweight )
- Edematous states ( overweight )

# Gender

- Slow metabolism in females due to more adipose tissue
- Avoid drugs causing pelvic congestion during menstruation and pregnancy: castor oil & senna
- **Antithyroids**: carbimazole, propylthiouracil
- **Antimetabolites**: Methotrexate, mercaptopurine
- Phenobarbitone and morphine

# Race / Species

- Japanese: Subacute myelo-optic neuropathy (SMON) by di-iodohydroxyquin & iodochlorohydroxyquin
- G-6-PD deficiency in African, Mediterranean, middle east & south east Asian
- Negroes need higher concentration of atropine to dilate pupil than Mongolians
- Indians tolerate **thiacetazone** more than Europeans
- Rabbits more sensitive to **d-tubocurarine** than cats
- Rats & mice resistant to **digoxin** but not dogs and cats

# Genetic Factor

- Altered clearance of drugs, resulting in functional overdose who are unable to metabolize
- Failure to convert to a **prodrug to an active** drug
- Altered pharmacodynamics, **hemolytic anemia** in G-6-PD deficiency
- Idiosyncrasy: Aplastic anemia & Hepatotoxicity
- **Pharmacogenetics**: Deals with genetically mediated variation in drug action
- Molecular diagnostic tests for Pharmacogenetics variation
- Specific patient's drug metabolism profile
- TCAs- Toxicity in CYP2D6 deficiency

# Psychological State

- More general anesthetics needed in nervous and anxious patients
- **Higher doses** of chlorpromazine 500-1000mg/day in **schizophrenics**
- Placebos (inert dosage forms) produce therapeutics benefits in psychomotor angina pectoris and bronchial asthma-  
**Placebo reactors**

## Physiological state

- **Salicylates** reduce body temperature only in presence of fever
- Uterus more sensitive to **oxytocin** during pregnancy
- **Tetracyclines** in lactating mothers
- Children need smaller dosage than adults

## Pathological state

- Thiazides induce marked diuresis in **oedematous** patients
- Adrenaline and digoxin cause arrhythmias in **myocardial infarction**
- **Hypothyroid** patients sensitive to digoxin, morphine
- **Myasthenic** patients sensitive to tubocurarine  
Hypnotics in sever pain cause mental confusion
- Hepatic & renal disease alter metabolism and excretion

# Drug Related factor -Dose

- Appropriate amount of drug needed to produce response
- Expressed in terms of weight (g, mg,  $\mu\text{g}$ ), volume (ml, IU)
- Prophylactic, therapeutics, toxic
- Dose too small- no effect, too large-toxicity

## Calculation of Child Dose(1-12yrs)

- According to **Age** -

- **Young's formula:**

$$\text{Child dose} = \frac{\text{Age}}{\text{Age}+12} \times \text{Adult dose}$$

- **Dilling's formula:**

$$\text{Child dose} = \frac{\text{Age}}{20} \times \text{Adult dose}$$

- According to **Body weight** –

### Clark's formula:-

$$\text{Child Dose} = \frac{\text{Body Weight (Kg)} \times \text{Adult Dose}}{70}$$

70

Dept. of Pharmacology, GMC  
Amritsar

15

## Child Dose calculation

- According to ***body surface area*** (BSA) =

$$\text{Dose} = \frac{\text{BSA} (m^2)}{1.7} \times \text{Adult Dose}$$

1.7

$$\text{Body surface area} (m^2) =$$

$$\frac{\text{Body Weight(Kg)} \times \text{Height(cm)}}{0.008}$$

0.008

Dept. of Pharmacology, GMC  
Amritsar

16

# Special Dosage Forms

- **Loading Dose:** given at onset of therapy with aim of achieving target concentration rapidly, e.g Digoxin, Digitoxin, Chloroquine

# Maintenance Dose

- Dose given to maintain steady state conc. Of drug in plasma within therapeutic range. It is required during use of digoxin, Chloroquine after giving loading dose

## Target Level Dose

- Dose required to produce target steady state conc. of drug adjusted by monitoring of plasma conc. of drug (***Therapeutic Drug Monitoring***).
- e.g. Antiepileptic drugs, Antidepressants, Lithium, Digoxin

## Titrated Dose

- Optimal dose required to produce maximum therapeutic effect with tolerable adverse effects
- High initial dose And downward titration
- Low initial dose and upward titration
- Optimal dose is calculated
- Anticancer agents, corticosteroids, levodopa

# Regulated Dose

Dose which is accurately adjusted by repeated measurement of affected physiological parameter.e.g:-

Antihypertensives

Anticoagulants

Hypoglycemics

Diuretics

# Dosage Forms & Time

- Injectables rapidly absorbed and efficacious
- Mixtures & powders rapidly absorbed than oral tablets and capsules for rapid effects
- Hypnotics at night have better efficacy than daytime
- Corticosteroid in single morning doses

# Route of drug Administration

- Oral magnesium sulphate acts as purgative
- Rectally it lowers intracranial tension
- IV it depress CNS & CVS
- Inhalation ***N-acetylcysteine*** is mucolytic
- IV it is drug of choice in acute paracetamol poisoning
- **Insulin and adrenaline not efficacious orally**

# Drug combinations

- Drug synergism: Syn = Together  
ergon = Work
- Additive effects: total effect of combination is equal to sum of effect of individual drug
- ***Levodopa + Carbidopa***
- ***Sulfamethoxazole + Trimethoprim***
- ***Acetylcholine + Physostigmine***

# Drug Antagonism

- One drug decrease or inhibit the effect of another drug by opposite action
- Physical
- Chemical
- Physiological
- Pharmacological

# Drug Antagonism

## Physical-

- **Activated charcoal** in Alkaloid poisoning
- Chemical- Chelating agent **BAL and Arsenic**
- **HCl & H<sub>2</sub>CO<sub>3</sub>**

# Physiological Antagonism

- Opposite effects of two drug on same function
- Insulin and glucagon on blood sugar level
- Hydrochlorothiazide and amiloride on urinary K<sup>+</sup> excretion
- Histamine and adrenaline on BP or bronchial muscles

# Pharmacological Antagonism

- Opposite effect of two drugs binding to same receptor
- Competitive or non competitive antagonism is reversible i.e. by increasing dose of agonist
- ***Adrenaline and propranolol***
- ***Acetylcholine and atropine***
- ***Morphine and naloxone***
- ***Diazepam and flumazenil***

# Non-Competitive Antagonism

- Irreversible/ insurmountable
- Adrenaline and phenoxybenzamine
- Diazepam and bicuculine
- Acetylcholine and decamethonium

# Drug Cumulation

- Repeated drug administration
- Rate of administration  $>$  rate of elimination

## **Cumulative toxicity** –

- Digoxin
- Digitoxin
- Chloroquine
- Arsenic

***USE MAINTENANCE DOSE &  
CHECK RENAL/ HEPATIC FUNCTION***

# DRUG TOLERANCE

- Gradual decrease in tissue response on repeated administration
- Acute Tolerance ( Tachyphylaxis ) develops in few minutes or hours
- Chronic tolerance develops over few days or weeks

## Pharmacokinetic Tolerance

- Changes in A, D, M, E
- Decreasing availability at target site
- Barbiturate increase their metabolism by enzyme induction
- Pseudotolerance: decreased drug absorption in diarrhea

# Pharmacodynamic Tolerance

- Tissues cross-sensitive due to down regulation of receptors

**Pharmacogenetic** Tolerance due to decreased drug metabolism, e.g. Isoniazid, halothane, succinylcholine

# Racial/ Species Tolerance

- Negroes tolerant to ephedrine and atropine
- Rabbits tolerate larger doses of atropine - esterase in liver and plasma.

# Cross Tolerance

- Initial tolerance to a particular drug of one group, person develops tolerance to other drug to the same group
  - Alcohol and general anesthetics
  - Glyceryl trinitrate and Isosorbide dinitrate
  - Morphine and pethidine

Dept. of Pharmacology, GMC  
Amritsar

35



# Thank You

Dept. of Pharmacology, GMC  
Amritsar

36