

# Factors Modifying Drug Action

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# Introduction

- Responses variation to a Drug – (1) person to person; and (2) also same person on different occasions
- Individuals differ in pharmacokinetic handling of drugs – varying plasma/target site conc. – Metabolized drug Vsexcreted unchanged drugs – Propranolol and Atenolol
- Variation in number or state of receptors, coupling proteins or other components of response effectuation
- Variations in hormonal/neurogenic tone or concentrations – atropine, propranolol, captopril
- **Categories of factors:** Genetic and Nongenetic including environmental, circumstantial and personal variables
- Factors modify drug action
  - Quantitatively – action increased or decreased
  - Qualitatively: Altered response – allergic reaction or idiosyncrasy

Example – 40 kg / 70 x 500 mg  
2000 / 7 == 285 mg

# 1. Body Size

☐ Influences the conc. of the drug attained at the site of action –  
**obese/lean/children** – Body weight (BW) and Body Surface area  
(BSA)

☐ Individual dose =  $\frac{\text{BW (kg)}}{70}$  x average adult dose

☐ Individual dose =  $\frac{\text{BSA (m}^2\text{)}}{1.7}$  x average adult dose

☐ BSA can be calculated by Dubois Formula

$$\text{BSA (m}^2\text{)} = \text{BW (kg)}^{0.425} \times \text{Height (cm)}^{0.725} \times 0.007184$$

Example : (8 years / 8 years + 12) x 500 mg

- (8 x 500) / (8 + 12) = 200 mg

## 2. Age

- Young's formula

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

- Dilling's formula

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

- Note: Infants & children are not small adults – physiological differences
  - Low g.f.r and tubular transport – Gentamicin and Penicillin
  - Low hepatic drug metabolizing systems in newborns – *gray baby syndrome*
  - Blood brain barrier (BBB) is more permeable - Kernicterus
  - Absorption of drugs altered – lower gastric acidity and slow intestinal transit
  - Faster transdermal absorption and faster rectal absorption - Diazepam
  - After 1 (one) year faster metabolism than adults – phenytoin, carbamazepine
  - **Caution** – Corticosteroids, androgens, tetracyclines .... **Elderly ????**

## 3. Sex

- ❑ Females have smaller body size – required doses are lower
- ❑ Digoxin in Maintenance therapy of heart failure – mortality higher
- ❑ Beta blockers, methyldopa, diuretics – sexual function interference in males
- ❑ Gynaecomastia – Metoclopramide, chlorpromazine, ketoconazole etc.
- ❑ Pregnancy – particularly 3<sup>rd</sup> trimester

## 4. Species and Race

- ❑ Species variation in drugs responses do exist
- ❑ Some strains of rabbits – resistant to atropine
- ❑ Rat and mice are resistant to digitalis
- ❑ Race – racial differences have been observed
- ❑ Blacks require higher doses of atropine and ephedrine, while Mongols require lower doses
- ❑ Africans – beta blockers are less effective
- ❑ SMON – Japan but not among Indians

# 5. Genetics

❑ Determinants of drug responses – transporter, enzymes, ion channels, receptors and couplers – controlled genetically –  
**Individual variation of responses**

❑ Pharmacogenetics: Use of genetic information to guide the choice of drug and dose on an individual basis – to identify individuals who are either more likely or less likely respond to a drug

❑ so far genetic abnormalities have been identified

❑ Personalized medicine goal yet to achieve

❑ G-6PD deficiency – Primaquine, chlroquin, quinine, dapson, aspirin

❑ Malignant hypothermia with halothane etc.

❑ Low variants of CYP2C9 – Warfarin bleeding; Isoniazid - acetylators

## 6. Route of administration

- ❑ Route determines the speed and intensity of drug response –  
Parenteral for speedy action
- ❑ A drug may have different actions via different routes –  
Magnesium sulfate

## 7. Environmental factors

- ❑ Drug metabolism may get induced – exposure to insecticides, carcinogens, tobacco smoke and charcoal broiled meat etc.
- ❑ Food interferes absorption of some drugs while enhances some drugs – ampicillin gets reduced griseofulvin gets enhanced
- ❑ Hypnotics taken at night



# 8. Psychological factors

❑ Efficacy of a drug can be affected by patient`s beliefs, attitudes and expectations – particularly CNS drugs – more GAin nervous and anxious patients – alcohol and performance

❑ **Placebo:** An *inert* substance which is given in the garb of medicine. Works by psychodynamic effects (not pharmacodynamics) – sometimes responses equivalent to active drugs

❑ Placebo reactors

❑ Induce psychological responses – release of endorphins in brain

❑ **Uses** – Control device in clinical trials and to treat a patient

❑ Lactose tablet/capsules or water injections etc.

❑ **Nocebo:** Negative psychodynamic effects of drugs

# 9. Pathological states

- ❑ Diseases can influence drug disposition – GIT diseases, Liver diseases, Kidney diseases, Congestive heart failure and Thyroid etc.
- ❑ **GIT:** Coeliac diseases – amoxicillin absorption decreased while Cephalexin and cotrimoxazole increased; Achlorohydria – Reduced aspirin absorption – NSAIDs aggravate peptic ulcer
- ❑ **Liver diseases:** Liver disease (cirrhosis) influence drug action
  - ❑ Increased bioavailability of drugs with high first pass metabolism
  - ❑ Serum albumin reduced – protein bound drugs like Warfarin – more free drug
  - ❑ Metabolism and elimination of drugs may be reduced – Doses should be reduced – Morphine, Propranolol, lignocaine etc.
  - ❑ Prodrugs are less effective (becampicillin)

# 9. Pathological states – contd.

- ❑ **Kidney diseases:** Pharmacokinetics of many drugs are affected
  - ❑ Clearance of drugs in unchanged form (aminoglycosides, digoxin, phenobarbitone) reduced – parallel to  $CL_{cr}$ - loading dose not altered – dose should be reduced
  - ❑ Plasma protein, albumin reduced – binding of acidic drugs affected
  - ❑ Permeability of BBB increased – Opiates etc. more CNS depression
  - ❑ Drugs acting via kidney mechanism – become ineffective – Thiazides and urinary antiseptics
- ❑ **CCF:** (1) Alter drug kinetics by decreased absorption (Thiazide), (2) modifying Volume of distribution (Lignocaine), (3) retarding the elimination (lignocaine)- decreased perfusion and congestion of liver; reduced g.f.r, increased tubular reabsorption – doses need reduction

# Contd.

**Thyroid diseases:** Hypothyroid states – sensitive to digoxin, morphine and CNS depressants;  
Hyperthyroid states – resistant to inotropic action – prone to cause arrhythmia by digoxin

**10. Presence of other drugs:** Drug interactions –  
Pharmacokinetic and Pharmacodynamic

**11. Cumulation:** If Rate of administration  $>$  Rate of elimination – cumulation. Slowly eliminating drugs are prone – Prolonged use of Chloroquine

# 12. Tolerance

- ❑ Requirement of higher dose of a drug to produce a given response – refractoriness – sulfonylureas in type 2 diabetes and beta-2 agonists in bronchial asthma - adaptive biological phenomena
- ❑ **Natural:** Species/individual inherently less sensitive – Rabbits to atropine and Blacks to beta – blockers
- ❑ **Acquired:** Repeated use of a drug in an individual who was initially responsive become non-responsive (tolerant) – CNS depressants
  - ❑ Due to uninterrupted presence of drug in the body – no tolerance to cocaine and atropine
  - ❑ Tolerance may develop to one action of the drug – but not to other action – Chlorpromazine, phenobarbitone, Morphine
- ❑ **Cross tolerance:** Tolerance to pharmacologically related drugs – alcoholics to barbiturates and GA; Morphine and Pethidine

# Contd.

## ❓ Tolerance Mechanism:

❓ **Pharmacokinetic/drug disposition tolerance** – effective concentration of the drug at the site of action is decreased – due to enhancement of elimination on chronic use – Barbiturates and Carbamazepine induce own metabolism

❓ **Pharmacodynamic tolerance:** lesser drug action – cells of target organs become less responsive – Morphine, Barbiturates, Nitrates etc. .... Down regulation/desensitization of receptors

❓ **Tachyphylaxis (Tachy – fast' phylaxis – protection):** Rapid development of tolerance when a drug is repeated in quick succession – reduction of responses

❓ Usually with indirectly acting drugs – Ephedrine, tyramine, nicotine etc.  
Also down regulation of receptors

# Summary

- ❑ Remember the different factors modifying drug actions
- ❑ Remember: Young's formula, Placebo, Cumulation, Tolerance, cross tolerance and Tachyphylaxis
- ❑ Drug use in children, elderly, pregnancy and different pathological states will be discussed individually

Thank you