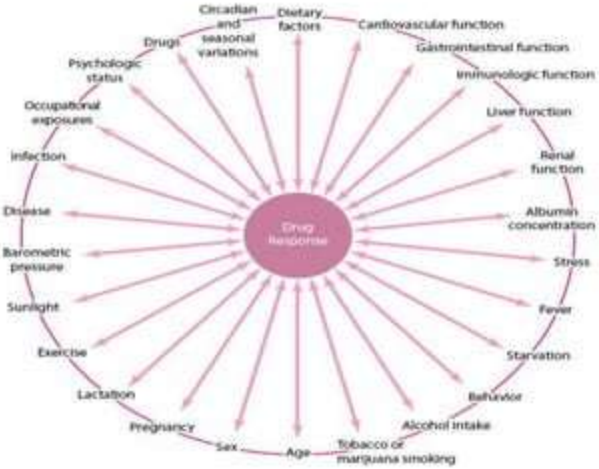
FACTORS MODIFYING DRUG ACTION



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INTRODUCTION

- Same dose of a drugs can produce different degrees of responses – (1) person to person; and (2) also same person under different situations.
- Individuals differ in pharmacokinetic handling of drugs – varying plasma/target site conc. – Metabolized drug Vs excreted.
- Variation in number of receptors, coupling proteins or other components
- Variations in hormonal/neurogenic tone or concentrations – atropine, propranolol, captopril

THE FACTORS MODIFY DRUG ACTION EITHER

- Factors modify drug action –
- Quantitatively – action increased or decreased
- Qualitatively: Altered response – allergic reaction or idiosyncrasy

FACTORS MODIFYING DRUG ACTION

- Physiological Factors
- Pathological Factors
- Genetic Factors
- Environmental Factors
- Psychological factors
- Drug interactions
- Tolerance

FACTORS MODIFYING DRUG ACTION

Physiological Factors

- Age & weight
- Gender
- Pregnancy/Lactation
- Food

1. AGE

Newborn:

- ↓ gastric acid secretion
  - GIT absorption of Ampicillin & Amoxicillin greater
- ↓liver enzymes
  - Inadequate glucouronidation of Chloramphenicol --- Gray baby syndrome
- ↓ Plasma protein binding
- ↓ GFR & tubular secretion
- Immature BBB
  - Sulfonamides ----- Hyperbilirubinemia & Kernicterus

CHILDREN

- Tetracyclines
  - Permanent teeth staining
- Corticosteroids
  - Growth & development retardation
- Antihistaminics
  - Hyperactivity

Young's formula: $\frac{\text{Age (yrs)}}{\text{Age (yrs)} + 12} \times \text{Adult dose}$

Dilling's formula: $\frac{\text{Age (yrs)}}{20} \times \text{Adult dose}$

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

CHILDREN

Clark's formula:

$$\frac{\text{Child's weight}}{70} \times \text{Adult dose}$$

E.g. 40 kg / 70 x 500 mg 2000 /7 = 285 mg

Body surface area (BSA)

Dubois formula:

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

$$\text{Child's dose} = \frac{BSA(m^2)}{1.73} \times \text{Adult dose}$$

ELDERLY

- ↓ Liver function
  - Diazepam, theophylline
- ↓ Kidney function
  - Digoxin, lithium
- ↓ Plasma protein binding
- ↑sensitivity to CNS depressants
  - Diazepam, morphine

2. GENDER

Males

- Testosterone increases the rate of biotransformation of drugs.
- Beta blockers, methyldopa, diuretics – sexual function interference
- Gynaecomastia – Metoclopramide, chlorpromazine, ketoconazole etc.

GENDER CONT…

Female

- Females have smaller body size – required doses are lower
- Decreased metabolism of some drugs (Diazepam)
- Females are more susceptible to autonomic drugs (estrogen inhibits choline esterase)
- Digoxin in maintenance therapy of heart failure – mortality higher in female.

3. PREGNANCY

- Causes several physiological change that influence drug disposition.
- ↑ aVd (total body water may increase by up to 8 liters) providing large space for water soluble drugs.
  - Maternal plasma albumin concentration is reduced, more free drugs will be available
- ↑ Cardiac output
- ↑ GFR & renal elimination of drugs
- ↑ Metabolism of some drugs
- Lipophilic drugs cross placental barrier
- Pregnancy – particularly 3rd trimester

4. Pathological Factors

- Diseases cause individual variation in drug response

Liver Disease

- Prolong duration of action: ↑ $t_{1/2}$
- ↓ Plasma protein binding for warfarin, tolbutamide → adverse effects
- ↓ Hepatic blood flow → ↓ clearance of morphine, propanolol
- Impaired liver enzymes → ↓ dose of Diazepam, rifampicin, theophylline

HEPATOTOXIC DRUGS

- Paracetamol
- Phenytoin
- Chlorpromazine

Hepatic cell injury

- Rifampicin
- Erythromycin
- Androgens

Cholestatic jaundice

- Alcohol
- Methotrexate

Cirrhosis

- Isoniazid
- Halothane
- Enflurane

Hepatitis

PATHOLOGICAL FACTORS

Renal Disease

- ↓GFR
- ↓ tubular function
- ↓ Plasma albumin
  - Digoxin, Lithium, Gentamycin, Penicillin

Malnutrition

- ↓ plasma protein binding of drugs
- ↓ amount of microsomal enzymes
- ↑ Increase portion of free, unbound drug
  - Warfarin

NEPHROTOXIC DRUGS

- NSAIDs (interstitial nephropathy)
- ACE inhibitors
- Penicillamine

] Nephrotic syndrome

- Sulfonamides (glomerulonephritis)
- Aminoglycoside (tubular necrosis)
- Kanamycin
- Capreomycin

8. Genetic Factors

- Acetylation
  - Acetyl transferase: Isoniazid, sulphonamides
- Succinylcholine apnea
  - Pseudocholinesterase deficiency
  - Due to paralysis of respiratory muscles
- G6PD-deficiency
  - Hemolytic anemia upon exposure to some oxidizing drugs. E.g. Primaquine

9. SPECIES/ RACE

- Response to drugs may vary with species and race e.g.
- Rabbits are resistant to atropine
- Blacks need higher doses of atropine to produce mydriasis

10. 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
- $MgSO_4$: Oral: as purgative; IV: as anti-convulsant (eclampsia of pregnancy)
- N-acetylcysteine: Oral/ IV: as antidote in PCM poisoning; Inhaled: act as a mucolytic

11. TIME

- Chronopharmacology
  - Study of correlation of drug effects to circadian rhythm
- it has been observed that endogenous body clock (circadian cycle) may affect the response of the drug. e.g.
- Statins given at bed time

12. Environmental factors

- Drug metabolism may get induced – exposure to insecticides, carcinogens, tobacco smoke and charcoal broiled meat etc.
  - Microsomal Enzyme Inducers
    - Smokers metabolize drugs more rapidly than non smoker

13. Food

- Food depress the rate and extent of drug absorption.
- Medicines are usually taken after a meal to reduce the risk of gastric irritation, nausea and vomiting.
- Drug may be given on empty stomach -to prevent mixing with food stuffs-e.g. anthelmintics -to get an immediate action -to prevent drug inactivation in the stomach. e.g. penicillin v
- Tetracyclines form insoluble chelates with Ca, Al etc. reduce their absorption.

14. PSYCHOLOGICAL FACTORS

- Affected by patients' beliefs, attitudes, expectations

- **Placebo** (I shall please)
  - Inert substance which is given in the garb of medicine
  - Psychological adv, no pharmacological role
  - Depends on doc-patient relationship

PSYCHOLOGICAL FACTORS

Placebo

- Inert dosage form with no specific biological activity but only resembles the actual preparation in appearance
- Used as a control in clinical trials (dummy) & to treat a patient who doesn't require an active drug
- Induce physiological responses (endorphins in CNS→ analgesia)
- Does not produce drug–drug interactions
- Never works in unconscious patient
- Distilled water, lactose, dextrose, vitamins, minerals

TOLERANCE

- Reduction in the response due to continued use or repeated administration of drug
- Higher doses of drug are needed to produce a given response
- **Drugs producing tolerance:** Benzodiazepines, Alcohol, Caffeine, Barbiturates, Opioids, Nitroglycerine
- Types
  - **Natural**: blacks intolerant to mydriatics
  - **Acquired**: chlorpromazine to sedation

MECHANISM OF TOLERANCE

- Changes in pharmacokinetics
- Down regulation of receptors
  - E.g. morphine

Cross tolerance: Development of tolerance to pharmacologically related drugs e.g. chronic alcoholics show tolerance to barbiturates & general anesthetics

TACHYPHYLAXIS

- **Acute tolerance:** tachy: fast; phylaxis: protection
- Rapid reduction in responsiveness due to repeated administration of drug at frequent intervals
- **Mechanism**
  - Depletion of neurotransmitters
  - Slow dissociation of drugs from receptors
- Cannot be overcome by increasing the dose
- Nitroglycerin (Monday disease), Amphetamine, Ephedrine, tyramine, nicotine

TERATOGENICITY

- Congenital malformations occurring in the fetus due to exposure to drugs during pregnancy
- Categories A, B, C, D, X

OTHER DRUGS

- Drugs can modify the response to each other by pharmacokinetic or pharmaco-dynamic interaction between them.
- Many ways in which drugs can interact are:
- Synergism
- Antagonism

SYNERGISM:

- When the action of one drug is facilitated or increased by the other, they are said to be synergistic.
- 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.
- Effects of drug A + Effects of drug B is < Effect of Drug A+B

ANTAGONISM:

- When one drug decreases or abolishes the action of another, they are said to be

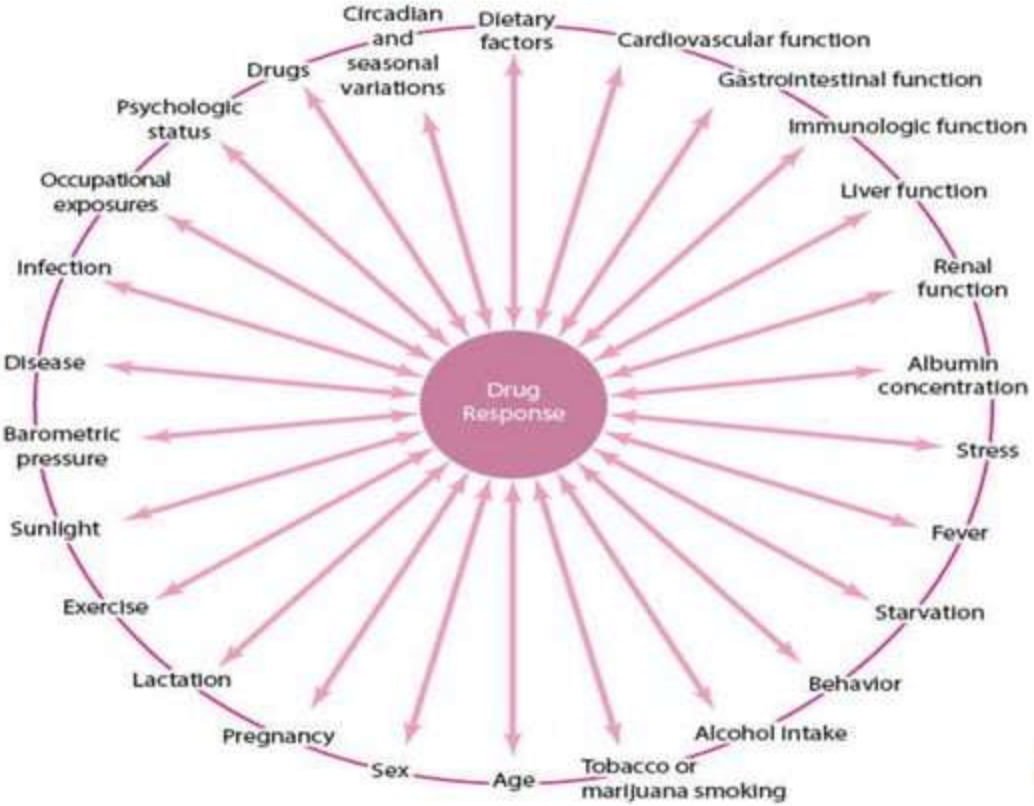
Antagonistic:

- Effect of drugs A + B < Effect of Drug A + Effect of drug B
- Usually in an antagonistic pair one drug is inactive as such but decreases the effect of the other.

DRUG – DRUG INTERACTION

- When two or more drugs are given or administered simultaneously response of one drug is altered to another drug.
- This may be
- Desired or beneficial

  e.g. Multi drug treatment of T.B, Naloxone to treat Morphine overdose
- Undesired or hamful


Drug Response
Circadian and seasonal variations
Dietary factors
Cardiovascular function
Gastrointestinal function
Immunologic function
Liver function
Renal function
Albumin concentration
Stress
Fever
Starvation
Behavior
Alcohol intake
Tobacco or marijuana smoking
Age
Sex
Pregnancy
Lactation
Exercise
Sunlight
Barometric pressure
Disease
Infection
Occupational exposures
Psychologic status
Drugs


Thank
you