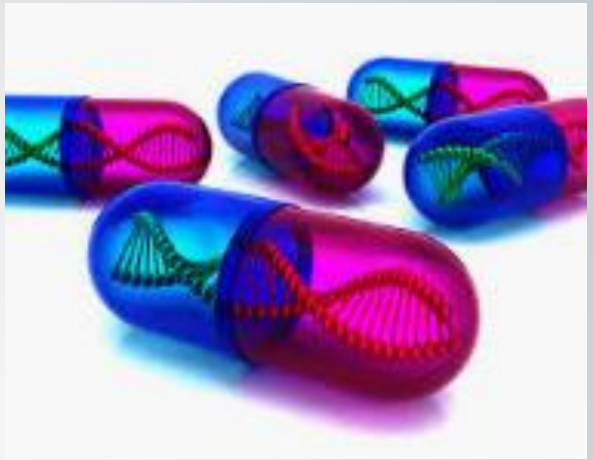


FACTORS MODIFYING DOSES AND ACTION OF DRUGS-I

SOURCES:

BERTRAM G. KATZUNG BASIC & CLINICAL PHARMACOLOGY 16TH EDITION

GOODMAN AND GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS 13TH EDITION.

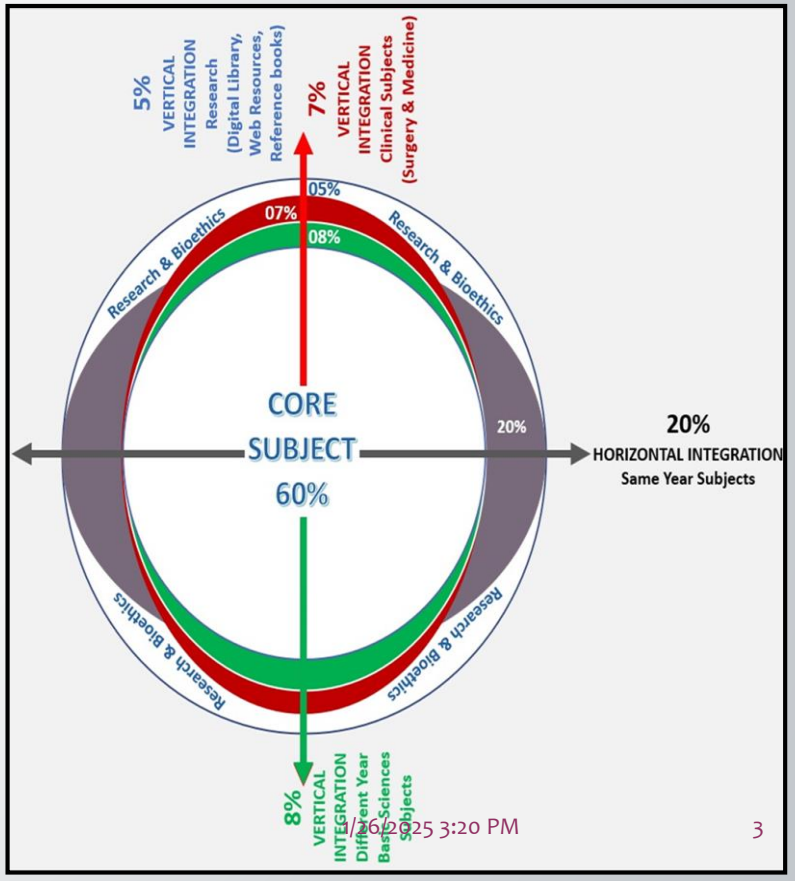
DR. ATTIYA MUNIR

AP PHARMACOLOGY

SEQUENCE OF LECTURE

- Spiral Integration
- Horizontal Integration
- Vertical integration
- Core Subject
- EOLA(End of lecture assessment)
- Digital Library References

(Research, Bioethics, Artificial Intelligence)



LEARNING OBJECTIVES

- At the end of session, the students of 3rd year should be able to:
- Discuss different factors affecting drug dose and action regarding Physiological, Pathological,Psychological,Genetic, Drug related (drug interactions) and Environmental factors
- Explain Synergism, Summation and Potentiation , Accumulation

FACTORS MODIFYING DOSES AND ACTION OF DRUGS

1. **Physiological Factors**
2. **Pathological Factors**
3. **Environmental factors**
4. **Psychological factors**
5. **Genetic Factors**
6. **Interaction with other drugs** (drug-drug interactions)

PHYSIOLOGICAL FACTORS

1. Age
2. Gender
3. Pregnancy & Lactation
4. Body size
5. Racial Difference
6. Food

AGE

- Neonates & infants, sensitive to certain drugs action b/c of immature state of their hepatic & renal function
- Drug metabolizing enzyme system under developed (Glucuronidation takes 3 months to develop)
- Neonates have low GFR & have immature renal tubular transport system
- ***↓GFR & immature renal tubular transport system ----*** prolongs half life of penicillins & gentamicin

AGE

ELDERLY, GERIATRIC AGE GROUP (> 75 YRS)

- Greater consumption of nonprescription drugs (eg, antacids and laxatives), reduced gastric emptying & GI motility especially in older diabetics … slower dg absorption
- V_d of lipid soluble dgs ↑es
- Renal function decline slowly after middle age >55 yrs (↓ RBF, GFR), adverse effects of dgs eliminated by kidneys ↑ed, e.g. lithium, digoxin

GENDER

- Men & women may respond differently to same dg due to different body size & amount of body fats
- Difference in activity of liver enzymes b/w men & women
- Digoxin in maintenance therapy of heart failure ----
- Beta blockers, methyldopa, diuretics ----

PREGNANCY AND LACTATION

- GI motility reduced ---- delayed absorption of orally administered dgs
- Plasma & ECF volume expands →
- Albumin level falls →
- ↑ Cardiac output → ↑ RBF → ↑ GFR
- Hepatic microsomal enzyme induction, drugs metabolized faster

PREGNANCY AND LACTATION

EXAMPLES OF TERATOGENIC DRUGS

- **Sodium valproate → Spina Bifida**
- **Thalidomide → Phocomelia**
- **Alcohol → Fetal alcohol syndrome**

Category	Description
A	Studies in women fail to demonstrate a risk to fetus in first trimester (& there is no evidence of a risk in late trimesters)
B	Adequate human studies are lacking, but animal studies have failed to demonstrate a risk to fetus OR in humans adequate studies in pregnant women have failed to demonstrate a risk to fetus, but animal studies have shown an adverse effect on fetus
C	Animals studies revealed adverse effects on fetus (teratogenic) & there are no controlled studies in women OR studies in women & animals are not available. *Drugs should be given only if potential benefit justifies potential risk to fetus*
D	There is positive evidence of human fetal risk*, but benefits from use in pregnant women may be acceptable despite risk* (eg, if a drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective)
X	Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience or both & risk of use of drug in pregnant women clearly outweighs any possible benefit. *The drug is contraindicated in women who are or may become pregnant*

LACTATION

- Dgs excreted through milk during lactation & affect infant
- Tetracycline
- Isoniazid
- Barbiturates
- Diazepam

BODY WEIGHT

- Normal doses of dgs decided considering 70Kg body wt. as normal body wt. of an adult

- For obese & underweight person dose calculated individually

$$\text{Individual dose} = \frac{\text{BW(Kg)}}{70} \times \text{average adult dose}$$

DOSE CALCULATION IN CHILDREN

Age(Young's rule):

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

Weight(Clark's rule):

$$\text{Dose} = \text{Adult dose} \times \frac{\text{Weight(kg)}}{70} \quad \text{OR} \quad \text{Adult dose} \times \frac{\text{Weight(lb)}}{150}$$

BODY SURFACE AREA

- Body surface area (BSA) provides a more accurate basis for dose calculation
- The average body surface area of a 70-kg adult is about 1.8 m^2

$$\text{Dose} = \frac{\text{BSA}(m^2)}{1.8} \times \text{Adult dose}$$

SPECIES

There is difference in response to dgs among different species

EXAMPLES

1) Rabbits are resistant to atropine
2) Rats & mice are resistant to digitalis
3) Rat is more sensitive to curare than cat

These differences are important while extrapolating results from experimental animals to man

RACE

- Blacks require higher & Mongols require lower concentration of atropine & ephedrine to dilate their pupil

- ß blockers are less effective as antihypertensive in blacks

FOOD

- Fatty food in stomach ↓ absorption (Ampicillin & rifampicin)
- Anti-emetics dgs & anti helminthics…empty stomach
- Calcium in milk…
- Grapefruit juice

PATHOLOGICAL FACTORS

- Several pathological states particularly those affecting liver, kidney or altering body fluid pH & electrolytes affect dg effects & dg dosage

GASTROINTESTINAL DISEASES

- Can increase or decrease absorption of orally administered dg

PATHOLOGICAL FACTORS

IN LIVER DISEASES

- Increased bioavailability of dgs with high first pass metabolism
- Serum albumin reduced & protein binding of dgs like Warfarin ↓
- Metabolism & elimination of dgs may reduced

PATHOLOGICAL FACTORS

KIDNEY DISEASES

- Renal disorders lead to slower excretion of dgs

PATHOLOGICAL FACTORS

CONGESTIVE HEART FAILURE

- Expansion of extracellular fluid volume → increase Vd of some dgs

ENVIRONMENTAL FACTORS AND TIME OF ADMINISTRATION

- Several environmental factors affect dg responses
- ***Examples:***
- exposure to insecticides, tobacco smoke & consumption of charcoal broiled meat Hypnotics act better when given at night & smaller doses are required

ROUTE OF ADMINISTRATION

- Route determines speed & intensity of dg response –Parenteral route for speedy action
- Magnesium sulfate

PSYCHOLOGICAL FACTOR

- Efficacy of a dg can be affected by patient's beliefs, attitudes & expectations
- E.g. a nervous & anxious patient requires more general anesthetic
- **PLACEBO:**
- **PLACEBO EFFECT:**
- Substances commonly used as placebo are lactose tablets/capsules & distilled water injection

GENETIC FACTORS

- **Pharmacogenomics**, a modern term for **pharmacogenetics**, study of genetic factors that affect dug responses
- All determinants of dg response, *like* metabolizing enzymes, transporters, ion channels, receptors are controlled genetically
- Polymorphism

IDIOSYNCRASY

- *Idiosyncrasy* is an abnormal reactivity to a drug that is peculiar to a given individual
- Idiosyncratic response may be extreme sensitivity to low doses or extreme insensitivity to high doses of drug
- Highly unpredictable response seen even after first dose of drug
- Seen only in small percentage in a population

IDIOSYNCRASY

Examples of idiosyncratic reactions:

- Chloramphenicol-
- Halothane-
- Penicillins & sulfonamides -

DRUG-DRUG INTERACTION

- Administration of one drug can alter action of another by one of two general mechanisms:

1. Altering concentration of a dg at its site of action (***pharmacokinetic interaction***)

2. Modifying pharmacological effect of a dg without altering its concentration in tissue fluid (***pharmacodynamic interaction***)

PHARMACOKINETIC INTERACTION

Interaction of Absorption:

- A dg may increase or decrease absorption of another dg from intestinal lumen

- Ca^{2+} & Fe^{2+} each form insoluble complexes with **tetracycline** that retard their absorption

DRUG-DRUG INTERACTION

Interaction of distribution:

- Are primarily due to displacement of one drug from its binding sites on plasma proteins by another drug
- Displacement of bound drug by other drugs raise concentration of free form of drug in plasma that may result in toxicity

DRUG-DRUG INTERACTION

Interaction of Metabolism:

- Enzyme inducers
- Enzyme inhibitors

DRUG-DRUG INTERACTION

Interaction of Excretion:

Main mechanisms by which one dg can affect rate of renal excretion of another are by:

I. Altering protein binding & hence filtration
II. Inhibiting tubular secretion
III. Altering urine flow or urine pH

DRUG-DRUG INTERACTION

Pharmacodynamic interactions

- Are derived from modification of action of one dg at target site by another dg, independent of a change in its concentration

This may result

- In an enhanced response (synergism)
- Decreased response (antagonism)

DRUG-DRUG INTERACTION

- Drug interactions are:

Additive when combined effect of two dgs equals the sum of effect of each agent given alone (like one plus one getting two)

- Dgs acting on same receptor or process are usually additive
- benzodiazepines plus barbiturates sedative/hypnotic effect

DRUG-DRUG INTERACTION

Synergistic or Synergism when combined effect exceeds the sum of effects of each drug given alone (like combining two plus two & getting five)

- Drugs acting on different receptors or sequential processes may be synergistic, sulfonamides plus trimethoprim

Potentiation:

Describes the creation of a toxic effect from one drug due to presence of another drug

ANTAGONISM

Antagonism: One drug opposes or inhibit the action of another drug

TYPES:

- Chemical Antagonism
- Physical antagonism
- Physiological Antagonism
- Pharmacological Antagonism
  - ✓ Competitive (Reversible)
  - ✓ Non-competitive (Irreversible)

CHEMICAL ANTAGONISM

A type of antagonism where a dg counters the effect of another by simple chemical reaction (not binding to receptor)

EXAMPLES:

- Protamine sulphate & Heparin

PHYSICAL ANTAGONISM

- When one dg decreases action of another dg by physical mean like adsorption
- E.g Charcoal adsorbs alkaloids & prevents their absorption

PHYSIOLOGICAL/ FUNCTIONAL ANTAGONISM

- A type of antagonism in which **o**ne drug antagonize/ reverses effect of another dg by binding to a different receptor to produce opposite **physiological actions**

EXAMPLES:

- ***Adrenaline and histamine***

PHARMACOLOGICAL ANTAGONISM

- **Pharmacological antagonist** binds to same receptor as agonist does
- Antagonist occupies binding site of receptor & prevents binding of agonist to receptor, in this way, prevents activation of receptor

TYPES:

- Competitive / Reversible/Surmountable antagonism
- Non competitive/Irreversible antagonism

CUMULATION

- Dg accumulate in body if rate of administration is more than rate of elimination
- Slowly eliminated dgs cause more cumulative toxicity
- EXAMPLES: Digoxin & Chloroquine
- Prolonged use of chloroquine cause retinal damage
- Renal toxicity of aminoglycoside antibiotics(eg , gentamicin) greater when administered as a constant infusion than with intermittent dosing due to accumulation of aminoglycoside in renal cortex that cause renal damage.

ARTIFICIAL INTELLIGENCE AND RESEARCH

- Chen C, Liu F, Ren Y, Suttner L, Sun Z, Shentu Y, Schmidt EV. Independent drug action and its statistical implications for development of combination therapies. Contemporary Clinical Trials. 2020 Nov 1;98:106126.

- D'Alessandro C, Benedetti A, Di Paolo A, Giannese D, Cupisti A. Interactions between food and drugs, and nutritional status in renal patients: a narrative review. Nutrients. 2022 Jan 4;14(1):212.

TAKE HOME MESSAGE/ BIOETHICS

- Important concept in selecting the dose and dosage form for a particular indication.
- Pharmacogenetic studies focus on biotransformation of drugs

EOLA

- Trimethoprim and sulfamethaxazole are bacteriostatic drugs when given alone. However the combination is bactericidal. Which of the following term best defines this drug interaction:
- 1. Additive effect
- 2. Summation
- 3. Potentiation
- 4. Sensitization
- 5. Tolerance