FACTORS MODIFYING DRUG ACTION

MPHL – 231

Dr. Hanan Hagar

FACTORS MODIFYING DRUG ACTION

- I. Physiological Factors.
- II. Pathological Factors (Diseases).
- III. Genetic Factors.
- IV. Environmental Factors.
- V. Interaction with other drugs.

I. Physiological Factors

- Age
- Sex
- Pregnancy
- Body weight
- Lactation
- Food

I. Physiological Factors

1. AGE

Newborn: Decreased

- ↓ gastric acid secretion.
- ↓ liver microsomal enzymes (glucuronyl transferase).
- ↓ Plasma protein binding.
- ↓ GFR & tubular secretion.
- Immaturity of BBB in neonates.

- **GIT absorption of ampicillin and amoxicillin is greater in neonates** due to decreased gastric acidity.

- **Chloramphenicol --- Grey baby syndrome**
  Inadequate glucouronidation of chloramphenicol with drug accumulation).

- **Sulfonamides ------ Hyperbilirubinemia & Kernicterus**

CHILDREN

- **Tetracyclines**

Permanent teeth staining

- **Corticosteroids**

Growth & development retardation

- **Antihistaminics**

Hyperactivity.

Old Age

– **↓ Liver function.**

diazepam, theophylline.

– **↓ Kidney function.**

Digoxin, lithium.

– **↓ Plasma protein binding**

– **↑sensitivity to CNS depressants.**

diazepam, morphine

2. SEX.

- **Testosterone increases the rate of biotransformation of drugs.**
- **Decreased metabolism of some drugs in female (Diazepam).**
- **Females are more susceptible to autonomic drugs (estrogen inhibits choline estrase).**

3. Pregnancy

- ↑ Cardiac output
- ↑ GFR and renal elimination of drugs.
- ↑ Vd
- ↑ Metabolic rate of some drugs.
- Lipophilic drugs cross placental barrier & slowly excreted.

4. Plasma Protein Binding

- Malnutrition.
- Drug Interaction.

II. Pathological Factors

Diseases cause individual variation in drug response

(A) Liver Disease

- Prolong duration of action = ↑ (t1/2).
- ↓ Plasma protein binding for warfarin, tolbutamide → adverse effects.
- ↓ Hepatic blood flow → ↓ clearance of morphine- propanolol.
- Impaired liver microsomal enzymes ↓ Diazepam- rifampicin- theophylline

(B) Renal Disease

- ↓ GFR.
- ↓ tabular function.
- ↓ Plasma albumin

  digoxin-lithium- gentamycin- penicillin.

(C) Malnutrition

- ↓ plasma protein binding of drugs.
- ↓ amount of microsomal enzymes.
- ↑ Increases portion of free, unbound drug
- warfarin

III. Genetic Factors

Pharmacogenetics

is the study of the relationship b/w genetic factors and drug response.

Idiosyncrasy abnormal drug reaction due to genetic disorder .

- Acetylation.
- Oxidation.
- Succinylcholine apnea.
- Glucose 6-phosphate dehydrogenase deficiency.

III. Genetic Factors

GENETIC POLYMORPHISM

The existence in a population of two or more phenotype with respect to the effect of a drug.

Acetylation enzymes deficiency

- acetyl transferase (non-microsomal).
- Isoniazid, sulphonamides, etc.
- **Slow** acetylator phenotype → peripheral neuropathy .
- **Rapid** acetylator phenotype → hepatitis.

Pseudocholinesterase deficiency.

- Succinyl choline (Sk.muscle relaxant) → Succinylcholine apnea due to paralysis of respiratory muscles.

Malignant hyperthermia

- By succinyl choline due to inherited inability to chelate calcium by sarcoplasmic reticulum.
- ↑ Ca release, muscle spasm, ↑ Temp.

Oxidation Polymorphism

Debrisoquine.

- **Extensive metabolizers (EM) – need larger dose.**
- **poor metabolizers (PM) – need smaller dose.**

Porphyria

Deficiency of Glucose–6 phosphate dehydrogenase (G-6-PD).

G-6-PD Deficiency in RBCs → hemolytic anemia upon exposure to some oxidizing drugs.

- Antimalarial drug, primaquine.
- Long acting sulphonamides.
- Fava beans (favism).

IV. Environmental Factors

Microsomal Enzyme Inducers

- Tobacco Smoke
- Smokers metabolize drugs more rapidly than non smoker.

Adverse drug effects

Undesirable or harmful effects which can occur at therapeutic doses and need a reduction of dose or drug withdrawal .

- **Nausea and vomiting**
- **Deafness with gentamycin**
- **Death with penicillin**

Types of adverse drug reactions

A, B, C, D and E

1) Type A reactions

- Excessive therapeutic effect
- Side effects

I) Type A reactions

- Common
- 75 % of all adverse reaction
- Related to pharmacological actions.
- Dose-dependent
- Predictable
- Can be avoided by adjusting the dosage regimen
- Most of them are reversible upon stopping drug.
- Hypotension (antihypertensives)
- Hypoglycemia (insulin)

Type A reactions

1. Excessive therapeutic effect

Unwanted effects related to the main pharmacological actions of the drug that occur when the drug produce greater therapeutic effect than is necessary.

- **Warfarin → Anticoagulant → Bleeding**
- **Insulin → Normoglycemia → Hypoglycemia**

2. SIDE EFFECTS

Unwanted effects unrelated to the main pharmacological actions of the drug but due to other normal actions of the drug.

e.g. morphine constipation during its use as analgesic.

II) Type B reactions

- are bizarre reactions
- Not related to the normal pharmacological actions of the drug.
- Unpredictable
- Not dose-related.
- Occur only in minority of patients.

Types

- allergic reactions (Hypersensitivity)
- Genetic disorders (Idiosyncrasy)

Type B

1) Hypersensitivity (allergic reactions)

Abnormal response tio the drug due to antigen- antibody reactions e.g. Penicillin

- allergic response to a drug.
- rashes, hypotension and bronchospasm (anaphylactic reaction).

Type B

2) Idiosyncrasy

- is abnormal response to the drug due to genetic disorders.
- Succinylcholine apnea
- Malignant hyperthermia
- Favism
- Porphria

SECONDARY EFFECTS

- Unwanted effects that occur secondary to the wanted actions of the drug.
- Overgrowth of microorganisms following use of broad spectrum antibiotics.

Type C reactions (Continuous reaction)

- Due to long term use e.g. NSAIDs analgesic nephropathy

Type D reactions (Delayed adverse reactions)

Teratogenesis

Is congenital malformations occurring in the fetus due to exposure to drugs during pregnancy

e.g. Thalidomide → phocomelia

Carcinogenesis

Ability of some substances to induce cancer.

Stilbesterol → adenocarcinoma of vagina in female off springs.

Mechanisms

1. DNA alteration

griesofulvin& alkylating cytotoxics

2. Immunosuppression

immunosuppressant increase incidence of cancer

e.g. organ transplantation & rheumatoid arthritis

3. Hormonal

long term use of estrogen replacement in PMW induce endometrial cancer

Type E reactions (Ending of drug)

- Sudden discontinuation (abrupt withdrawal).
- Rebound adrenal insufficiency

e.g. corticosteroids