FACTORS MODIFYING DRUG ACTION

MPHL – 231

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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.