Drug Combination

Two or more drugs are taken at the same time (**Drug-drug interaction**).

TYPES of Drug-drug interaction

1. Harmful
2. Useful (multidrugs treatment of T.B.)

Clinically important D-D interactions:

1. Patients with impaired liver or kidney functions.
2. Elderly patients.
3. Drugs known a enzyme inducers and inhibitors.
4. Drugs with small therapeutic index (digoxin-Lithium).
5. Drugs used for prolonged time and precise plasma levels (lithium-antiepileptics).

Drug Combination

Where

1. **Outside the body.**
2. **Inside the body.**

Drug interaction outside the body.

- Soluble insulin and protamine zinc → delayed absorption

- incompatibility

Diazepam or phenytoin + Infusion fluid (saline) →Precipitation .

Carbenicillin + Gentamycin → Inactive gentamycin

Thiopental + Suxamethonium → Precipitation

Drug INTERACTION INSIDE THE BODY

Mechanisms

Pharmacokinetic interactions

- Absorption
- Distribution
- Metabolism
- Elimination

Pharmacodynamics Interactions

- Synergism
  - Potentiation
  - Addition
- Antagonism

I. Interactions During Absorption

A. Direct chemical interaction

- Iron and tetracyclines form complex.
- Antacids: Aluminium or magnesium chelate with tetracyclines ↓ bioavailability of tetracycline (2 hr apart).

- Cholestyramine interfere with absorption of:
  - Digoxin
  - Warfarin.
  - Thyroxine

(B) Alteration of GIT Motility

- Purgatives ↓ absorption
- Antidepressants & anticholinergic drugs e.g. Atropine ↓ gastric emptying & delay absorption.
- Prokinetics e.g. Metoclopramide ↑ gastric emptying and absorption.

(C) Alteration in GIT Flora

broad spectrum antibiotics
potentiates anticoagulants $\rightarrow \downarrow$
bacterial synthesis of Vit K.

(D) Absorption from other sites

Local anesthetic (lidocaine) + Adrenaline
delay in absorption $\rightarrow \uparrow$ duration of action

II. Distribution

A) Displacement from plasma protein binding sites.

Sulphonamide + Bilirubin → Kernicterus

B) Displacement from other tissue binding sites.

Quinidine + digoxin → more digoxin → toxicity

III. Biotransformation

A) Enzyme Induction.

Rifampin + Contraceptives $\rightarrow$

Failure of conception

Barbiturates + Warfarin $\rightarrow$

$\downarrow$ Anticoagulant effect

B) Enzyme Inhibition.

Cimetidine $\rightarrow$ potentiates effects of Warfarin, theophylline.

IV. Interaction During Excretion

a) Interference with active transport.

Primary Drug	Competing Drug	Result
Penicillin	Probenicid	↑ Penicillin Level
Salicylates	Probenicid	Salicylate toxicity
Indomethacin	Probenicid	Indomethocin toxicity

Pharmacodynamic Interactions

- DRUG SYNERGISM.
- DRUG ANTAGONISM.

Synergism

When the therapeutic effect of one drug is enhanced by another drug.

types:

- Addition.
- Potentiation.

Addition

- When the effect of two drugs having similar action are additives
- the net effect of two drugs used together is equal to the sum of the individual drug effect.

1 + 1 = 2

Thiazide diuretics + Beta blocker have an additive antihypertensive action.

Potentiation

- When the net effect of two drugs used together is greater than the sum of the individual drug effects.

  1 + 1 > 2 or 1 + 0 > 2

- when one drug increases the action of other drug e.g. sulphamethoxazole + trimethoprim → cotrimoxazole **(bactericidal)** 1 + 1 > 2

- or when drug has no effect as own but increases the effect other drugs (1 + 0 > 2)

  L-dopa and carbidopa.

Antagonism

The effect of one drug is decreased or abolished by the administration of another one .

- **Physiological antagonism.**
- **Chemical antagonism.**
- **Pharmacological antagonism.**