DRUG INTERACTION

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DRUG INTERACTION

Pharmacokinetic-interaction

Drug/Food/Disease alters the **ADME** profile of a DRUG and changes its pharmacological effects

Drug Interaction

- **Drug interaction** refers to alteration of effect of one drug by another like Foods, Drugs and or diseases

- **Drug-drug interaction** means effect of one drug is altered by another drug (i.e. drug-drug interaction).

Types of Drug Interaction

There are three types of Drug-Interaction

- (1) Drug-Drug interaction : Drug alters the effect of drug action
- (2) Drug-Food interaction: Food alters the effect of drug action
- (3) Drug-Disease interaction: Disease alters the effect of drug action

Mechanism of Drug-Interaction

How Drug/Food/Disease alters the pharmacological effect of a drug ???

The mechanisms of drug interactions are often categorized as:

1. **Pharmacokinetic interactions** : Those interactions which affects the process of drug absorption **(A)**, distribution **(D)**, metabolism **(M)** and excretion **(E)** are called as pharmacokinetic interactions or **ADME interactions**.
2. **Pharmacodynamic interactions** : Those interactions where the effect of one drug is altered by the presence of another drug at its site of action are called as pharmacodynamic interactions.

PHARMACOKINETIC DRUG INTERACTION

Drug/Food/Disease alters the **ADME** profile of a DRUG and change its pharmacological effects

P'Kinetic Interaction: **Absorption**

Alteration of Gastrointestinal Absorption: Any interaction which occurs in G.I.T. will effect absorption

A) Alteration of pH : Most of the drugs are absorbed by passive diffusion and depends on pK_a, lipid solubility etc. e.g. :

→ ***Aspirin - Antacids :*** Long term use of aspirin causes systemic acidosis, gastric ulceration. So an antacid is given along with it in order to **minimize gastrointestinal side effects**. **(Good interaction)**

→ ***Ketoconazole-Antacids/PPIs/H2 blocker :*** Ketoconazole is a base, so it needs lower pH to dissolve. If an antacid is given along with it, absorption decreases due to increase in pH that cause decrease the dissolution rate of *Ketoconazole and* ***decrease in antifungal action*** **(Bad Interaction)**

P'Kinetic Interaction: **Absorption**

B)Adsorption/Chelation : Chelation of a drug interfere its absorption

→ ***Tetracycline – Cations:*** Tetracycline forms chelate with divalent or trivalent cations (Al^{+++}, Ca^{2+}, Mg^{2+}, Fe^{3+}, Bi^{2+}) present in milk, antacids, iron preparation etc. These complexes are less soluble and cant absorbed properly and **they may have reduced antibacterial activity**

C) G.I. Motility

→ A cathartic/Laxative by increasing gastrointestinal motility, may increase the rate at which another drug passes through the G.I. tract. And **decrease the absorption**

P'Kinetic Interaction: **Absorption**

D) The Presence of food : Food can also influence the absorption of a number of drugs by :
- *binding with drugs*
- *decreasing the access of drugs to site of absorption.*
- *altering the dissolution rate of drugs*
- *altering the pH of gastrointestinal contents.*

→ ***Antibiotics - Food :*** The presence of food in G.I. tract will **reduce the absorption** of many antibiotics, with exceptions (e.g. penicillin V potassium, amoxicillin, doxycycline, minocycline etc.).

→ ***Griseofulvin - Food :*** The solubility as well as **absorption of griseofulvin increases**, if taken with high fat diet.

P'Kinetic Interaction: **Distribution**

These interactions are mostly associated with protein binding & **Displacement Reaction**.

- ***Acidic & neutral*** drugs binds to ***albumin***.
- ***Basic drugs*** binds to α_1 ***glycoprotein***.

→ ***Warfarin- Phenyl butazone :*** Both of these drugs are extensively bound to plasma Albumin. Phenyl butazone however has a greater affinity thereby displacing warfarin and making increased quantities of free drug warfarin available, **thus increasing the anticoagulant activity of warfarin**.

→ ***Methotrexate - salicylates :*** Salicylates (NSAID) replaces methotrexate, so methotrexate level goes up. It also reduces elimination of methotrexate from kidney **leading to toxic effects.**

P'Kinetic Interaction: **Metabolism**

Most of the interaction are due to either microsomal **enzyme induction** or **inhibition** by drug

A) Enzyme Inducer: Metabolic inducers increases the metabolism of certain drugs thereby decreasing their drug concentration (unchanged) and therapeutic effects.

e.g. Enzyme Inducer: (P C BAR PG)= Phenytoin, Carbamezapine, Barbiturates, Alcohal, Rifampicin, Phenylbutazone, Griseofulvin

→ **Warfarin/Anticogulant – Inducer:** Anticoagulant effect decreases

→ **Contraceptives** – **Inducer:** Levels of contraceptive decreases, chances of bleeding or failure of contraception

P'Kinetic Interaction: **Metabolism**

B) Enzyme Inhibitors: These inhibit the metabolism of certain drugs thereby increasing their concentration or effect.

e.g. Enzyme Inhibitors : (COKE PI) = Cemitidine, Omeperazole, Ketakonazole, Erythromycin, Protease Inhibitor (Saquinavir), INH

→ **Warfarin/Anticogulant – inhibitors**: Anticoagulant drug level as well as effect increases

→ **Phenytoin – Isoniazid (INH):** Increase Phenytoin toxicity

→ **Corticosteroids- Erythromycin**: Increase level of Corticoids and leads to toxicity.

P'Kinetic Interaction: **Metabolism**

C) Inhibition of Gastrointestinal enzymes :

→ ***Folic acid - Phenytion :*** Folic acid generally is present in dietary sources in the form of poorly absorbed polyglutamates, to be efficiently absorbed it must be converted to readily absorbed derivative by action of an **intestinal conjugate enzyme**. Phenytoin inhibit this enzyme leading to folic acid deficiency anemias.

→ ****MAO inhibitors-Tyramine :*** If a patient taking MAO inhibitors takes tyramine rich food (e.g. yeast, cheese, banana etc.), this results in **life threatening hypertension**. This is because tyramine is metabolised by MAO, and when this enzyme is inhibited, large quantity of unmetabolised tyramine can accumulate and act to release norepinephrine **leading to hypertensive crisis.**

P'Kinetic Interaction: **Excretion**

A) Alteration of urinary pH : Alteration of urinary pH can influence the activity of certain drugs. (Drug excretion depends on urine pH)

- A change in urinary pH will influence ionization and reabsorption of weak acids and weak bases and thus affect the extent to which these agents are reabsorbed and excreted.
- Weak acidic drugs are excreted in basic pH or reabsorbed in acidic urine. Thus for excretion of weak acidic drugs, we can use urine alkalizer ($NaHCO_3$).
- Weak basic drugs are excreted in acidic pH or reabsorbed in basic urine. Thus for excretion of weak basic drugs, we can use urine acidifier (NH_4Cl).

→ ***Salicylates - Alkanizing Agents :*** As the urinary pH increases, serum salicylate concentration decreases.

P'Kinetic Interaction: **Excretion**

B) Alteration of Active transport system in renal tubules:

- Anionic trasnport (OAT)- for acidic drug (Pencilline, probenecid, salicylate, MTX). And Cationic transport (OCT)- for basic drug (Thiazides, quinidine, procainamide, cemitidine).

→ ***Penicillins - Probenecid :*** Probenecid can increases serum levels and prolong activity of penicillin derivative by blocking their tubular secretion.

→ ***Digoxin - Quinidine :*** Serum digoxin levels increases when quinidine is administered concurrently. **(Cardiac arrhythmia)**

→ ***Digoxin-Verapamil :*** Verapamil has been reported to increases serum digoxin levels. Verapanil may inhibit both the renal tubular secretion and non-renal elimination of digoxin, resulting in the increase in serum levels of digoxin. **(Cardiac arrest)**

PHARMACODYNAMIC DRUG INTERACTION

A Drug alters the **Pharmacodynamic** profile (**Potency** & **Efficacy**) of an another DRUG and change its pharmacological effects

"COMBINED EFFECTS OF DRUGS"

DRUG INTERACTION
Pharmacodynamic-interaction

A Drug alters the **Pharmacodynamic** profile (**Potency** & **Efficacy**) of an another DRUG and change its pharmacological effects

"COMBINED EFFECTS OF DRUGS"

Pharmacodynamic Drug Interaction

- **Drug-drug interaction** means effect of one drug is altered by another drug (i.e. drug-drug interaction).
- **Combined Effect of Drugs:** When two or more drugs are given simultaneously or in quick succession, they may be either indifferent to each other or exhibit *synergism* or *antagonism*.

1. Synergistic action: (Greek: *Syn*—together; *ergon*—work)

- 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. Synergism can be: **Additive and supraadditive**

Pharmacodynamic Drug Interaction

A) Additive effect: *The effect of the two drugs is in the same direction and simply adds up:*

Effect Drugs A + Drug B = effect of drug A + effect of drug B

- Therapeutic effects can add up only
- Side effects of drug A and B do nor add up, thus combination therapy is better than high dose of monotherapy.

→ Aclophenac + Paracetamol: better analgesic and antipyretic effects

→ Alcohol + diazepam may have an excessive CNS depressant effect

→ Nitrus oxide + Halothane: Enhance general anesthetic action

→ Amlodipine + Atenolol: enhance antihypertensive action

Pharmacodynamic Drug Interaction

B) Supra-Additive effect (Potentiation): The effect of combination is greater than the individual effects of the components:

Effect of Drugs A + Drug B > effect of drug A + effect of drug B

- This is always the case when one component given alone produces no effect, but enhances the effect of the other (potentiation).

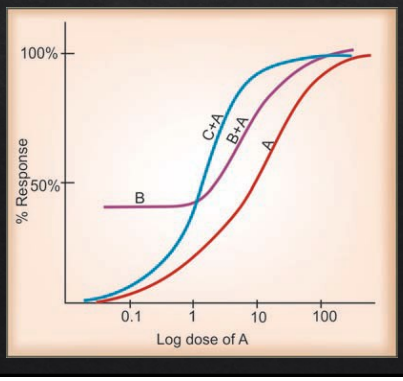


Figure: Log dose-response curves of a drug 'A' depicting additive synergism (in purple) and potentiation (Supra-additive synergism) in blue.

A: An agonist drug.
B: Another agonist in a fixed submaximal dose producing 40% response.
C: A potentiating drug which itself has no agonistic activity.

Pharmacodynamic Drug Interaction

B) Supra-Additive effect:

→ **Acetylcholine + Physostigmine –** Inhibits (ChE) the breakdown of Ach and potentiate the action of Ach.

→ **L-DOPA + Carbidopa-** Inhibits (dopa-decarboxylase) the preripheral breakdown of L-dopa and potentiate antiparkinsonian effect of l-dopa.

→ **Adrebaline + Cocaine-** inhibits the neuronal uptake of adrenaline

→ **Tyramine + MAO inhibitor-** Inhibits the breakdown of tyramine and increase the Catecholamines level

→ **Enalapril + thiazide:** Taking two contributing factors

Pharmacodynamic Drug Interaction

2. Antagonism: When one drug decreases or abolishes the action of another, they are said to be antagonistic:

Effect of Drugs A + Drug 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.

◈ Depending on the mechanism involved, antagonism may be:

A) Physical Antagonism: Based on physical properties.

→ Charcoal adsorbs alkaloids and can prevent their absorption—used in alkaloidal poisonings.

→ Kaolin adsorbs the poisons and reduces their effects.

Pharmacodynamic Drug Interaction

B) Chemical Antagonism: Reduces the action by chemical reaction

- → KMnO4 oxidized alkaloid —used for gastric lavage in alkaloidal poisonings
- → Antacids neutralize the acids
- → Chelating agents (BAL, EDTA) form complexes with heavy metal and eliminate poisoning.

Pharmacodynamic Drug Interaction

C) Physiological Antagonism: Two drugs act on different receptors, but have opposite effects on the same physiological function.

- → Histamine and adrenaline on bronchial muscles and BP. Histamine (H1R) causes bronchoconstriction effect and fall in BP, while Adrenaline causes Bronchodilation (beta-2) and Rise in BP (alfa-1)
- → Glucagon and Insulin on blood glucose level.

Pharmacodynamic Drug Interaction

B) Receptor Antagonism: Two drugs act on same receptors. In this case Antagonist block the action of Agonist.

- → Atenolol blocks the action of adrenaline by blocking Beta-1 receptor and decrease the cardiac activity
- → Prazosine blocks the action on nor-adrenalin by blocking alfa-1 receptor and decrease the blood pressure
- → Ranitidine blocks the H2 receptor and decrease the acid secretion.
- → Losartan blocks the AT1 receptor of Angiotensin II and abolish their effects.

Receptor Antagonism

Allosteric site

Competitive Antagonist

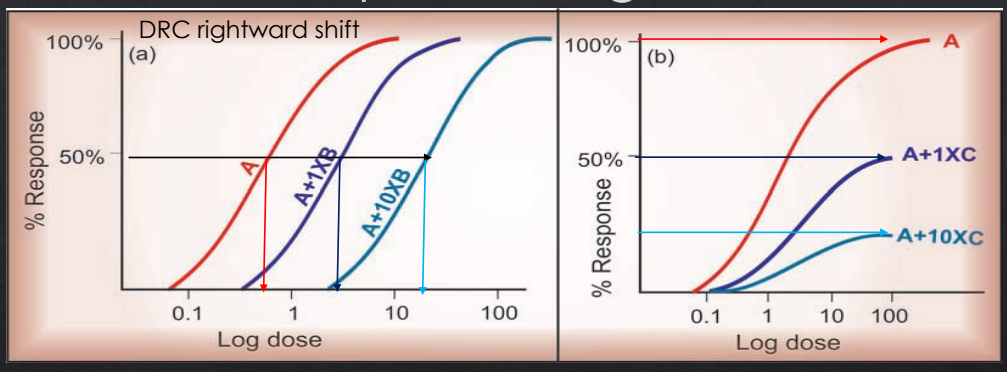
- Antagonist binds with the same receptor of agonist.
- Chemically resemble with agonist
- Decrease the potency of agonist (require high dose to produce 50% effects)
- Ach—MR-- Atropine

Non-Competitive Antagonist

- Binds with allosteric site of receptor of agonist
- Dose not Resemble
- Decrease Efficacy of agonist (suppress the maximal response)
- Diazepam—BDZ R-- Bicuculine

 Agonist  Competitive Antagonist  Non-Competitive Antagonist

Receptor Antagonism



A. Compitive antagonism **B. Non-Comipitive Antagonism**

Figure Dose-response curves showing competitive (a) and noncompetitive (b) antagonism
A—agonist, B—competitive antagonist, C—noncompetitive antagonist

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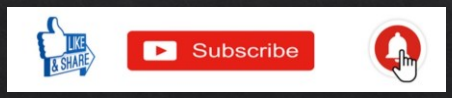

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