DRUG-DRUG INTERACTIONS

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Definition

- It is the modification of the effect of one drug (object drug) by the prior concomitant administration of another drug (precipitant drug).

- Concomitant use of several drugs in presence of another drug is often necessary for achieving a set of goals or in the case when the patient is suffering from more than one diseases.

- In these cases, chance of drug interaction could increase.

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Epidemiology

- In a Harvard medical practice study of adverse events due to drugs, 8% were consider to be due to drug interaction.
- US community pharmacy study revealed 4.1 % incidence of drug interactions in hospitalised patient.
- Australian study found that 4.4% of all ADR that resulted in hospitalization were due to interactions.

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Risk factors

- Poly pharmacy
- Multiple prescribers
- Multiple pharmacies
- Genetic make up
- Specific population like e.g, females , elderly, obese, malnourished , critically ill patients, transplant recipients
- Specific illness, e.g. hepatic disease, renal dysfunction
- Narrow therapeutic index drugs, e.g. cyclosporine, digoxin, insulin, lithium , antidepressants, warfarin

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Outcomes of drug interactions

1) Loss of therapeutic effect
2) Toxicity
3) Unexpected increase in pharmacological activity
4) Beneficial effects, e.g. additive & potentiation or antagonism
5) Chemical or physical interaction, e.g. I.V incompatibility in fluid or syringes mixture

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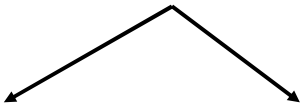
Mechanisms of drug interactions



Pharmacokinetics Pharmacodynamics

Pharmacokinetics involve the effect of a drug on another drug kinetics that includes absorption, distribution, metabolism and excretion.

Pharmacodynamics are related to the pharmacological activity of the interacting drugs, e.g., synergism, antagonism, altered cellular transport, effect on the receptor site.

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Pharmacokinetic interactions

- Altered pH
- Altered bacterial flora
- Formation of drug chelators or complexes
- Drug-induced mucosal damage
- Altered GIT motility

a) Altered pH;

The non-ionized form of a drug is more lipid soluble and more readily absorbed from GIT than the ionized form.

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Ex1. antacids → Decrease the tablet dissolution of ketoconazole (acidic)

Ex2. H_2 antagonists →

Therefore, these drugs must be separated by at least 2h in the time of administration of both.

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b) *Altered intestinal bacterial flora*

EX. 40% or more of the administered digoxin dose is metabolized by the intestinal flora.

Antibiotics kill a large number of the normal flora of the intestine → Increase digoxin conc. and increase its toxicity

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c) Complexation or chelation;

Ex1. Tetracycline interacts with iron preparations

or

Milk (Ca^{2+}) → Unabsorbable complex

Ex2. Antacid (aluminum or magnesium) hydroxide → Decrease absorption of ciprofloxacin by 85% due to chelation

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d) Drug-induced mucosal damage.

Antineoplastic agents e.g., cyclophosphamide
vincristine
procarbazine

Inhibit absorption of several drugs eg., digoxin

e) Altered motility

Metoclopramide (antiemetic)

Increase absorption of cyclosporine due to the acceleration of stomach emptying (through M receptors)

Increase the toxicity of cyclosporine

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f) Displaced protein binding

It depends on the affinity of the drug to plasma protein.

The free drug is increased by displacement by another drug with higher affinity.

Examples of drugs that are highly bound to plasma proteins: Phenytoin is (90%), Tolbutamide (96%) and warfarin (99%)

Drugs that displace these agents are Aspirin
Sulfonamides
phenylbutazone

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g) Altered metabolism

The effect of one drug on the metabolism of the other is well documented. The liver is the major site of drug metabolism but other organs can also do e.g., WBC, skin, lung and GIT.

CYP450 family is the major metabolizing enzyme in phase I (oxidation process).

Therefore, the effect of drugs on the rate of metabolism of others can involve the following examples.

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E.g., Enzyme induction

A drug may induce the enzyme that is responsible for the metabolism of another drug or even itself, e.g.

Carbamazepine (antiepileptic drug) increases its own metabolism.

Phenytoin increases hepatic metabolism of theophylline leading to decreased levels → Reduces its action

Enzyme induction involves protein synthesis. Therefore, it needs time up to 3 weeks to reach a maximal effect

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Eg. Enzyme inhibition

It is the decrease of the rate of metabolism of a drug by another

This will lead to the increase of the concentration of the target drug, leading to the increase of its toxicity.

Inhibition of the enzyme may be due to the competition on its binding sites, so the onset of action is short, may be within 24 h

When an enzyme inducer (e.g. carbamazepine) is administered with an inhibitor (verapamil) → The effect of the inhibitor will be predominant

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Ex. Erythromycin inhibits metabolism of *astemazole and terfenadine*

↓

Increase the serum concentration of the antihistaminic leading to the life threatening cardiotoxicity

Ex. Omeprazole —Inhibits oxidative metabolism→ of diazepam

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Onset of drug interaction

It may be seconds up to weeks. For example, in case of enzyme induction, it needs weeks for protein synthesis, while enzyme inhibition occurs rapidly.

The onset of action of a drug may be affected by the half lives of the drugs
e.g. cimetidine inhibits metabolism of theophylline.

Cimetidine has a long half life, while theophylline has a short one.

When cimetidine is administered to a patient regimen for theophylline, interaction takes place in one day.

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First-pass metabolism:

Oral administration increases the chance for liver and GIT metabolism of drugs, leading to the loss of a part of the drug dose, decreasing its action. This is more clear when such drug is an enzyme inducer or inhibitor.

Ex. Rifampicin induces the hepatic metabolism of verapamil

Rifampicin lowers serum concentrations of verapamil by increasing its first pass metabolism.

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Renal excretion

•Active tubular secretion

▪ It occurs in the proximal tubules.
The drug combines with a specific protein to pass through the proximal tubules.

▪When a drug has a competitive reactivity to the protein that is responsible for active transport of another drug. This will reduce such a drug excretion increasing its concentration and hence its toxicity.

Ex. Probenecid → Decreases tubular secretion of methotrexate.

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* Passive tubular reabsorption

Excretion and reabsorption of drugs occur in the tubules by passive diffusion, which is regulated by concentration and lipid solubility.

Ionized drugs are reabsorbed lower than non-ionized ones

Ex1. Sodium bicarbonate → Increases lithium clearance and decreases its action

Ex2. Antacids → Increase salicylates clearance and decrease its action

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Pharmacodynamic interaction

It means alteration of the drug action without change in its serum concentration by pharmacokinetic factors.

EX., Propranolol + verapamil ⟶ Synergistic or additive effect

Additive effect : 1 + 1 =2

Synergistic effect : 1 +1 > 2

Potentiation effect : 1 + 0 =2

Antagonism : 1-1 = 0

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Pharmacodynamic interactions

- Receptor interaction
  - Competitive
  - Non-competitive
- Sensitivity of receptor
  - Number of receptor
  - Affinity of receptor
- Alter neurotransmitter release /drug transportation
- Alter water/electrolyte balance

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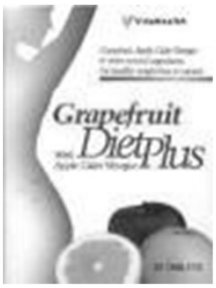
Drug-Food interactions



- Grapefruit juice and Terfenadine
- Grapefruit juice and cyclosporin
- Grapefruit juice and felodipine
- Grapefruit contains : furanocoumarin compounds that can selectively inhibit CYP_3A_4

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Pharmacogenetics / Pharmacogenomics

Pharmacology + Genetics/Genomics

• The study of how individual's genetic inheritance affects the body's response to drugs (efficacy & toxicity)

• The use of genetic content of humans for drug discovery

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Management of an adverse interaction

Dose related events may be managed by changing the dose of the affected medicine.

- E.g. when miconazole oral gel causes an increase in bleeding time of warfarin ⇨⇨ reducing the warfarin dose will bring the bleeding time back into range and reduce the risk of hemorrhage
- It is important to re-titrate the dose of warfarin when the course of miconazole is complete.

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The potential severity of some interactions requires immediate cessation of the combination.

- E.g., the combination of erythromycin and terfenadine can produce high terfenadine level, with the risk of developing torsades de points.

Dose spacing is appropriate for interactions involving the inhibition of absorption in the GI tract .

- E.g., avoiding the binding of ciprofloxacin by ferrous salts

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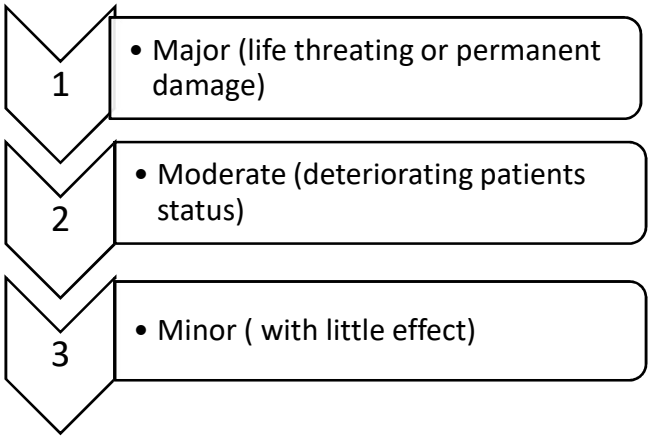
Severity of interactions is classified in 3 categories:



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To What Extent Do Sex/Gender or Race/Ethnicity Matter When Prescribing?

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To What Extent Does Age Matter When Prescribing?

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