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Defination

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

•Concomitant use of several drug in presence of another drug is often necessory for achiving a set of goal or in the case when the patient is suffering from more than one disease.

- **In these cases chance of drug interction coud increase.**

Epidemiology

- In harvard medical practice study of adverse event 8% were consider to be due to drug interaction.
- US community pharmacy study revealed 4.1 % incidence of drug interaction in hospitalised patient.
- Australian study found that 4.4% of all ADR , which resulted in hospital due to interaction.

Risk factors

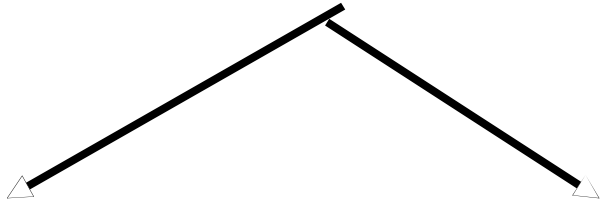
- Poly pharmacy
- Multiple prescribers
- Multiple pharmacies
- Genetic make up
- Specific population like e.g,
  females , elderly, obese, malnouresed , criticaly ill patient , trasplant recipient
- Specific illness E.g. Hepatic disease,
  Renal dysfunction,
- Narrow therapeutic index drugs

  Cyclosporine, Digoxin, Insulin, Lithium , Antidepressant, Warfarin

Outcomes of drug interactions

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

Mechanisms of drug interactions



Pharmacokinetics Pharmacodynamics

Pharmacokinetics involve the effect of a drug on another drug kinetic 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.

Pharmacokinetic interactions

1) Altered GIT absorption.

- **Altered pH**
- **Altered bacterial flora**
- **formation of drug chelates 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 does.

Ex1., antiacids → **Decrease the tablet dissolution of Ketoconazole (acidic)**

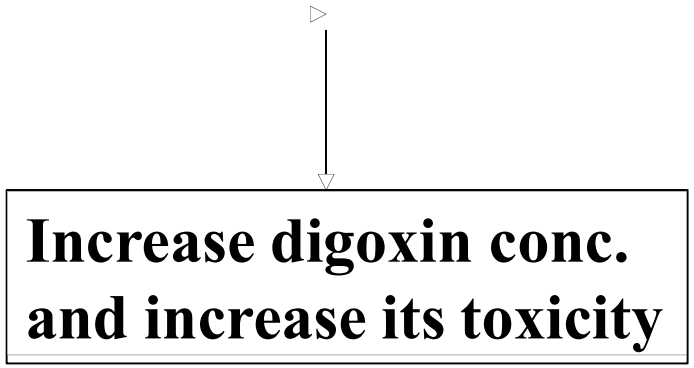
Ex2., H2 antagonists

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

b) ***Altered intestinal bacterial flora ;***

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

Antibiotics kill a large number of the normal flora of the intestine



;c) Complexation or chelation

EX1., Tetracycline interacts with iron preparations

or

Milk (Ca^{2+}) ▷ **Unabsorpable complex**

Ex2., Antacid (aluminum or magnesium) hydroxide

Decrease absorption of ciprofloxacin by 85% due to chelation

d) Drug-induced mucosal damage.

Antineoplastic agents — **e.g., cyclophosphamide, vincristine, procarbazine**

Inhibit absorption of several drugs eg., digoxin

e) Altered motility

Metoclopramide (antiemitic)

Increase absorption of cyclosporine due to the increase of stomach empting time

Increase the toxicity of cyclosporine

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.

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 decrease its level ⟶ Reduces its action and Vice versa

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

Ex.,Erythromycin inhibit metabolism of *astemazole and terfenadine*

Increase the serum conc. of the antihistaminic leading to increasing the life threatening cardiotoxicity

EX., Omeprazole —**Inhibits oxidative metabolism**→ **of diazepam**

•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., cimitidine inhibits metabolism of theophylline.

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

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

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

Variations in drug response and drug toxicity may result from

Variation in drug metabolizing enzymes

- Cytochromes P450
- Thiopurine S-methyltransferase

Variation in drug targets

- Beta2-adrenergic

Variation in drug transporters

- P-glycoprotien

Variation in disease modifying genes

- Apolipoprotein (APOE

DNA polymorphism

- Changes in the DNA sequence such as
  - Nucleotide mutation
    - The most frequent DNA variation found in the human genome is single nucleotide

Management of an adverse interaction

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

- Eg.,when miconazole oral gel causes an increase in bleeding time of warfarin then redusing the warfarin dose will bring the bleeding time back into range and reduse the risk of haemorrhage

- It is important to retitrate the dose of warfarin when the course of miconazole is coumplete.

- θ The potential severity of some interaction require immediate Cessation of the combination.
- Eg,.the combination of erythromycin and terfenadine can produse high terfenadine level with the risk of developing Torsel de Points.
- θ Dose spacing is appropriate for interction involving the inhibition of absorption in the GI tract .
- Eg.,avoidig the binding of ceprofloxacin by ferous salts