• Drug interaction:

- Drug interaction is modification of response to one drug by another when they are administered together.

• Pharmacokinetic interaction:

- Pharmacokinetic interaction is alteration the concentration of a drug at its site of action.
- Pharmacokinetic interaction occurs during the absorbtion, distribution, metabolism or excretion.
- Altered bioavailability (absorption from the site of administration, first-pass metabolism)
- Altered plasma protein binding and tissue distribution
- Altered drug metabolism
- Altered excretion

Types of drug interactions:

- Drug-Drug interaction
- Drug-Food/Nutrition interaction (eg: Milk, Grape fruit juice etc).
- Drug-Herb interaction: Garlic, Ginseng
- Drug-Disease interaction (Hepatic failure, Renal failure, Hypothyroidism, Hyperthyroidism etc).

i- Drug-Drug interaction:

-It occurs when a drug interacts with another drug. This changes the way one or both of the drugs act or causes unexpected side effects.

ii- Drug-Food interaction:

This occurs when the prescription or OTC medication interacts, or interfers with something patient eat or drinks.

iii- Drug-Disease interaction:

It happens when the prescription or OTC medication interacts, or interfers, with a disease or condition that a patient has.

- Mechanisms of drug interactions:
  - a- Pharmacokinetic interactions
    - alterations in absorption
    - alterations in plasma protein binding
    - alterations in Hepatic metabolism
    - alterations in excretion
  - b- Pharmacodynamic interactions
  - c- Pharmaceutical interactions

- Outcomes of drug interactions:
  - Loss of therapeutic effect
  - Toxicity

© Pharmaceutical interactions are a physicochemical interaction that occurs when drugs are mixed in I.V. infusions causing precipitation or inactivation of active principles. Ex: barbiturates interacts with dextran in solutions.

- Unexpected increase in pharmacological activity
- Beneficial effects e.g. additive and potentiation (intended) or antagonism (unintended)
- Chemical or physical interaction (e.g I.V incompatibility in fluid or syringes mixture)

□ Risk factors:

- High Risk Patients:
  - → Elderly, young, very sick, multiple disease
  - → multiple drug therapy
  - → Renal, liver impairment

- High Risk Drugs:
  - → Narrow therapeutic index drugs
  - → Recognised enzyme inhibitors or inducers

□ Pharmacokinetic drug interactions:

1. Alterations in absorption:
   - a- Complexation/chelation
   - b- Altered GI transit
   - c- altered Gastric pH
   - d- alteration in gastrointestinal micro flora

2. Alterations in plasma protein binding

3. Alterations in hepatic metabolism
   - a- induction of metabolism
   - b- inhibition of metabolism

4. Alterations in renal clearance
   - a- increased renal blood flow
   - b- inhibition of active tubular secretion
   - c- alterations in tubular reabsorption

1. Alterations in absorption:

Unstable drugs undergo increased degradation, complexation, failure to undergo dissolution and alteration in GI pH and this will result in alteration in the absorption of a drug because of the interaction with another drug and the plasma level of either drug will be increased or decreased.

a- Complexation:

- Epinephrine causes vasoconstriction and slows the absorption of the local anaesthetics to systemic circulation from the site of injection.

. Complexation / chelation:

Antacids (Mg^{2+}, Al^{3+} ions) make complex with tetracycline, ciprofloxacin which reduces absorption of Tetracycline, ciprofloxacin.

b- Altered GI transit:

- Anticholinergic blocks M_3 receptors and reduces GI motility, this results in delays the absorption of Acetaminophen.
- Metoclopramide increases the GI motility and thus decreases the drug absorption due decreased time of stay of the drug in the GIT.
- Opioids, Atropine, Antidiarrheal drugs, decreased GI motility so the time drug spends in GI tract is more so its gets absorbed more and sometimes may give severe results also.

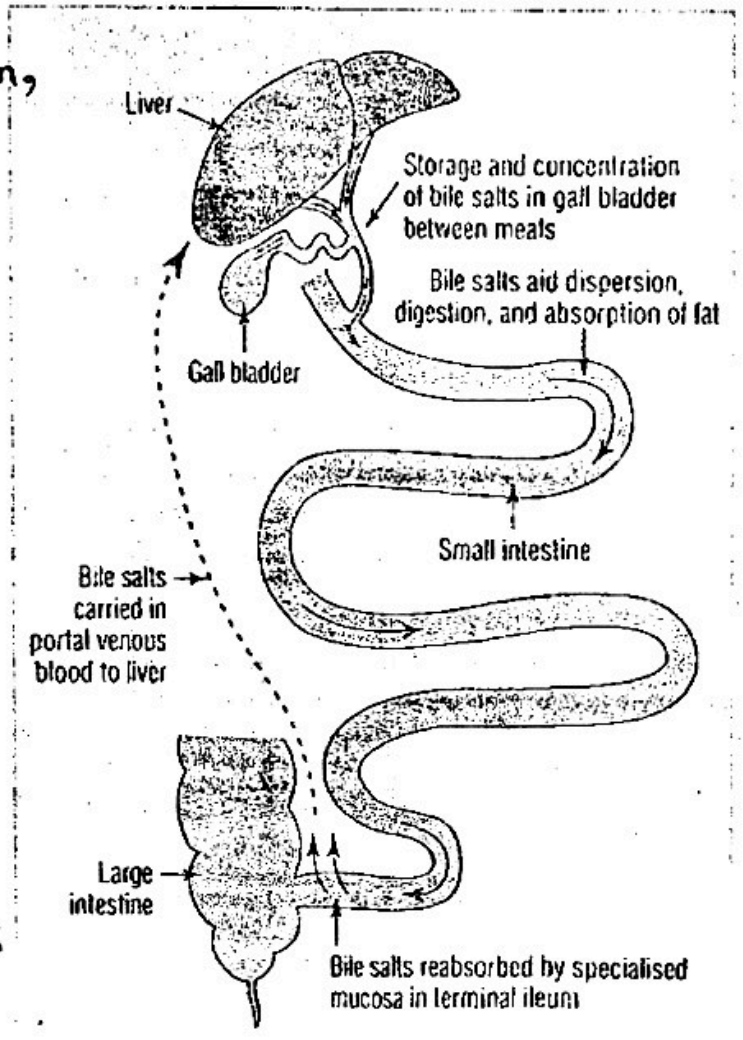
C- Altered gastric pH:

- Acid-blocking drugs, such as H_2-receptor blockers (cimetidine) and proton pump inhibitors (omeprazole), raise the pH of the stomach and decrease absorption of ketoconazole.

- Antacids prevent drug absorption (ex Tetracycline) by the gastric acid neutralization or insoluble drug chelating complex formation.
- Separating administration, (minimum 2 hours gap) help to avoid such interaction effect.

d- Alteration of absorption due to affecting GIT flora:

- Antibiotics (ampicillin, tetracyclines cotrimoxazole) reduce gut bacterial flora that normally deconjugates oral contraceptives and permits their enterohepatic circulation. So this will result in



unwanted pregnancy even after taking an oral contraceptives.

2. Alteration of distribution:

- Displacement from albumin binding sites by acidic drugs

a. Valproic acid displaces phenytoin - increases free fraction of phenytoin → increasing possibility of toxicity (total phenytoin concentration may appear normal - only free fraction has pharmacodynamics effect).

b - Aspirin displaces warfarin - increasing warfarin effect by both increasing free fraction and anti-platelet effect of aspirin.

- Displacement from other binding site:

c: Quinidine displaces digoxin from skeletal

muscles sites by interfering with PGP increasing serum concentration of digoxin-increase risk of toxicity (as well as quinidine interfering with renal clearance of digoxin)

3. Alterations in hepatic metabolism:

a- Induction of metabolism

b- Inhibition of metabolism

C- Genetic polymorphism and drug interaction

a- Induction of hepatic metabolism:

Increases the metabolic rate of second drug.

Eg: Phenobarbital (CYP Enzyme inducer) this increases the metabolism of warfarin and reduces the plasma level of warfarin because of this decreased anticoagulant effect is seen in patients who take phenobarbital with warfarin.

b- Inhibition of hepatic metabolism:

Agents which either compete with a drug for an enzyme system or inhibit enzyme activity and thus produces an increase in duration of drug action.

Eg: Metronidazole (CYP enzyme inhibitor) this inhibits metabolism of warfarin thus elevation of plasma Warfarin levels are seen and raise the anticoagulant effect thus resulting in increased risk of bleeding.

C- Genetic polymorphism and drug interaction:

Within different populations and ethnic grouping there are individuals who may have a deficiency in isoenzymes and so will be unable to metabolize drugs handled by the system.

Eg: Someone who is poor metabolizer through CYP2D6 would be at risk of toxicity when

given a standard dose of flecinide (a CYP2D6 substrate) or would experience therapeutic failure with a drug requiring conversation to a metabolite for activity, such as codeine.

4. Alteration in renal clearance:

- a. Increase in renal blood flow
- b. Inhibition of active tubular secretion
- c. Alterations in tubular reabsorption

a- Increase in renal blood flow:

Hydralazine is a vasodilator which dilates the renal blood vessels and increases the renal blood flow thus raise the clearance of Digoxin.

b- Inhibition of active tubular secretion:

Probenecid inhibits tubular secretion of Penicillin this increases the half-life of Penicillin so it is a single dose therapy and remains in body for longer period.

c- Alterations in tubular reabsorption:

Antacids reduce acid secretion and increases the pH of urine so there is reduced tubular reabsorption of Salicylates (Aspirin) so increased renal clearance of Aspirin is seen.

□ Prevention of drug interaction:

- Monitoring therapy and making adjustments
- Monitoring blood level of some drugs with narrow therapeutic index e.g: digoxin, anticancer agents etc.
- Monitoring some parameters that may help

to characterize the early events of interaction or toxicity e.g. with warfarin administration, it is recommended to monitor the prothrombin time to detect any change in the drug activity.

- Increase the interest of case report studies to report different possibilities of drug interaction.

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b- Pharmacodynamic drug interactions: It includes alteration of pharmacological action of the drug.

i- Antagonistic effect:

- Ex: Atropine and acetylcholine
  → Shows antagonistic effect on the GIT.

ii- Synergistic effect:

- Alcohol and CNS depressants (eg: barbiturates etc) exhibits synergistic effect which results in enhanced CNS depression.