By

Dr/Yasmeen Mohammed Ismail

Associate professor of pharmacology

Faculty of medicine

Hashemite university

Every Drug Interaction is Harmful ????

NO

- Several drug interactions are deliberately employed in therapeutics, e.g.
  - **ACE inhibitors + diuretics** to treat hypertension or
  - **Sulfamethoxazole + Trimethoprim** to treat bacterial infection or
  - **Furosemide + amiloride** to prevent hypokalaemia.

Drug interactions

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

Doctor should elicit a **detailed drug history** of the patient and record all the medication that he/ she is currently on.

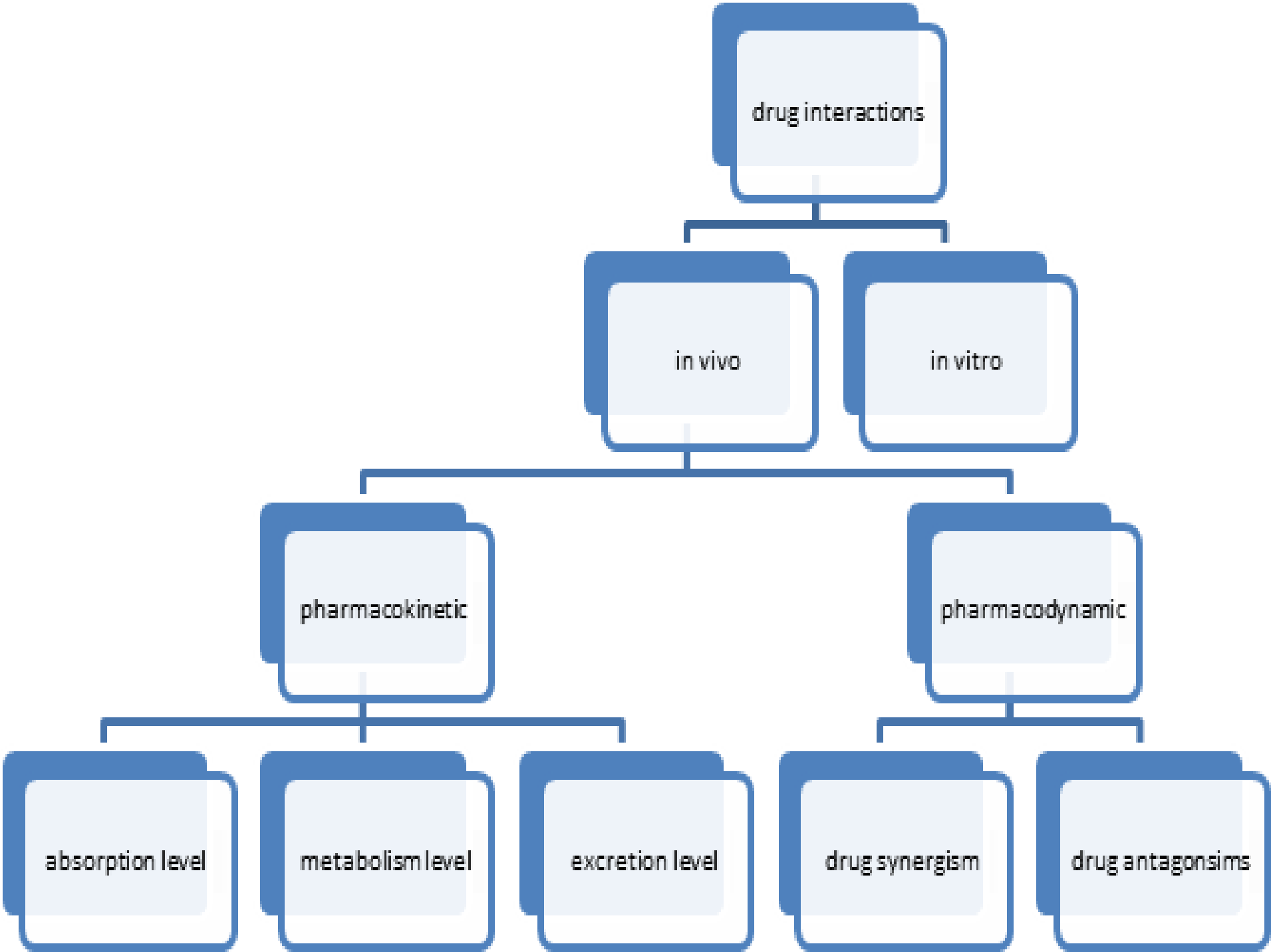
Consequences of drug interactions

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**

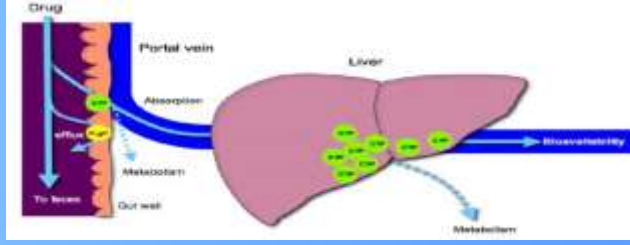
e.g I.V incompatibility in fluid or syringes mixture.

MECHANISM OF DRUG INTERACTIONS

- Drug interactions can be broadly divided into
  - **Pharmaceutical Interaction**
    - During dosage form preparation or at time of administrations.
    - Dissolving the drug in solvent,
    - Mixing drugs in powder, solution or injection forms.
  - **Pharmacokinetic (ADME)**
    - Absorption (Complex or Chelate formation, Altered stomach pH, Ionization, GIT motility, First Pass Metabolism)
    - Distribution (Protein binding)
    - Metabolism (Enzyme induction/inhibition)
    - Excretion (Altered pH, Ionization, Entero-hepatic recirculation)
  - **Pharmacodynamic (At receptor or tissue level)**


drug interactions
in vivo
in vitro
pharmacokinetic
pharmacodynamic
absorption level
metabolism level
excretion level
drug synergism
drug antagonsims

ABSORPTION

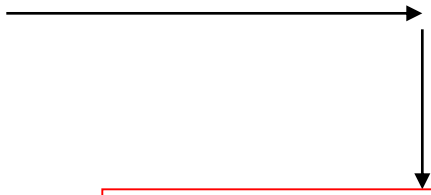


- **Insoluble and poorly absorbed complexes** in the gut
  - Example:-
    - Tetracyclines and calcium/iron salts.
  - Minimized by administering the two drugs with a **gap of 2-3 hours.**
- **Alteration in Entero-hepatic recirculation**
  - Antibiotics like Tetracyclines (Broad Spectrum) markedly **reduce gut flora** that normally deconjugates oral contraceptive steroids secreted in the bile as glucuronides and permits their **Entero-hepatic recirculation**. C**ontraceptive failure** when concurrent use of antibiotics due to lowering of the contraceptive blood levels.

a) ***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



Increase digoxin conc. and increase its toxicity

b) 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**

c) Drug-induced mucosal damage.

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

Inhibit absorption of several drugs eg., digoxin

d) Altered motility

Metoclopramide (antiemitic)

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

Increase the toxicity of cyclosporine

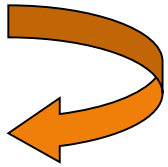
DISTRIBUTION

- **Primarily due to displacement** of one drug from its binding sites on plasma proteins by another drug.
- Drugs highly bound to plasma proteins that have a relatively small volume of distribution like oral anticoagulants, are particularly liable to displacement interactions.
- The drug which is in unbound form is active while portion which is in bound form woks as temporary storage.
- When the drug is displaced by the other drug or chemical the unbound form of the active drug becomes more leading to toxic level in the blood and **presenting as toxicity.**

e) Displaced protein binding

It depends on the affinity of the drug to plasma protein.
The most likely bound drugs is capable to displace others.
The free drug is increased by displacement by another drug with higher affinity.

Phenytoin is a highly bound to plasma protein (90%), and warfarin (99%)



Drugs that displace these agents are **Aspirin**
Sulfonamides

Metabolism

SOME IMPORTANT INHIBITORS OF METABOLISM OF MULTIPLE DRUGS:

- Macrolide antibiotics,
- Azole antifungals,
- Chloramphenicol,
- Omeprazole, SSRIs,
- HIV -protease inhibitors,
- Cimetidine,
- Quinolones (Ciprofloxacin)
- Metronidazole.

f) 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.

Eg., Enzyme inhibition;

- **It is the decrease of the rate of metabolism of a drug by another one .**
- **This will lead to the increase of the concentration of the target drug and leading to the increase of its toxicity .**

- **Inhibition of the enzyme may be due to the competition on its binding sites.**

When an enzyme inducer (e.g. carbamazepine) is administered with an inhibitor (verapamil)

→ **The effect of the inhibitor will be predominant**

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

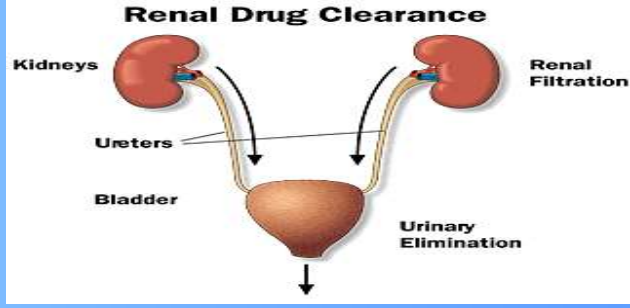
**Increase the serum conc.
of the antihistaminic leading to
increasing the life threatening
cardiotoxicity**

IMPORTANT MICROSOMAL ENZYME INDUCERS (RBC)

- Barbiturates,
- Phenytoin
- Carbamazepine
- Rifampin
- Cigarette smoking
- Chronic alcoholism

- Contraceptive failure and loss of therapeutic effect of many other drugs have occurred due to enzyme induction (Patient taking Rifampicin)
- Toxic dose of paracetamol is lower in chronic alcoholics and in those on enzyme inducing medication, because one of the metabolites of paracetamol is responsible for its overdose hepatotoxicity

EXCRETION



- Interaction involving excretion are important mostly in case of **drugs actively secreted by tubular transport** mechanisms. The alteration of urinary pH alters the process of reabsorption of the drug leading to increase or decrease excretion.
- Probenecid inhibits tubular secretion of penicillins and cephalosporins .

- Alkalization of urine increases the excretion of barbiturates

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 con. and hence its toxicity.

EX., Probenecid ….. → Decreases tubular secretion of methotrexate.

PHARMACODYNAMIC INTERACTIONS

- These interactions derive from modification of the action of one drug at the target site by another drug, **independent of a change in its concentration**.

- This may result in an **enhanced response (synergism)**, an **attenuated response (antagonism)** or an abnormal response.

PHARMACODYNAMIC INTERACTIONS

- **1-Addition or summation** : the resultant action is the algebric sum of the individual actions of the two drugs combined. In such case only half the normal dose of each drug is required to produce the desired effect. e.g. histamine and ACH on B.P.
- **2-Synergism:** both drugs are biologically active, but when combined, the net effect is more than the sum of their individual effects e.g. sulphonamide and trimethoprim.
- **3-Potentiation:** this occurs when one drug has no apparent action on one system but increase the effect of another drug on that system. e.g. barbiturates potentiate the analgesic effect of salicylates.

PHARMACODYNAMIC INTERACTIONS

- **4-Antagonism:** this occurs when drugs with opposing actions are given simultaneously it may be:
- Physiological antagonism: drugs with opposing actions on the same physiological system e.g. histamine and adrenaline.
- Chemical antagonism : one drug reacts chemically with an active drug to form an inactive compound e.g. heparin and protamine sulphate.
- Pharmacological antagonism:
- Competitive antagonism:
- Reversible e.g. atropine and Ach.
- Irreversible e.g. noradrenaline and phenoxybenzamine .
- Non competitive antagonism e.g. acetyl choline and hexamethonium or D-tubocurarine on autonomic ganglia.

- Excessive fall in BP and fainting due to concurrent administration of α1 adrenergic blockers, vasodilators, ACE inhibitors.

- Increased risk of bleeding due to concurrent use of antiplatelet drugs (aspirin, clopidogrel) with anticoagulants (warfarin).

DRUG INTERACTIONS BEFORE ADMINISTRATION

- Certain drugs react with each other and get inactivated **if their solutions are mixed before administration.**

- In practice situations, these in vitro interactions occur when injectable drugs are mixed in the same syringe or infusion bottle.

Some examples are:

- Penicillin G or ampicillin mixed with gentamicin or another aminoglycoside antibiotic.

- Heparin when mixed with penicillin gentamicin/hydrocortisone.

“ It is prudent to consider the possibility of drug interaction whenever two or more drugs are prescribed to a patient, or any drug is added to what the patient is already taking”

DRUG INTERACTIONS MAY BE ANTAGONISTIC

PRIMARY DRUG	INTERACTS WITH	RESULTING IN
SALBUTAMOL	-PROPRANOLOL	ANTIAGONISM OF BRONCHODILATION
ANTIHYPER-TENSIVES	-NSAIDS	ANTAGONISM OF HYPOTENSIVE EFFECT (Na^+ - RETENTION)
	- SELECTIVE COX 2 INHIBITORS	NO SIGNIFICANT EFFECTS ON Na
SULPHONAMIDES	-L. ANAETHETICS -(PABA)	ANTAGONISM OF ANTIMICROBIAL EFFECTS
WARFARIN	OESTROGENS	WARFARIN EFFECT ANTAGONIZED BY INCREASED CLOTTING FACTOR SYNTHESIS
OPIOIDS	NALOXONE	ANTAGONISM

Thanks