

Drug interactions

Definition;

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

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

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graph TD; A[Mechanisms of drug interactions] --> B[Pharmacokinetics]; A --> C[Pharmacodynamics]
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Pharmacokinetics

Pharmacodynamics

Pharmacokinetics involve the effect of a drug on another from the point of view 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.

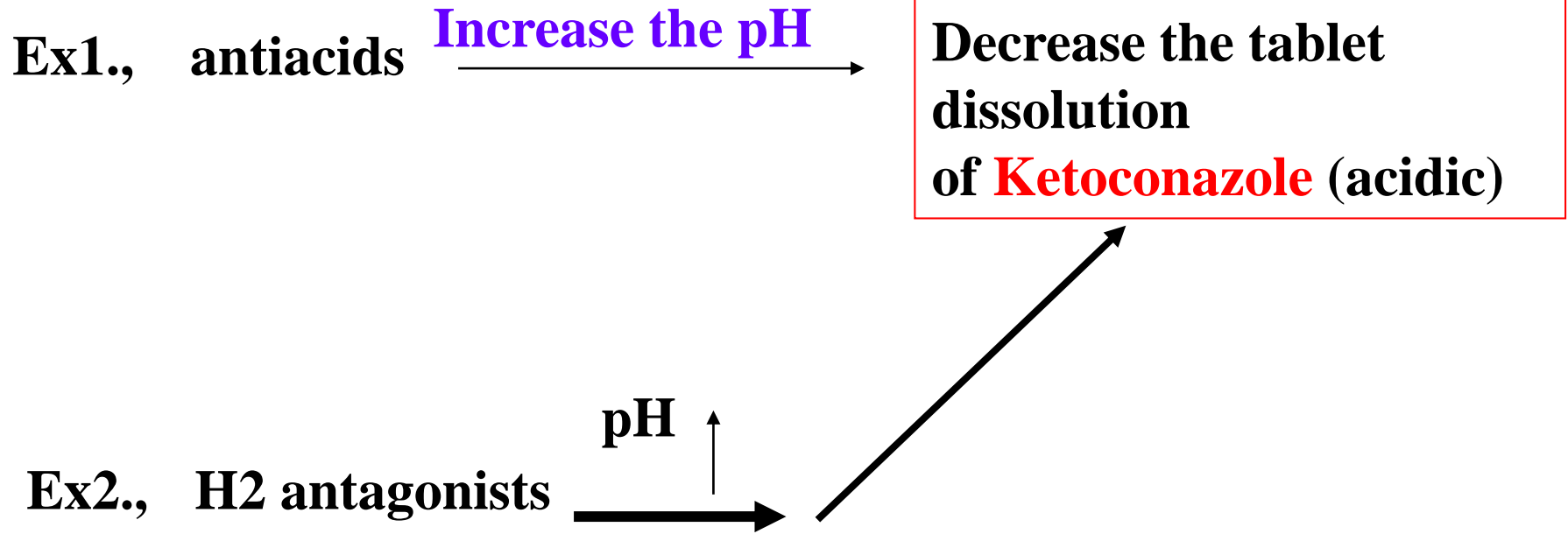
Pharmacokinetic interactions

1) Altered GIT absorption.

- Altered pH, Altered bacterial flora, formation of drug chelates or complexes, drug induced mucosal damage and 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.

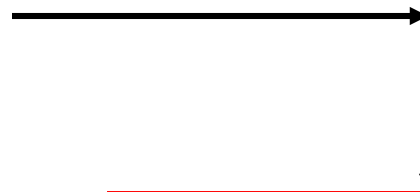


Therefore, these drugs must be separated by at least 2h in the time of administration of both .

b) Altered intestinal bacterial flora ;

EX., In 10% of patients receive **digoxin**.....40% or more of the administered dose is metabolized by the intestinal flora

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



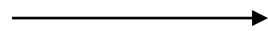
**Increase digoxin conc.
and increase its toxicity**

c) Complexation or chelation;

EX1., Tetracycline interacts with **iron** preparations

OR

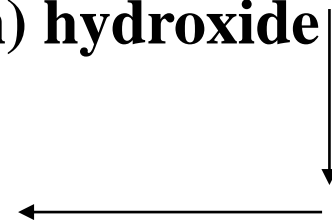
Milk (Ca²⁺)



Unabsorbable complex

EX2., Antacid (aluminum or magnesium) hydroxide

**Decrease absorption of
ciprofloxacin by 85%
due to chelation**



d) Drug-induced mucosal damage.

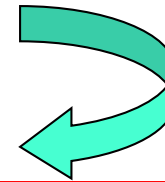
Antineoplastic agents e.g., cyclophosphamide
vincristine
procarbazine



**Inhibit absorption
of several drugs
eg., digoxin**

e) Altered motility

Metoclopramide (antiemetic)



**Increase the toxicity
of cyclosporine**

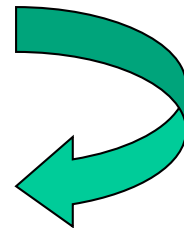


**Increase absorption of cyclosporine due
to the increase of stomach emptying time**

F) 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%),
Tolbutamide (96%), and warfarin (99%)



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

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.

EX1., 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

EX2., 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 , so the onset of action is short may be within 24h.

N.B; 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 astemizole and terfenadine



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

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

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., Rifampin lowers serum con. of verapamil level by increase its first pass . Also, Rifampin induces the hepatic metabolism of verapamil

Renal excretion:

- **Active tubular secretion;**

**It occurs in the proximal tubules (a portion of renal 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.**

*** Passive tubular reabsorption;**

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

N.B., Ionized drugs are reabsorbed lower than non-ionized ones

Ex1., Sod.bicarb.



**Increases lithium clearance
and decreases its action**

Ex2., Antacids



**Increases salicylates
clearance and decreases its
action**

Pharmacodynamic interactions;

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

EX., Propranolol + verapamil \longrightarrow **Synergistic or additive effect**

Synergism means $=1+1=3$

Additive means $=1+1=2$

Potentiation means $=1+0=2$

Antagonism means $1+1=0$ or 0.5

On the other hand

Effect at the receptor site

- Antiadrenergic**
- anticholinergic**

* Risk factors:

- 1) *High risk drugs*; these are the drugs that show a narrow therapeutic index e.g., **corticosteroids**, **rifampin**, **oral contraceptives**, **quinidine**, **lidoquine** and **theophyllin**
- 2) *High risk patients*; these are the groups of patients that should be treated with caution due to a specific health condition e.g., **pregnant women**, **malignant cases**, **diabetic patients**, **patients with liver or kidney disorders** **asthmatic patients** and **cardiac disorders**.

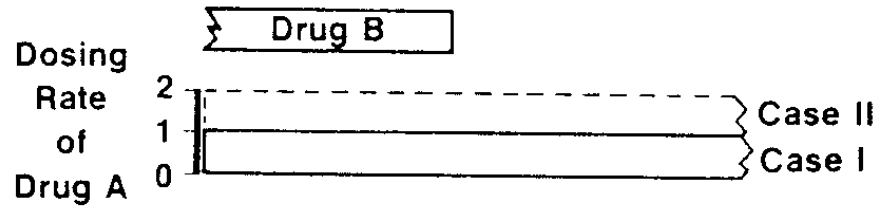
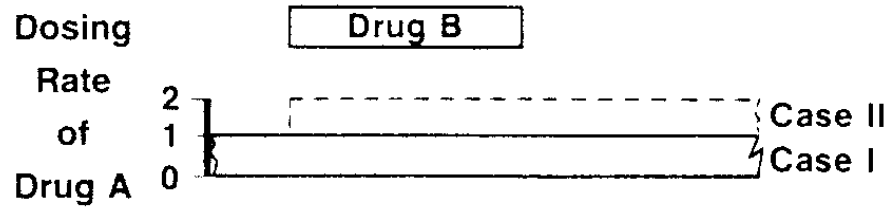
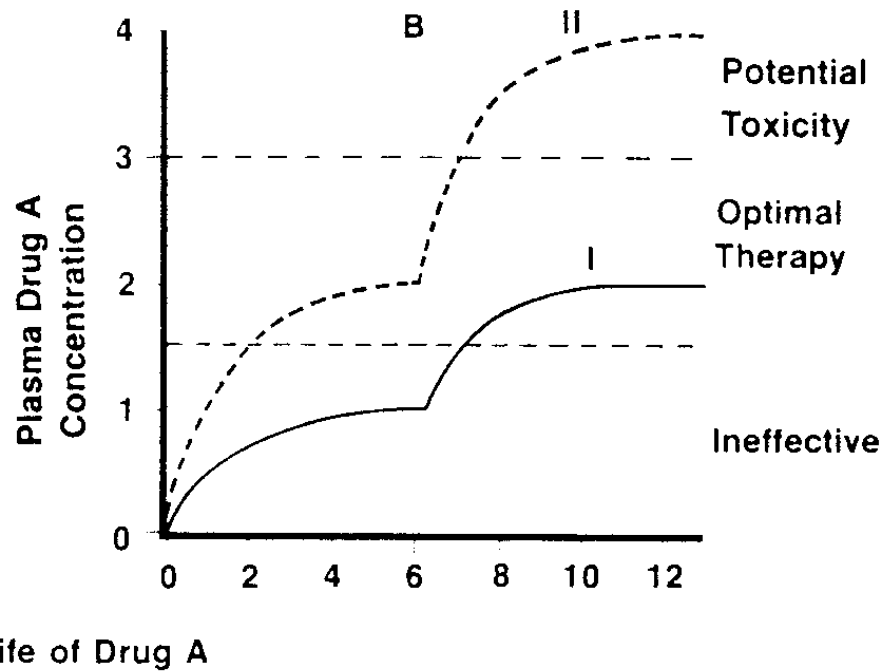
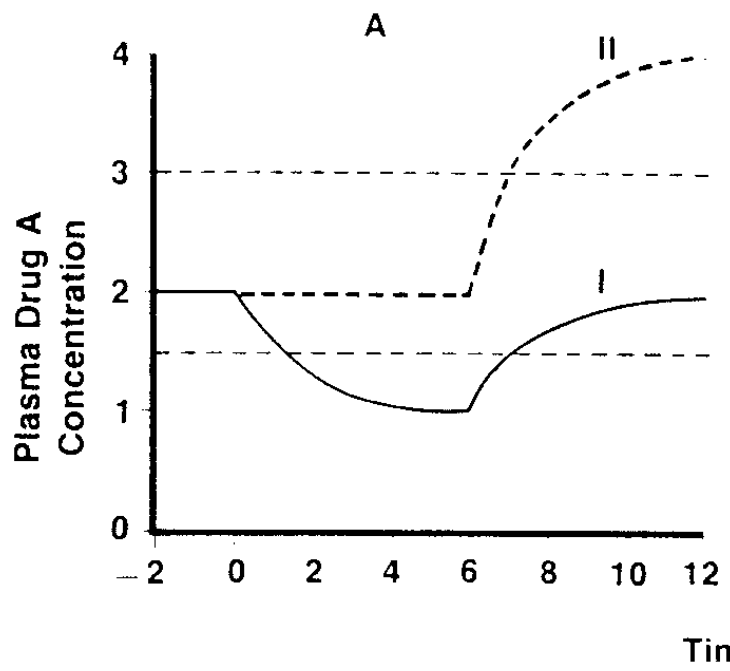
•Onset of drug interaction

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.



III. ALTERATIONS IN DRUG METABOLISM

A. Induction

$$E_H = \frac{f_{ub} CL_{u\text{int}}}{Q_H + f_{ub} CL_{u\text{int}}}$$

$$CL_H = \frac{Q_H f_{ub} CL_{u\text{int}}}{Q_H + f_{ub} CL_{u\text{int}}}$$

$$AUC_o = \frac{F \times \text{Dose}}{f_{ub} CL_{u\text{int}}}$$

$$F = \frac{Q_H}{Q_H + f_{ub} CL_{u\text{int}}}$$

* Prevention of drug interaction

- 1) **Monitoring therapy and making adjustments**
- 2) **Monitoring blood level of some drugs with narrow therapeutic index e.g., digoxin, anticancer agents...etc**
- 3) **Monitoring some parameters that may help to characterize the the early events of interaction or toxicity e.g., with **warffarin** administration, it is recommended to monitor the **prothrombin time** to detect any change in the drug activity.**
- 4) **Increase the interest of **case report** studies to report different possibilities of drug interaction**

