# Drug Interactions

# Definition

- An interaction occurs when the effects of one drug are changed by the presence of another drug, food, drink or by some environmental chemical agent.
- Drug-drug interactions can take place whenever a patient takes two or more drugs.
- Some interactions are desired but some interactions not.
- Some advers interactions are well known, and therefore avoidable. Many others are unpredictable

Drug interactions occur when patients frequently take more than one drug.

They may take multiple drugs because of:

- ✓ a single disorder
- ✓ multiple disorders
- ✓ OTC (over the counter)

They may take caffein, nicotine, alcohol, herbal medicine and drugs concurrently.

# RISK FACTORS FOR DRUG INTERACTIONS

## High Risk Patients

- ✓ Elderly, young, multiple disease
- ✓ Multiple drug therapy
- ✓ Renal, liver impairment

## High Risk Drugs

- ✓ Narrow therapeutic index drugs
- ✓ Recognised enzyme inhibitors or inducers

# Some drugs with a low therapeutic index

| | |
|---|---|
| Lithium | Digoxin |
| Carbamazepine | Cyclosporin |
| Phenytoin | Phenobarbitone |
| Theophylline (Aminophylline) | Warfarin |

## Consequents of Drug-Drug Interactions

**I. Drug A may intensify the effects of Drug B** ,which is termed Potentiative interactions, may be benefical or detrimental

**II. Drug A may reduce the effects of drug B** which is termed Inhibitory interactions, may be benefical or detrimental

**III. Combination may produce a new response not seen with either drug alone**

# Mechanisms of Drug Interactions

drug interactions can be related to the following mechanisms:

- ✓ Pharmaceutical interactions
- ✓ Pharmacokinetic interactions
- ✓ Pharmacodynamic interactions

# PHARMACEUTICAL INTERACTIONS

Interactions that occur prior to systemic administration.

For example:

incompatibility between two drugs mixed in an IV fluid. These interactions can be physical (e.g. with a visible precipitate) or chemical with no visible sign of a problem

# PHARMACOKINETIC INTERACTIONS

✓ One drug alters the rate or extent of absorption, distribution, metabolism or excretion of another drug.

✓ A change in blood concentration causes a change in the drug's effect.

**(the so-calledADME interactions).**

# Pharmacokinetic interactions

## Alterations in absorption

Drug absorbsion may be enhanced or reduced by drug interaction

**Complexation or chelation;**

Impact: tetracycline complexes with divalent cations forming an insoluble complex

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

**or**

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

**Ex2., Antacid (calcium,aluminum or magnesium) hydroxide**

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

# COMPOUNDS DEMONSTRATED TO BIND WITH IRON

ACETAMINOPHEN
AMPICILLIN
CAPTOPRIL
CARBIDOPA
CIPROFLOXACIN
ETHAMBUTOL
FOLIC ACID
INDOMETHACIN
LEVODOPA
METHYLDOPA
MINOXIDIL
NALIDIXI ACID
NORFLOXACIN
PENICILLAMINE
RIFAMPIN
TETRACYCLINE
THYROXINE
SALICYLIC ACID

## Effects of changes in gastro intestinal pH:

example:
ketoconazole + antacids
proton pump inhibitors
H2 receptor blokers

Impact: reduced ketoconazole absorption due to reduced dissolution.

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

## 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**

**EX., Antibiotics with Oral Contraceptives**

## Change in gastrointestinal motility:

✓ Laxatives can reduce absorbtion of other drugs by increasing their passage through the intestine

✓ Drugs that depress peristalsis (eg, morphine, atropin ) prolong drug transit time in the intestine, thereby increasing the time for absorption.

# Drug-Induced Constipation

| Therapeutic Category | Examples |
|---|---|
| Analgesics | Opioids (morphine), NSAIDs (ibuprofen) |
| Anticholinergics | TCA, antipsychotics (haloperidol), antiparkinsonian agents (benztropine), antihistamines (H1; diphenhydramine), antispasmodics (dicyclomine) |
| Cation-containing agents | Aluminum (antacids, sucralfate), calcium (antacids, supplements), bismuth, iron supplements, lithium |
| Chemotherapy | Vinca alkaloids (vincristine), alkylating agents (cyclophosphamide) |
| Antihypertensives | CCB (verapamil, nifedipine), diuretics (furosemide), centrally-acting (clonidine), antiarrhythmics (amiodarone), beta blockers (atenolol) |
| Bile acid sequestrants | Colestyramine, colestipol |
| $5HT_3$-receptor antagonists | Ondansetron |
| Laxatives | Chronic abuse |

Branch RL, Butt TF. Drug-induced constipation. **Adverse Drug Reaction Bulletin 2009;257.**

# Drug-Induced Constipation

| Therapeutic Category | Examples |
|---|---|
| Excess fiber | Dietary or prescribed |
| Other antidepressants | Monoamine amine oxidase inhibitors |
| Other antiparkinsonian agents | Dopamine agonists |
| Other antispasmodics | Peppermint oil |
| Anticonvulsants | Carbamazepine |
| Miscellaneous | Barium sulphate, octreotide, polystyrene resins, oral contraceptives |
| | Vitamin C tablets, $^{131}$I thyroid ablation, erythropoietin, baclofen |
| | Pamidronate, alendronic acid, PPI and $H_2$ antagonists |

Branch RL, Butt TF. Drug-induced constipation**. Adverse Drug Reaction Bulletin 2009;257.**

# Pharmacokinetic interactions

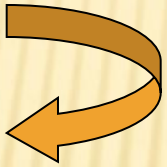
## Drug distribution interactions

**Protein binding interaction:**
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**

**Example: phenytoin + valproic acid**

# Pharmacokinetic interactions

## Drug Metabolism Interactions

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.

# CYP 450 SYSTEM DEFINITIONS

- Substrate:
  Drug is metabolised by the enzyme system

- Inducer:
  Drug that will increase the synthesis of CYP450 enzymes

- Inhibitor
  Drug that will decrease the metabolism of a substrate

# ENZYME INDUCERS EXAMPLES

- Rifampicin
- Phenobarbitone
- Carbamazepine
- Cigarette smoke
- Phenytoin
- Barbiturates
- St. John’s wort
- Omeprazole
- Isoniazid
- Ethanol
- Pomegrenate juice

# ENZYME INHIBITORS EXAMPLES

- Cimetidine
- Erythromycin
- Ketoconazole
- Amiodarone
- Grapefruit juice

## 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 → Reduces its action**
**Leading to decrease its level**

**Enzyme induction:**
Example:
Phenobarbital+warfarin

Impact: phenobarbital increases the metabolism of warfarin, resulting in reduced anticoagulation.,

**Enzyme inhibition:**
Example:
Cimetidine+theophylline
Impact: cimetidine reduces the clearance of theophylline, causing an increase in adverse effects

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

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

# 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.**

# Inhibition of Active Tubular Secretion

**Example: probenecid + penicillin**

**Impact: probenecid prolongs the half-life of penicillin, allowing single dose therapy**

**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.**

**Ionized drugs are reabsorbed lower than non-ionized ones**

# Drug Excretion Interactions

**Changes in urinary ph:**

Thus, pH changes increasing the amount in the Ionised form (alkaline urine for acidic drugs, acid for bases) increase the loss of the drug,

**Ex1., Sod.bicarb.** → **Increases lithium clearance and decreases its action**

**Ex2., Sodiumbicarbonate Antacids** → **Increases salicylates and quinidine clearance and decreases its action**

## Changes in renal blood flow:

The flow of blood through the kidney is partially controlled by the production of renal vasodilatory prostaglandins.

If the synthesis of these prostaglandins is inhibited ( e.g. by indometacin ) , the renal excretion of lithium is reduced and its serum levels rise as a result.

## Increase in Renal Blood Flow

**Example: hydralazine + digoxin**

Impact: hydralazine increases the renal clearance of digoxin

# FACTORS WHICH ALTER HEPATIC BLOOD FLOW

***Increased Flow***

- Glucagon
- Isoproterenol
- Phentolamine
- Phenobarbital
- PGE
- Supine posture
- High-protein meal
- Viral hepatitis

***Decreased Flow***

- Propranolol
- Norepinephrine
- Anesthetics
- Labetalol
- Upright posture
- Hypovolemia
- CHF
- cirrhosis

# PHARMACODYNAMIC DRUG INTERACTIONS

One drug causes a change in patient response to another drug without altering that drug's pharmacokinetics

# Additive Effects (summation)

Additive effects are the simplest case of combined drug action: the effects of the drugs simply summate. If a dose of Drug-A that produces 50% of the maximum response is given concurrently with a dose of Drug-B that produces 50% of the maximum response, then the maximum response is produced. If a dose of Drug-A that produces 25% of the maximum response is combined with a dose of Drug-B that produces 50% of the maximum response, then 75% of the maximum response is produced. This simple algebraic summation of effects is expected for full agonists.

Combined effect of two drugs = sum of effects

(drugs given separately)

Drugs acting on same receptors or having same mechanisms

e.g. combination of antacids, chemotherapeutic agents, diuretics, NSAIDs;

**Summation** $\Rightarrow$ 1+1 = 2

# Synergism

Synergism is said to occur when the combined effects of two agonists exceed that predicted by the individual actions of these compounds (i.e., the resulting effect is more than additive).

Drug A + Drug B = action ⇑ ⇒ **synergistic**

- Combined effects of two drugs = > sum of effects (drugs given separately)
- 1+1=>2

E.g., sulphamethoxazole & trimethoprim = bacteriostatic

**Co-trimaxozole**= bactericidal

**Antihypertensive** (captopril & diuretic); tyramine + MAOI

# Potentiation

The term *potentiation* is used differently by various investigators. Some pharmacologists use *potentiation* interchangably with *synergism* to describe a greater than additive effect (e.g., Tallarida & Jacob, 1979). Others (e.g., Palfai & Jankiewicz, 1997) use *potentiation* to describe what might better be termed *response enabling*. In this situation the effect is only present when two compounds act concurrently. One drug may be inactive (given alone)

1+0>1, ex. Acetaminophen+caffeine

## Additive or synergistic interactions and combined toxicity

Example:
Alcohol depresses the CNS and, if taken in moderate amounts with normal therapeutic doses of any of a large number of drugs (e.g. sedatives, tranquillisers,etc.) ,may cause excessive drowsiness

Eg increase toxicity of digoxin caused by diuretic induced hypokalaemia

# Antagonism

Interaction of two or more agents that in combination have an overall effect which is less than the sum of their individual effects

- Chemical antagonism
- Physiological antagonism
- Pharmacological antagonism

**Antagonistic or opposing interactions**:

Example:
the oral anticoagulants can prolong the blood clotting time by competitively inhibiting the effects of dietary vitamin K.

Beta-blocker given with beta-agonist

## Combined Toxicity

If drug A and drug B are both toxic to the same organ, the taking them together will cause more injury than if they were not combined.

Eg. Isoniazid and rifampin are hepatotoxic

## Food-Drug Interactions

Food can cause clinically important changes in drug absorbtion which can happen on GI absorbtion or motility.

Therefore, the certain drugs should not be taken with  certain food.

Food frequently decreases the *rate* of drug absorbtion and occasionally decreases the *extent* of drug absorbtion.

## Food-Drug Interactions

If Iron tablets are taken with food, the absorbtion of Iron is decreased thereby results in low therapeutic effect.

**To administer a drug on an empty stomach means to administer it either 1 hour before meal or 2 hours after**

**Tetracycline interacts with $Ca^{2+}$ - containing foods**

↓

**Insoluble and Unabsorpable complex**

↓

Absorbtion is reduced and

Antibacterial effects may be lost

**Drug -grapefruit interactions**:

Grapefruit juice is an inhibitor of CYP3A4 in liver and intestinal wall.

Grapefruit juice can inhibit the metabolism of certain drugs, thereby raising blood levels.

Amiodarone
Calcium channel blockers (felodipine, verapamil)
HMG-CoA Reductase inhibitors (Atorvastatin)
Benzodiazepines
Buspirone
Carbamazepine

## Food may also (rarely) have direct impact on drug action

✓ Foods rich in Vitamin K (broccoli, Brussels sprouts, cabbage) can reduce the effets of warfarin because warfarin acts by inhibiting Vit K- dependent clotting factors.

# Drug-food interactions sometimes increase toxicity

✓ Monoamine oxidase inhibitors and foods rich in tyramine (aged cheeses, yeast extracts, Chianti wine)

✓ Combination of MAO with these food can rise blood pressure

✓ Patients must be warned about the consequents of this interactions.

# Alcohol-drug Interactions

**Alcohol + Barbiturates**
Alcohol and the barbiturates are CNS depressants, which together can have additive and possibly synergistic effects.

**Mechanisms**
Both alcohol and the barbiturates are CNS depressants, and simple additive CNS depression provides part of the effects.

Acute alcohol ingestion may inhibit the liver Enzymes concerned with the metabolism of the barbiturates.

# Herbal-drug Interactions

Herbal products can interact with conventional drugs thereby reduces beneficial responses or increases toxicity

Garlic is used for lowering blood cholesterol, triglyceride levels and blood pressure.

Garlic may increase bleeding,especially in patients already taking certain anti-clotting medications.

Ginger is used for reducing nausea, vomiting and vertigo

Ginger may increase bleeding, especially in patients already taking certain anti-clotting medications.

St.John's Wort is used for mild to moderate depression or anxiety and sleep disorders.

St.John's Wort may induce drug-metabolizing enzymes and thereby reduce blood levels of many drugs.