DRUG INTERACTIONS

DEFINITION

Drug interaction occurs when the pharmacological activity of one drug is altered by the concomitant use of another drug or by the presence of some other substance.

The Drug whose Activity is affected by such an Interaction is called as "**Object drug**." The agent which precipitates such an interaction is referred to as the "**Precipitant**".

Types of drug Interactions

1. Drug-drug interactions.
2. Drug-food interactions.
3. Chemical-drug interactions.
4. Drug-laboratory test interactions.
5. Drug-disease interactions.

The Net effect of a Drug Interaction is:

- Generally quantitative i.e. increased or decreased effect.
- Seldom qualitative i.e. Rapid or slower effect.
- Precipitation of newer or increased adverse effect.

Drug interactions are:

Mostly undesirable

Rarely desirable (beneficial): for eg., enhancement of activity of penicillin's when administered with probenecid.

Factors contributing to drug interactions:

1. Multiple drug therapy.
2. Multiple prescribers.
3. Multiple pharmacological effects of drug.
4. Multiple diseases/predisposing illness.
5. Poor patient compliance.
6. Advancing age of patient.
7. Drug-related factors.

Mechanisms of drug interactions:

The three mechanisms by which an interaction can develop are-

1. Pharmaceutical interactions.
2. Pharmacokinetic interactions.
3. Pharmacodynamic interactions.

Pharmaceutical interactions:

Also called **incompatibility.** It is a physicochemical interaction that occurs when drugs are mixed in i.v . Infusions causing precipitation or inactivation of active principles. Example: Ampicillin, Chlorpromazine & barbiturates interact with dextran in solutions and are broken down or from chemical compounds.

Pharmacokinetic Interactions:

"These interactions are those in which ADME properties of the object drug are altered by the precipitant and hence such interactions are also called as ADME interactions ". The resultant effect is altered plasma concentration of the object drug. These are classified as:

1. Absorption interactions
2. Distribution interactions
3. Metabolism interactions
4. Excretion interactions.

Absorption interactions

Are those where the absorption of the object drug is altered. The net effect of such an interaction is:

- Faster or slower drug absorption.
- More, or, less complete drug absorption.

Major mechanisms of absorption interactions are:

l. Complexation and adsorption.
2. Alteration in GI pH.
3. Alteration in gut motility.
4. Inhibition of GI enzymes.
5. Alteration of GI micro flora.
6. Malabsorption syndrome.

ABSRPTION INTERACTIONS		
Object drug	**Precipitant**	**Influence on object drug**
Complexation & adsorption		
Ciprofloxacin, Pencillamine	Antacids, food & minerals supplements containing Al, Mg, Fe, Zn & Ca^{2+} ions	Formation of poorly soluble and absorbable complex with such heavy metal ions.

Alteration of GI pH		
Sulphonamides, Aspirin, Ferrous sulphate	Antacids, Sodium bicarbonate, Calcium carbonate	Enhanced dissolution and absorption rate. Decreased dissolution and enhance absorption
ALTERATION OF GUT MOTILITY		
Aspirin, Diazepam, Levodopa, Mexiletine	Metoclopramide	Rapid gastric emptying, increased rate of absorption.
Levodopa, Mexiletine, Lithium carbonate	anti-cholinergic,delayed gastric emptying	decreased rate of absorption
Alteration of GI micro flor a		
Digoxin	anti-biotic	Increased bioavailability due to destruction of bacterial flora that inactivates digoxin in lower intestine.
Malabsorption syndrome		
Vitamin A,B12, digoxin	Neomycin	Inhibition of absorption due to malabsorption

DISTRIBUTION INTERACTIONS: Are those where the distribution pattern of the object drug is altered: The major mechanism for distribution interaction is alteration in protein-drug binding.

Competitive displacement interactions		
Object drug	Precipitant Drug	Influence on object drug
Displaced drug Displacer		
Anti-coagulants	Phenylbutazone, Chloral hydrate	Increased clotting time. Increased risk of hemorrhage.
Tolbutamide	Sulphonamides	Increased hypoglycemic effect

METABOLISM INTERACTIONS: Are those where the metabolism of the object drug is altered. Mechanisms of metabolism interactions include:

l. Enzyme induction: Increased rate of metabolism.
2. Enzyme inhibition: Decreased rate of metabolism. It is the most significant interaction in comparison to other interactions and can be fatal.

Metabolism interactions		
Object drug	Precipitant	Influence on object drug
Enzyme Induction		
Corticosteroids, Oral contraceptives, Coumarins, phenytoin	Barbiturates	Decreased plasma levels; decreased efficacy of object drugs
Oral contraceptives, Oral hypoglycemic	rifampicin	decreased plasma levels
Enzyme Inhibition		
Tyramine rich food	MAO inhibitors	Enhanced absorption of unmetabolized tyramine
Coumarins	metronidazole phenyl butazone	increased anti-coagulant activity

EXCRETION INTERACTIONS: Are these where the excretion pattern of the object drug is altered.

Excretion Interactions		
Object drug	Precipitant	Influence on object drug
Changes in active tubular secretion		
Penicillin, cephalosporin, and nalidixic acid	Probenicid	Elevated plasma levels of acidic drugs
Changes in urine pH		
Amphetamine	Antacids, Thiazides, Acetazolamide	Increased passive reabsorption of basic drugs. Increased risk of toxicity
Changes in renal blood flow		
Lithium Bicarbonate	NSAIDS	Decreased renal clearance of lithium. Risk of toxicity

Major mechanisms of excretion interactions are:

- Alteration in renal blood flow
- Alteration of urine PH
- Competition for active secretions
- Forced diuresis

PHARMACODYNAMIC INTERACTIONS:

In Pharmacodynamic interaction the activity of the object drug at its site of action is altered by the precipitant. Such interactions may be direct or indirect.

These are of two types

l . Direct pharmacodynamics interactions.
2. Indirect pharmacodynamics interactions.

Direct pharmacodynamics interactions:

In which drugs having similar or opposing pharmacological effects are used concurrently. The three consequences of direct interactions are

1. Antagonism.
2. Addition or summation.
3. Synergism or potentiation.

Antagonism: The interacting drugs have opposing actions Example: Acetylcholine and noradrenaline have opposing effects on heart rate.

Addition or summation: The interacting drugs have similar actions and the resultant effect is the sum of individual drug responses. Example: CNS depressants like sedatives and hypnotics etc Synergism or potentiation: It is an enhancement of action of one drug by another Example: Alcohol enhances the analgesics activity of aspirin.

Indirect pharmacodynamics interaction:

In which both the object and the precipitant drugs have unrelated effects. But the latter in some way alerts the effects but latter in some way alerts the effects of the former.

Example: salicylates decrease the ability of the platelets to aggregate thus impairing the

Homeostasis if warfarin induced bleeding occurs.

Reducing the risk of drug interactions:

- Identify the patient's risk factors.
- Take through drug history.
- Be knowledge about the actions of the drugs being used.
- Consider therapeutic alternatives.
- Avoid complex therapeutic regiments when possible.
- Educate the patient.
- Monitor therapy.

CONSEQUENCES OF DRUG INTERACTIONS:

The consequences of drug interactions may be:

Major: Life threatening.

Moderate: Deterioration of patients' status.

Minor: Little effect.

Influence of smoking on drug interactions:

Smoking increases the activity of drug metabolizing enzymes in the liver, with the result that certain therapeutic agents. Example: Diazepam, propoxyphene, theophylline, olanzapine are metabolized more rapidly, and their effect is decreased

Influence of alcohol on drug interaction:

Chronic use of alcohol beverages may increases the rate of metabolism of drugs such as warfarin and phenytoin, probably by increasing the activity of hepatic enzymes.

- Acute use of alcohol by non-alcoholic individuals may cause an inhibition of hepatic enzymes.
- Use of alcoholic beverages with sedatives and other depressants drugs could result in an excessive depressant response.

Influence of Food on Drug Interaction:

Food affects the rate and extent of absorption of drugs from the GI tract. Example: Many anti biotic should be given at least 1hr before or 2hr after meals to achieve Optimal absorption.

- The type of food may be important with regard to the absorption of concurrently administered Drugs. Example: Dietary items such as milk and other dairy products that contain calcium may decrease. The absorption of tetracycline and flour quinolone derivatives.
- Diet also may influence urinary pH values.

Table 01 - Examples of drugs with his appointment, the possible changes in laboratory tests and its mechanism. (Part 2)

Medicine	Indication	Laboratory	Changes	Mechanism of action
Enalapril	Antihypertensive	Potassium	Increase	Hypoaldosteronism Decreased renal excretion
Ethambutol	Antitubercular agent	Uric acid	Increase	
Furosemida	Antihypertensive	Magnesium	Decrease	Diuretic action
	Diuretic	Potassium	Decrease	Diuretic action
		Sodium	Decrease	Diuretic action
		Ammonia	Increase	
		Amylase	Increase	
		Uric acid	Increase	
Gentamicin	Antibiotic	Magnesium	Decrease	Urinary loss of potassium, magnesium
		Potassium	Decrease	Renal tubular toxicity
		Protein	Increase	
		Urea	Increase	
		AST	Increase	
		Alkaline phosphatase	Increase	
		Creatinine	Increase	
		Sodium	Decrease	
		Calcium	Decrease	
Glibenclamide	Antidiabetic oral	Prothrombin time	Decrease	
		Sodium	Decrease	
Indapamide	Antihypertensive diuretic	Glucose	Increase	
		Uric acid	Increase	
		Chlorine	Decrease	
		Magnesium	Decrease	
		Potassium	Decrease	
		Sodium	Decrease	
Insulin	Antidiabetic	Potassium	Decrease	
		Catecholamine	Increase	
Levothyroxine	Repositor hormone	Glucose	Increase	
		Calcium	Increase	Promoter mobilization
Mannitol	Laxative	Sodium	Decrease	Diuretic effect
Metformin	Antidiabetic oral	Bicarbonate	Decrease	Acidosis
		Iron	Decrease	Bad absorption of vit. B12
Metronidazole	Antifungal	Glucose	Decrease	
Omeprazole	Antiulcerous	Gastrin	False	
Oxacillin	Antibiotic		False (+)	
		Urinary protein	False (+)	
Penicillin	Antibiotic	Albumin	Decrease	
		Urinary protein	Increase	
		Protein	False (+)	
		Urinary protein	False (+)	
		Direct Coombs	Positive	
Piroxicam	Anti-inflammatory	Chlorine	Increase	
		Sodium	Increase	
Reserpine	Antihypertensive	Catecholamine	Decrease	
Risperidone	Antipsychotic	Potassium	Decrease	Hypokalemia
		Sodium	Decrease	Hyponatremia
Spironolactone	Anti -hypertensive diuretic	Potassium	Increase	
		Digoxin	False ?	
		Sodium	Decrease	Diuretic Effect
Sulfamethoxazole	Antibiotic	Protein	Increase	
		Uric acid	Increase	
Vancomycin	Antibiotic	Urea	Increase	Nephrotoxicity
Valsartan	Antihypertensive	Potassium	Increase	

Source: Barros; Barros[10]; Santos; Torriani[3]

Table 01 - Examples of drugs with his appointment, the possible changes in laboratory tests and its mechanism. (Part 1)

Medicine	Indication	Laboratory	Changes	Mechanism of action
Paracetamol	Antipyretic	Alkaline phosphatase	Increase	High dosage associated with ???
	Analgesic1	Bilirubin	Increase	Hepatic injury due to high dosage
		Glucose	Decrease	
		Chlorine	Increase	
		Uric acid	Increase	
		Sodium	Decrease	
		Bicarbonate	Decrease	
		Calcium	Decrease	
		Chlorine	Increase	
Acetazolamide	Ocular hypotensive; Diuretic	Bilirubin	Increase	
		Uric acid	Increase	
		Glucose	Increase	
		Ammonia	Increase	
		Alkaline phosphatase	Increase	
		Sodium	Decrease	
		Bicarbonate	Decrease	
		Calcium	Decrease	
Acyclovir	Initial treatment and prophylactic treatment of mucosal and cutaneous herpes infection	Urea	Increase	Leukopenia
		Alkaline phosphatase	Increase	
		Bilirubin	Increase	
		Creatinina	Increase	Reversible renal failure
Amitriptyline	Antidepressant	Alkaline phosphatase	Increase	
Ascorbic acid	Food supplement	Bilirrubin	Increase	
		Urinary glucose	False (+)	Reagent cupric sulfate
			False (-)	Glucose oxidase method
Baclofen	Relaxing skeletal muscle	Glucose	Increase	
		Ammonia	Increase	
		Bilirubin	Decrease	
Corticosteroids	Anti-inflammatory steroid	Chlorine	Increase	Salt-water Retention
Dexamethasone		Glucose	Increase	Gluconeogenesis
Hydrocortisone		Phosphor	Decrease	Glucose spending
Betamethasone		Potassium	Decrease	Renal loss
Methylprednisolone		Sodium	Increase	Salt-water Retention
Prednisone		Amylase	Increase	
Prednisolone		Cholesterol	Increase	
		Protein	Increase	
		Thyroxine	Decrease	
Buspirone	Anxiolytic	AST	Increase	
		ALT	Increase	
Calcitriol	Food supplement	Cholesterol	Increase	
		Magnesium	Increase	
		Urea	Increase	
Captopril	Antihypertensive	Direct coombs	Increase	
		Cholesterol	Decrease	
		Urinary acetone	False (+)	Use of the reagent based on sodium nitroprusside
		Potassium	Increase	Hypoaldosteronism
		Urea	Increase	
		Creatinine	Increase	
Cephalexin	Antibiotic	Urinary glucose	False (+)	Reagent cupric sulfate
Chlorpropamide oral	Antidiabetic	Direct coombs	Positive	
		Cholesterol	Decrease	
		Sodium	Decrease	Uncontrolled increase secretion of ADH5
Cimetidine	Antiulceroso	AST	Increase	
		ALT	Increase	
Cyclosporine	Immunosuppressant	Potassium	Increase	Decreased excretion
Diazepam	Anxiolytic	Urinary glucose	False (-)	Method of glucose oxidase
Diltiazem	Antianginal	Bilirubin	Increase	
		Uric acid	Increase	Leads to the appearance of the drop