Drug Interactions

Defination:

The pharmacological result, either desireable or undesireable, of drugs interacting with themselves or with other drugs, with endogenous chemical agents, with components of diet, or with chemicals used in or resulting from diagnostic tests.

Outcomes of Drug Interactions:

- Loss of therapeutic effect
- Toxicity
- Unexpected increase in pharmacological activity
- Beneficial effects e.g additive & potentiation (intended)
- or antagonism (unintended).
- Chemical or physical interaction

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

Risk Factors for Drug Interactions:

- **<u>High Risk Patients</u>**
  - Elderly, young, very sick, multiple disease
  - Multiple drug therapy (Polypharmacy)
  - Renal, liver impairment
- **<u>High Risk Drugs</u>**
  - Narrow therapeutic index drugs *(e.g., corticosteroids , rifampin, oral contraceptives, quindine, lidoquine)*
  - Recognised enzyme inhibitors or inducers

Types of Drug Interactions:

- Drug-Drug Interactions
- Drug-Food Interactions
- Drug-Chemical Interactions
- Drug-Disease Interactions
- Drug-Herbal Interactions
- Drug-Laboratory Interactions

Drug-Drug Interactions:

The modulation of pharmacological activity of one drug by the prior or concomitant administration of another drug.

A drug-drug interaction may be defined as the pharmacological or clinical response to the administration of a drug combination different from that anticipated from the known effects of the two agents when given alone. The clinical result of the drug-drug interaction may manifest as

- Antagonism (i.e., 1+1<2)
- Synergism (i.e., 1+1> 2)
- Idiosyncratic (i.e., a response unexpected from the known effects of either agents)

A drug interaction pair typically consists of the:

- Object drug
- Precipitant drug

The activity of the "object" drug is altered; the drug causing this change is the "precipitant" drug.

Significance:

When evaluating any potential drug interaction, a primary concern is the clinical relevance or significance of the interaction. Significance relates to the type and magnitude of the effect and, subsequently, to the necessity of monitoring the patient or altering therapy to avoid potentially adverse consequences.

The primary factor that define clinical significance include;
SIGNIFICANCE RATE; the time of ONSET of the effects of the interactions;
The potential SEVERITY of the interaction;
And the DOCUMENTATION level assigned to each drug interaction.

Significance Rating:

A number 1 through 5 will be assigned to each interaction monograph, based on the editorial Group's assessment of interaction's severity and Documentation (defined below).

1 is severe and well documented interaction.

5 is an interaction of no more than unlikely or possible documentation.

The formula for these number ratings is given in following table:

Significance Rating	Severity	Documentation
1	Major	Suspected or >
2	Moderate	Suspected or <
3	Minor	Suspected or <
4	Major/Moderate	Possible
5	Minor	Possible
	Any	Unlikely

Onset:

How rapidly the clinical effects of an interaction can occur determines the urgency with which preventive measures should be instituted to avoid the consequences of the interaction. Two levels of onset are used:

Rapid: The effects will be evident within 24 hours of administration of the interacting drug. The immediate action is necessary to avoid the effects of the interaction.

Delayed: The effect will not be evident until the interacting drug is administered for a period of days or weeks. Immediate action is not required.

Severity:
The potential severity of the interaction is particularly important in assessing the risk vs benefit of therapeutic alternatives. With appropriate dosage adjustments or modification of administration schedule, the negative effects of most interactions can be avoided. Three degrees of severity are defined:

Major: the effects are potentially life threatening or capable of causing permanent damage.

Moderate: the effects may cause deterioration in a patient's clinical status. Additional treatment, hospitalization, or an extended hospital stay may be necessary.

Minor: The effects are usually mild; consequences may be bothersome or unnoticeable but should not significantly affect the therapeutic outcome. Additional treatment is usually not required.

Documentation:

Documentation determines the degree of confidence that an interaction can cause an altered clinical response. This scale represents the Editorial Group's Evaluation of the quality and clinical relevance of primary literature supporting the occurrence of an interaction. However, multiple factors can influence whether even a well-documented interaction occurs in a particular patient. The documentation does not address the incidence or frequency of the interaction. It is also independent of the potential severity of the effects of the interaction.

The following guidelines are used to establish the five documentation levels:

Established: Proven to occur in well-controlled studies.

- An altered pharmacological effect has been demonstrated in well-controlled human studies….or…
- A pharmacokinetic interaction has been demonstrated in well-controlled human studies. An altered pharmacological response is expected based on magnitude of the kinetic effect; clinical observations support the occurrence of the interaction.

Probable: Very likely but not proven clinically.

- A pharmacokinetic interaction has been demonstrated in well-controlled studies. Based on the magnitude of kinetic changes and the known plasma level-reponse relationship of the affected drug, an altered pharmacological response will probably occur…or….
- When controlled human experimentation is impractical, well-designed studies animal experiments confirm an interaction that is suggested by multiple case reports or uncontrolled studies.

Suspected: May occur; some good data; needs more study.

- A pharmacokinetic interaction has been demonstrated in well controlled studies. Although an altered pharmacological response might be expected to occur based on the magnitude of kinetic changes, no confirm conclusion can be drawn because a plasma level-response relationship has not been established for the affected drug….or….
- An altered pharmacological response has been reported in multiple case reports or repeated uncontrolled clinical studies.

Possible: Could occur, but data very limited.

- Although a pharmacokinetic interaction has been demonstrated, the kinetic changes are of such magnitude that it is not possible to predict if an altered response will occur….or….
- An altered pharmacological response is suggested by limited data.

Unlikely: Doubtful; no good evidence of an altered clinical effects.

- A pharmacokinetic interaction has been demonstrated; however, based on the magnitude of kinetic change, a pharmacological alteration in unlikely….or…

- In spite of reports of an interaction, well-controlled studies refute the existence of a clinically relevant interaction.

Drug interactions assigned documentation levels of "Established," "Probable" or "Suspected" are considered to be reasonably well substantiated and have a significance rating of "1," "2," "3". It is the opinion of the Editorial Group that these interactions have a reasonable probability of occurring. Drug interaction assigned a significance rating of "4," or "5" have a documentation level of "possible" or "unlikely" and are not substantiated. Because there is insufficient evidence of supporting the existence of a clinically relevant interaction, prospective screening is probably not warranted. If an unanticipated effect occurs, the information in these monographs will be useful in reviewing what is known about these potential interactions.

CAUSES OF DRUG INTEARCTION:

1. Physician and pharmacist unawareness.
2. Self medication.
3. Poly pharmacy.
4. Inappropriate dose.
5. Individual Variations (genetics).

SITES FOR DRUGS INTERACTIONS:

1. Plasma: Drug competes with protein binding site.
2. Liver: inhibition or induction of metabolizing enzymes.
3. Intestine: Drug interacting with absorption and distribution.
4. Receptor site: Drug competition.
5. Excretory system: Drug interacting with excretion.
6. In Vitro: Excipients interacting with drug formulation.

TYPES OF DRUG INTERACTIONS:

1. DRUG-DRUG INTERACTION.
2. DRUG-HERBAL INTERACTION.
3. DRUG-FOOD INTERACTION.
4. PHARMACOGENETIC INTERACTION.
5. CHEMICAL-DRUG INTERACTION.
6. DRUG-LAB INTERACTION.

1. DRUG-DRUG INTERACTION:

"The change in the pharmacological response of a drug by the action of another drug". (change in pharmacokinetic or pharmacodynamics or both)

FOR EXAMPLE:

a. Antacid decreases gut absorption due to reaction with tetracycline.

b. When diuretics are given concurrently in the treatment of CHF. Diuretics can cause potassium depletion that if uncorrected could become excessive and lead to an increased action of digoxin and adverse events.

c. Erythromycin inhibit the metabolism of carbamazepine and increases the risk of toxicity.

2. DRUG-HERBAL INTERACTION:

"The interaction of herbs and herbal products with drug, when administered both concomitantly, and changes the pharmacological response of drug".

FOR EXAMPLE:

a. St. john's wort, a flowering plant, increases the metabolism of cyclosporine and oral contraceptives and decreases efficacy.

b. Kava causes additive sedation when given concomitantly with sedative hypnotics.

c. Garlic, gingko interact with anti-coagulants and antiplatelet agents and increases risk of bleeding.

3. DRUG-food INTERACTION:

"The interaction of food or certain dietary items influence the activity of a drug".

FOR EXAMPLE:

a. Griseofulvin given with fatty food to increase absorption.

b. Grapefruit juice interacts with increasing the amount of benzodiazepines, vincristine, atorvastatin, clarithromycin in blood.

c. Dietary fiber, especially insoluble fiber such as wheat bran can slow down the absorption of digoxin and lessen its effects.

4. PHARMACOGENETIC INTERACTION:

"Pharmacogenetic interaction occurs when the pharmacokinetic effect of drug is effected by genetic polymorphism in effecting processes".

FOR EXAMPLE:

a. Isoniazid may inhibit the metabolism of phenytoin, and adverse drug reaction occurs and this isoniazid related toxicity with phenytoin according to study are seen in slow acetylators.

b. Plasma pseudo cholinesterase deficiency, about 1/1500 people, decreased succinylcholine inactivation. With conventional succinylcholine doses, prolonged paralysis of respiratory muscles and sometimes persistant apnea requiring mechanical ventilation until the drug can eliminated by alternate pathway.

c. G6PD dehydrogenase 10% of black males higher prevalence in people of Mediterranean descent, with use of oxidant drugs such as certain antimalarials (e.g chloroquine, primaquine) and increases the risk of hemolytic anemia.

5. CHEMICAL-DRUG INTERACTION:

"The interaction of drug with chemical substances, to change the activity of drug".

FOR EXAMPLE:

a. When patient is on antihistamine (chlorpheniramine maleate), also consume alcohol, leads to increase sedative effects.

b. In combination with acute alcohol consumption, some antibiotics (furoxone, metronidazole, griseofulvin) may cause nausea, vomiting, headache and possibly convulsions.

c. Acute alcohol consumption enhances the warfarin availability.

6. DRUG-LABORATORY INTERACTION:

"It is the interaction of drug with the laboratory test and alter the laboratory tests results".

FOR EXAMPLE:

a. Cimetidine raises LFT. (ALT, AST)

b. When prednisolone is given with theophylline, cortisol and digoxin there is a false increase in levels of all these drugs.

c. Prednisolone also shows the false –ive skin allergy test.

CLASSIFICATION OF DRUG INTERACTION:

Drug interactions are divided into:

1. INVIVO DRUG INTERACTION.

2. INVITRO DRUG INTERACTION.

1. IN-VIVO DRUG INTERACTION:

Divided into:

A). Pharmacokinetic Drug interaction or Biopharmaceutical interaction.

B.) Pharmacodynamic Drug interaction.

C.) Pharmacogenetic Drug interaction.

IN-VITRO DRUG INTERACTIONS;

The drug interactions occurring outside the body are of following types:

1. **DRUG EXCIPIENT INTERACTIONS:**
   Excipients facilitate formulations of active drug substance to a stable, uniform and acceptable medicine with required bioavailability, Sometimes excipient may cause interaction with drug.

	DRUG AFFECTED	EXCIPIENT	EFFECT OF INTERACTION
1	Phenytoin	Lactose	Increase dissolution and bioavailability
2	Rifampicin	Bentonide	Decreased efficacy of Anti TB action.

2. **I/V FLUID INTERACTIONS WITH ADDITIVES:**
   Addition of different drugs or solution to I/V fluids or drug may modify the effect of I/V fluids.

	I/V FLUID OR DRUG AFFECTED	INTERACTING ADDITIVE
1	Verapamil HCl	In dextrose or saline infusion color may change or precipitation occurs.
2	Fat emulsion	Addition of electrolyte may cause cracking or aggregation.
3	NaCl I/V Dextrose	Amphotericin-B, Dobutamine HCl may cause color change and precipitation.
4	Lignocaine	Amphotericin and Ampicillin.

3. **DRUG CONTAINER INTERACTIONS:**
   These are of two types:
   a. Plastic container interactions.
   b. Glass container interactions.

PLASTIC CONTAINER INTERACTIONS:

Sorption of drug to I/V container made of PVC leads to significant loss of drug e.g diazepam, Glycerol trinitrite, lsosorbide dinitrite, lignocaine, Warfarin, Vitamin A, insulin, theopentine sodium.

PREVENTION:

i. Loss of drug through sorption can be minimized by using short length of small diameter tubing inert plastic e.g I/V infusion sets made of inert plastic material like butadiene Styrene.

ii. Generally any gas e.g. cyclopropane is incompatible with plastic or rubber tubing.
iii. Volatile anesthetics significantly absorbed by rubber and partially solublize in PVC plastics.
iv. Paraldehyde has solvent action on rubber.

GLASS CONTAINER INTERACTIONS:

i. Chloroquine binds strongly to soda glass leading to large reduction in drug concentration. Clinical test indicate that Plasmodium falciparum is resistant to Chloroquine due to sorption of chloroquine to glass container which change the pka of the resultant solution.
ii. Alkalinity of glass may also modify the effect of some acidic drugs.

Mechanism of Drug Interactions:

Drug interactions are classified into two types depending upon the Mechanism of interaction.

1. Pharmacokinetic Drug Interactions
2. Pharmacodynamic Drug Interactions

Pharmacokinetic Drug Interactions:

Pharmacokinetic interactions are those in which one drug alters the rate or the extent of absorption, distribution or elimination (metabolism or excretion) of another drug. This is most commonly measured by a change in one or more kinetic parameters, such as maximum serum concentration, area under the concentration-time curve, half life, and total amount of drug excreted in urine, etc.

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

Altered Absorption:

The absorption of orally administered drugs from GI tract is a complex process and is subject to many sources of variability. One cause of the variation in the response to orally administered drugs is the concomitant administration of drugs that are capable of affecting the absorption process.

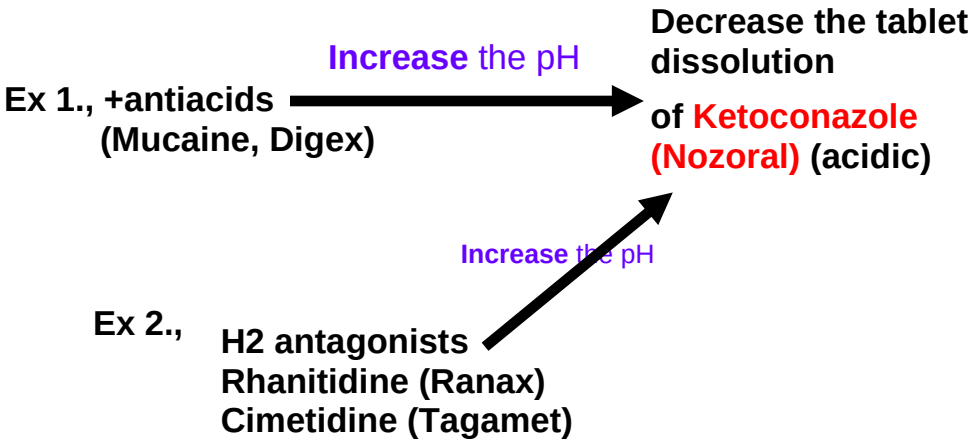
There are several mechanisms by which one drug may affect the GI absorption of another;

1. Altered pH
2. Altered bacterial flora
3. Formation of drug chelates or complexes
4. Altered GIT motility

1) Altered pH:

Many drugs are weak acids or weak bases and it is their non-ionized form that can transverse the intestinal membrane into the bloodstream. Thus, drugs that are weak acids theoretically would be better present in its more lipid soluble form. The apposite would be true for weak bases. On the other hand, weak acids do not dissolve as well in an acidic medium, and dissolution is a prerequisite to absorption. Moreover, some drugs manifest pH-dependent degradation to inactive products in the GI tract. In addition, the pH of GI tract may affect GI motility as well as other determinants of drug absorption. Thus, the effect of GI pH on drug absorption can be complex, and it often is difficult to predict what effect pH changes will have on the absorption of a given drug.

The importance of pH on drug dissolution can be seen with ketoconazole which requires an acidic medium in order to dissolve adequately for absorption. Thus, the administration of H2- antagonists or antacids, by increasing gastric pH, may markedly reduce the bioavailability of ketoconazole.



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

2) Altered bacterial flora:

Although bacterial flora is present in large numbers in the large bowl, the stomach, duodenum, jejunum, and upper ileum normally contain relatively few bacteria. Thus, drugs that are well absorbed from the small bowel would have little opportunity to be effected by the changes in GI tract flora. Accordingly, drugs that have been shown to be affected by the bacteria in the intestine tend to be those that are incompletely absorbed in the small intestine or those drugs that are secreted back into the intestine after absorption.

EX., In 10% 0f patients receive digoxin…..40% or more of the administered dose is metabolized by the intestinal flora

Antibiotics (erythromycin, Erythrocin) kill a large number of the normal flora of the intestine

Increase digoxin (Lanoxin) conc. and increase its toxicity

3) Formation of drug chelates or complexes:

Agents are capable of forming insoluble complexes or chelates with the drugs leads to decreased absorption of those drugs.

EX1., Tetracycline interacts with iron preparations or

Milk (Ca2+)  **Unabsorpable complex**

Ex2., Antacid (aluminum or magnesium) hydroxide *(MUCAINE, DIGEX)*

Decrease absorption of Ciprofloxacin *(CIPROXIN)* by 85%due to chelation

4) Altered Motility:

Although the absorption rate of many drugs is likely to be affected by alteration in GI motility, there are relatively few examples of changes in the extent of absorption as a result of this mechanism. One situation where changes in extent of absorption may occur

due to effects on GI motility involves drugs that do not dissolve well in GI fluids. In this situation, slowing GI motility may allow more of the drug to dissolve before reaching the absorption site in the small bowl, thus increasing bioavailability. Conversely, speeding GI motility would have the opposite effect on dissolution, thus reducing the extent of absorption. For example, the bioavailability of one digoxin tablet formulation was enhanced by the treatment with propantheline and reduced by the treatment with metclopramide.
Another situation in which alteration of GI motility may affect the extent of absorption involves the drugs that are degraded to inactive products in the stomach. Here, slowing of gastric emptying would tend to allow more intact drug to the intestine for absorption. A possible example of this phenomenon involves levodopa, where speeding gastric emptying with an antacid was associated with enhanced levodopa absorption.

Altered Distribution

1. Protein-binding Displacement

1) <u>Protein binding Displacement:</u>

The binding of drugs to the proteins can change as result of disease, accumulation of endogenous compounds, or concomitant drug administration. The outcome and clinical significance of drug interactions that are mediated by displacement of drug from protein-binding sites are frequently misunderstood and often result in an over estimation of their importance.

Phenytoin *(DILANTIN)* is a highly bound to plasma protein (90%),Tolbutamide *(ORINASE)* (96%), and warfarin *(COUMADIN)*(99%)

Drugs that displace these agents are Aspirin *(DISPRIN)*
Sulfonamides
Phenylbutazone *(BUTAZOLIDINE)*

Beta blocker such as propranolol *(INDERAL)*^{R} may displace a beta agonist, such as terbutaline *(<u>Brethine</u>, <u>Bricanyl</u>, <u>Brethaire</u>)*, from beta$_2$ receptors and increase the likelihood of precipitating an asthmatic attack.

Altered Metabolism:

To produce a systemic effect most drugs must reach receptor sites, which means they must be able top cross the lipid plasma membranes. Therefore, most drugs must be somewhat lipid soluble. The role of metabolism is to change these active lipid soluble compounds to inactive water soluble substances that can be efficiently excreted. Enzymes, many of which are concentrated in the smooth surface of the endothelium of liver sells, 1st oxidized, demethylate, hydrolyze etc. the drug. Then large water soluble molecule e.g. Glucoronic acid or sulphate are attached to the during to form the usually inactive water soluble metabolite.

An important group of hepatic microsomal enzymes are "mixed functions oxidases", factorized by the CY P-450 isoenzymes. They are responsible for the oxidation of many drugs, such as warfrin, phenytoin etc. These mixed function oxidases are the enzymes most commonly reported to be "induced" by the other drugs.

Based on the current classification scheme, the entire group of cytochromes-P 450 enzymes represent a superfamily (CYP) consisting of families designated by an Arabic or roman numeral (eg, CYP2 OR CYPII) and subfamilies designated by a capital letter (eg. CYP2D), according to the similarity of aminoacid sequence of the encoded P450 isozyme protein. The individual gene is designated by an Arabic numeral (e.g. CYP2D6 or CYPIID6). Of the CYP gene that have been identified , families CYP1, CYP2 and CYP3 appear to be involved primarily with drug metabolism; however, the specific CYP isozyme responsible for the oxidation of the most drugs is unknown. A number of drugs have been identified as substrates, Inhibitors, and Inducers of metabolism by CYP enzymes.

Enzyme Induction:

Enzyme Induction is a stimulated increase in enzyme activity. The increase in enzyme activity is caused by an increase in the amount of enzyme present; therefore, because synthesis of enzymes requires time, enzyme induction is delayed.

Approximately 400drugs and chemicals (e.g., insecticide, chemicals in cigarette smoke or certain vegetables) are enzyme inducers in animals. Clinically Phenobarbital, phenyotin, carbmazepine and rifampin are the enzymes inducers of great interest. For drugs whose metabolism is stimulated by enzyme inducer, the dose may need to be increased upon initiation of inducer therapy and decreased when the enzyme is discontinued. Drugs whose action has been clinically altered by enzyme inducers are warfrin, oracontraceptivs and cyclosporine etc.

Enzyme inhibition

Enzyme inhibition of drug-metabolizing enzymes generally decreases the rate of metabolisms of the object drug. This is likely to result in increased serum concentration

of the object drug and, if the drug has a narrow therapeutic index, potential drug toxicity. Drug metabolizing enzymes may become saturated when at least two drugs using the same metabolic pathways are administrated, resulting in a decrease in the metabolism of 1 or the both drugs (e.g., fluoxetine-imipramine).

On the other hand, certain drugs may bind to an enzyme system and may inhibit the enzyme function (e.g., cimitidine binds to a certain isoenzyme of cytochorme P450),. Cimitidine and erythromycine is the enzyme inhibitors most frequently reported in clinically important interactions. Other enzyme inhibitors include isoniazid, verapamil, choleamphenicol and ketocoazole etc.

Alteration in Renal Clearance:

1. **Altered Glomerular Filtration**
2. **Altered Active Tubular Secretion**
3. **Alterations in Tubular Reabsorption**

Altered Glomerular Filtration:

Perhaps the most commonly observed drug interactions involving glomerular filtration result from the combination of nephrotoxic drug with a second drug that is primarily eliminated from the body by glomerular filtration. This is an indirect interaction and often is not considered a drug-drug interaction because it originates with drug induced renal toxicity.

For example, a patient stabilized on Digoxin *(LANOXIN)* is treated with an aminoglycoside antibiotic (ie. Amikacin *(GRASIL)*^{R}). if the patient develops the aminoglycosides induced renal failure, Digoxin toxicity may develop if the digoxin dose is not appropriately adjusted.

Excess antihypertensive therapy can result in hypotension and reduced renal blood flow. Under these circumstances, drugs principally eliminated by Glomerular filtration will accumulate and potentially result in drug toxicity. The clinical significance of these interactions depends upon the degree and duration of the reduction in Glomerular filtration and the characteristics of the accumulating drug. The appropriate dose adjustment of drug eliminated by the glomerular filtration will avoid drug accumulation secondary to drug induced nephrotoxicity.

Altered Tubular Secretion:

Many drugs, in addition to undergoing glomerular filtration, are subject to tubular secretion. Numerous acidic and basic drugs are susceptible to tubular secretion and to the drug interactions resulting from altered secretion. Inhibition of tubular secretion can result in accumulation of drug in serum.

Interactions with Acidic Drugs:

The interaction between probencid and penicillins has been used to enhance the therapeutic effect of the penicillins, particularly in the treatment of sexually transmitted diseases. Probencid competes with penicillins to reduce its tubular secretion and renal clearance.

Interactions with basic Drugs:

Perhaps the best known interaction involving altered renal excretion involves Quinidine (e.g *QUINORA)* and Digoxin (*LANOXIN).* In addition to inhibition of digoxin nonrenal clearance and tissue binding, Quinidine reduces the digoxin clearance 30%to 50% by inhibiting the tubular secretion of Digoxin. Amiodarone I*(CARDARONE)* inhibits the renal and nonrenal clearance of digoxin in same manner.

Altered Tubular Reabsorption:

The excretion and reabsorption of most drugs from th renal tubules is by passive diffusion across the cell membranes. This diffusion is governed by the concentration and lipid solubility of the nonionic form of the drug on each side of the membrane. Nonionized drug molecules in the tubular fluid are preferentially reabsorbed over the ionized molecules. The relative ratio of nonionized to ionized molecule is dependent upon the urinary pH and pKa of the drug. Strong acids and bases tend to be ionized when urine pH is approximately 5to 8. For a weak acid with pKa between 3 to 7 and weak bases with pKb between 7 and 11, the proportion of the drug in the ionized vs nonionized state will depend upon urine pH. In an acidic urine, weakly acidic drugs tend to reabsorbed while weak basis drugs will tend to be excreted in the urine and vice versa.

For example Quidnidine is a weak base whose urinary excretion may be altered by changes in urine pH. The urinary excretion of Quinidine was reduced nearly 90%, when urine pH was increased from less than 6 to over 7.5. Alkalinization of the urine with systemic antacids or acetazolamide (DIAMOX) can result in accumulation of other weak bases, including amphetamine. Acidification of the urine would increase the excretion of weak bases.

Pharmacodynamic Drug Interactions:

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

- E.g. increase toxicity of digoxin caused by diuretic induced hypokalaemia
- Additive effects of alcohol and benzodiazepines
- Beta-blocker given with beta-agonist

1.Duaplication:

- **Additive effect : 1 + 1 =2**

- Cofcol + Panadol → Duplication of paracetamol

2. Opposition (Antagonism):

- **Antagonism : 1-1 = 0**
- NSAIDs + Diuretics → ↓Diuretic effect

4. Alteration:

- Acid blocking drugs decreases absorption of Ketoconazoles (NIZORAL)^{R}
- Phenobarbital (LUMINAL, SOLFOTON)^{R} inactivates the Warfrin (COUMADIN)^{R}

4. Potentiation:

- **Potentiation effect : 1 + 0 =2**
- Carbidopa + Levodopa (SINEMET)^{R} → Prolongation of DOPA

5. Synergism:

- **Synergistic effect : 1 +1 > 2**
- Penicillin + Gentamicin (GARAMYCIN)^{R} → ↑ Antipseudomonal activity

Beneficial Interaction:

In some instances, drug interactions may be clinically useful. Concurrent administration of probenecid (BENEMID)^{R} and penicillin enhances the effectiveness of the antibiotic. These drugs are frequently co-administered to the patient's therapeutic advantage.

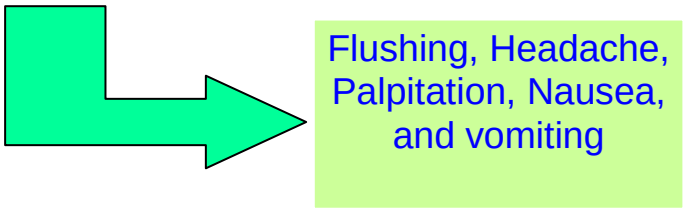
Drug-Food Interactions:

Drug-Food Interactions can modify the activity of the drug or impair the nutritional benefit of certain food.

- Effect of Food on Drug Absorption
  Penicillins, Tetracycline, Levodopa, Phenetoin, Digoxin
  Spirinolactone, Grisofulvin, itraconazole
- MAOIs (Phenelzine, Tranylcypromine) And Tyramine
  ↓
  Acute Exacerbation of Blood Pressure

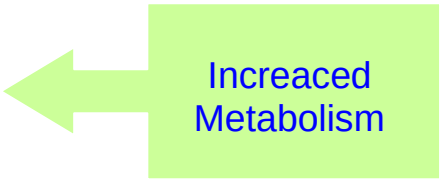
Drug-Chemical Interactions:

- Ex., Alcohol + Metronidazole



Phenytoin

- Ex., Alcohol +



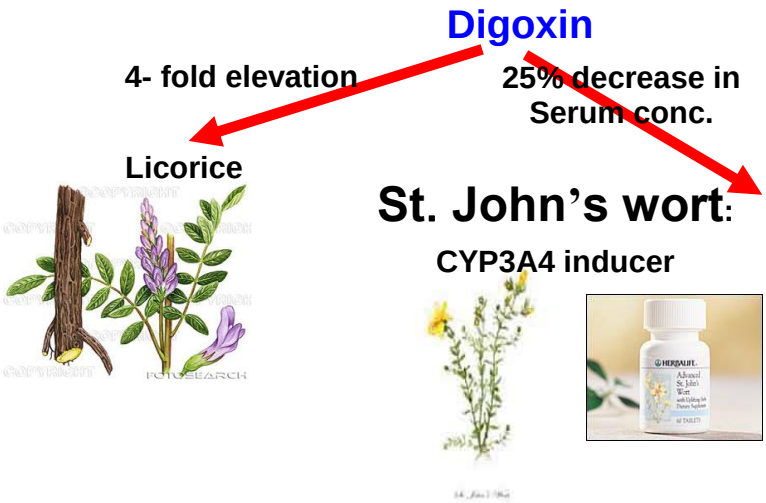
Warfrin

Drug-Disease Interaction:

- Beta-adrenergic blocking agents can precipitate and exacerbate disease such as asthma and COPD
- Verapamil have –ve inotropic and –ve chronotropic effects on heart and can exacerbate Congestive Heart Failure.

Drug-Herbal Interaction:

- Patients generally do not consider these products as drugs, and may not mention their use during medication history.



Drug-Laboratory Interactions:

Alteration in diagnostic Laboratory tests by the drugs

Ex., Salicylates decreases blood glucose level

- **Coloring Agent:**

  Compounds which add their own color to urine

  Ex., Cholroquine, Anthraquinone, Rifampicin

  Result: False colorimetric determinations

- **Reducing Agents:**

  The agents that excrete in urine.

  Ex., Penicillin, Streptomycin, Ascorbic Acid