**DRUG INTERACTIONS**

**Defination :**

A drug interaction is an interaction between a drug and some other substance , such as another drug or certain type of food which leads to interaction that could manifest as an increase or decrease in the effectiveness or adverse reaction or a totally new side effect that is not seen with either drug alone that can be severe enough to alter the clinical outcome

Drug interactions are thus ;

* Mostly undesirable
* Rarely desirable [BENEFICIAL]
* Eg: enhancement of activity of Penicillin when administered with Probenecid.
* The drug whose activity is effected by such an interaction is called as OBJECT DRUG.
* The drug which precipitates such an interaction is called as PRECIPITANT.

**Epidemiology**

* In Harvard medical practice study of adverse event 8% were consider to be due to drug interaction.
* US community pharmacy revealed 4.1% incidence of drug interaction in hospitalized patients.
* Australian study found that 4.4% of all ADR, which resulted in hospitals, due to interactions.
* In a prospective UK study carried out on hospital inpatients, ADR were responsible for hospital admission in 6.5% of cases. Drug interactions were involved in 16.6% of adverse reactions,

Therefore being directly responsible for leading to hospital admission in approximately 1% of cases

(Pirmohamed et al., 2004).

**Factors affecting drug interactions:**

**Outcomes of drug interactions**

* Loss of therapeutic effect
* Toxicity

**The net effect of drug interaction is**;

* Generally quantitative; increased or decreased effect.
* Seldom qualitative; Rapid or slower effect.
* Precipitation of newer or increased adverse effect.

**Types of Drug Interaction**

* Typically ,interactions between drugs come to mind like drug-drug interactions. However interactions may also exist between drug and foods [Drug-Food interactions],as well as drugs and medicinal plants or herbs [Drug-Plant interactions] and also Drug-Disease interactions.

**1.Drug-drug interaction**

**2.Drug-disease interaction**

**3.Drug-herb interaction**

**4.Drug-food interaction**

**5.Drug-laboratory interaction**

**1.Drug-drug interactions**

* A drug-drug interaction is said to occur when there is modification of the effects of one drug by the presence of another drug/drugs.
* It may result in following consequences ;

**Duplication :**

* Duplication occurs when both the drugs administered concurrently contains the same therapeutic moiety .
* Example: Benadryl and sominex both contain diphenhydramine are used for cough and sleep, duplication results.

**Antagonism:**

* One drug may antagonize the effects of other drug when administered at the same time.
* E. g. Betablockers (propranolol) with selective beta stimulants (e.g:salbutamol) have antagonistic effects.

**Alteration:**

* One drug may alters the effects of another drug by changing its pharmacokinetic and pharmacodynamics.
* E. g ascorbic acid makes urine acidic as a result of acidic drugs remain unionized and their reabsorption through urine will be enhanced while basic drugs are ionized and will not be reabsorbed &excrete.

**Synergism and potentiation**:

* Synergism occurs when two or more different drugs have same effects but with different mechanism of actions.
* Potentiation occurs when one drug helps to increase the effect of another drug having same effects.
* E.g: Ibuprofen and Diclofenac Sodium are both NSAIDS.

**2-Drug-disease interactions**

It occurs when a drug has potential to worsen the pre-existing disease.

Example:

* NSAIDS in peptic ulcer.
* Hypnotics in live failure.

**3- Drug-herbal interactions**

Occurs as pharmacokinetic and pharmacodynamic interactions.

* Example: drugs with narrow therapeutic window are at greater risk. E.g: warfarin with ginger,garlic and wheat grass.

**4- Drug-food interactions**

* Food can **increase or decrease the absorbtion of drugs** e.g; decrease absorption of NSAIDS and increase absorption of morphine, phenytoin.
* **Influence bioavailibility** of drugs from modified release and immediate release dosage forms; fatty food increases systemic absorption of lipid soluble drugs and decrease absorption of water soluble drugs.
* **Complexation of drug with food elements** e.g: quinoline antibiotics with calcium and magnesium.

**5-Drug laboratory interactions**

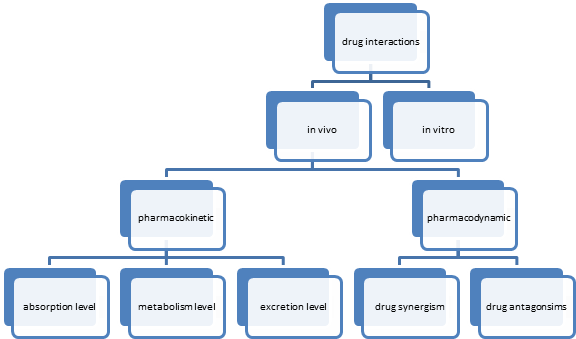
* When a medication interferes with a laboratory test. This can result in inaccurate test results. For instance, certain antidepressants (tricyclic antidepressants) have been shown to interfere with skin prick tests used to determine allergies someone may have.

**Mechanism of drug interaction**

Mechanism of drug interaction involved

* Invitro drug interaction
* Invivo drug interaction

1. Pharmacokinetic drug interaction
2. Pharmacodynamic drug interaction



**In-vitro drug interaction**

Invitro drug interaction also known as pharmaceutical drug interactions occur outside the body.

Pharmaceutical drug interaction is a physicochemical interaction that occurs

* During dosage form preparation or at time of administrations.
* Dissolving the drug in solvent
* Mixing drugs in powder, solution or injection forms.

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.

* For example: Ampicillin, chlorpromazine & barbiturates interact with dextran in solutions and are broken down or from in active chemical compounds.

**In-vivo drug interaction**

Invitro drug interaction occur inside the body.

Invitro drug interaction includes

* pharmacokinetic interactions and
* pharmacodynamic interactions

**Pharmacokinetic interactions**

Pharmacokinetic interaction are those that affects the process by which drug is

* Absorbed
* Distributed
* Metabolized and
* Excreted

Such interactions may result in a change in the drug concentration at the site of action with subsequent toxicity or decreased efficacy

Due to marked inter-individual variability in these processes, these interactions may be expected but their extent cannot be easily predicted.

1. **Absorption**

 Absorption interactions are those where the absorption of the drug is altered.

Since the oral route is the one, most frequently used to administer drugs, interactions influencing absorption are more likely to occur within the gastrointestinal tract.

The net effect of such an interaction is:

* Fast or slow the drug absorption.
* More or, less complete drug absorption.

Most clinically significant interactions occur due to the following factors:

* Changes in gastrointestinal pH
* Changes induced by adsorption, chelation and another complexing mechanism
* Changes in gastrointestinal motility
* Transporter based interactions
* Malabsorption

**Changes in gastrointestinal pH**

Absorption across mucous membranes depends on the

* non-ionized form
* lipid-soluble form.

The ionization state depends on

* pH of medium
* pKa of the drug
* formulation factors

While changes in gastric pH induced by H2 and proton pump blockers and antacids containing Al/Mg formulations have been shown to significantly reduce drug bioavailability; in clinical practice the outcome is a bit uncertain due to other compounding factors such as chelation and gastric motility.

However the alteration in pH has certain clinical implications

* For example:
* By alteration in pH result in a significant reduction in the absorption of ketoconazole and itraconazole which are insoluble in water and are only ionized at low pH, hence gastric acidity plays an important in the absorption of these drug.
* Likewise salicylic acid absorption is greater at low pH.

**Changes induced by adsorption, chelation and another complexing mechanism**

The most clinically significant interactions occur due to chelation or formation of insoluble complexes or when drugs are bound to resins that bind to bile acids.

* For example:
* Tetracycline as well as ciprofloxacin form insoluble chelates with Ca, Al, Bi and iron, resulting in its reduced antibacterial effects.
* Bisphosphonates are often co-prescribe with calcium supplements in the treatment of osteoporosis if both drug are taken concomitantly the bioavailability of both drugs are significantly reduced with the possibility of therapeutic failure

Most chelation and absorptioninteraction can be avoided if the interval between the medications is at least 2-3 hours.

**Changes in gastrointestinal motility**

Drugs that alter the stomach-emptying rate can affect the rate of absorption of drugs as most of them are absorbed in the small intestine.

The drug with anticholinergic effects, such as tricyclic antidepressants, phenothiazines and antihistamines, decrease gut motility and delay gastric empting

The outcome of the reduced gut motility can either be an increase or a decrease in drug given concomitantly.

* For example:
* Tricyclic antidepressants increase the dicoumarol absorption, by increasing dissolution and absorption time.
* Anticholinergi c agents used in the management of movement disorder by decreasing the B.A of levodopa by increasing the metabolism in intestinal mucosa

**Transporter based interactions**

The oral bioavailability of some drug is limited by the action of drug transporter protein, which eject drugs that have diffused across the gut lining back into the gut

P-glycoprotein is the well-characterized drug transporter.

* For example: Verapamil increased the bioavailability of digoxin due inhibition of P-glycoprotein by verapamil

**Malabsorption**

* Neomycin cause a malabsorption syndrome leading to reduced absorption of digoxin

1. **Drug distribution**

During the process of distribution, drug interactions may occur, principally as a result of displacement from protein-binding sites.

“A drug displacement interaction is defined as a reduction in the extent of plasma protein binding of one drug caused by the presence of another drug, resulting in an increased free or unbound fraction of the displaced drug”.

Albumin is the main plasma protein to which acidic drugs such as warfarin are bound.

While basic drugs such as tricyclic antidepressants, lidocaine, disopyramide and propranolol are generally bound to α1-acid glycoprotein.

Drugs highly bound to plasma proteins that have a relatively small volume of distribution like oral anticoagulants, sulfonylureas, certain NSAIDs and anti-epileptics 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.

1. **Drug metabolism**

Most clinically important interactions involve the effect of one drug on the metabolism of another.

“Metabolism refers to the process by which drugs and other compounds are biochemically modified to facilitate their degradation and subsequent removal from the body”.

Liver is the principal site of drug metabolism, although other organs such as the gut, kidneys, lung, skin and placenta are also involved.

Drug metabolism consists of

* Phase I reactions such as oxidation, hydrolysis and reduction
* Phase II reactions, which primarily involve conjugation of the drug with substances such as glucuronic acid and sulphuric acid.
* Phase I metabolism generally involves the cytochrome P450 (CYP450) mixed function oxidase system.
* The liver is the major site of cytochrome 450-mediated metabolism.
* CYP450 isoenzymes: The CYP450 system comprises 57 isoenzymes
* Each derived from the expression of an individual gene.

**CYP450 Nomenclature**

* Four main subfamilies CYP1, CYP2, CYP3 and CYP4. CYP2D6
* CYP3A is probably the most important of all drug-metabolizing enzymes because it is abundant in both the intestinal epithelium and the liver

**Enzyme induction**

 Increased rate of metabolism.

Interfere with the ability of enzyme to metabolize substrate.

Increased metabolism →decreased concentrations of substrate

Inducer: Drug that will increase the synthesis of CYP450 enzymes

The most powerful enzyme inducers in clinical use are

* rifampicin
* Antiepileptic agents such as barbiturates, phenytoin and carbamazepine.

**Auto induction**: Some enzyme inducer can induce there on metabolism. E.g:Barbiturates and carbamazepine.

Some enzyme inducer with shorter half lives such as rifampin will induced metabolism more rapidly than inducer with longer half lives

Enzyme induction process is dose dependent although some drug induced enzyme at any dose.

Enzyme induction usually decreased the pharmacological effect of the drug but is the metabolite of the drug is active than this may lead to increased the pharmacological effect

For example: Rifampicin increased the metabolism of oral contraceptives and corticosteroids result in therapeutic failure

**Enzyme inhibition**

Inhibitor Drug that will decrease the metabolism of a substrate

A strong inhibitor is one that can cause ≥5-fold increase in the plasma area-under the curve (AUC) value ü

A moderate inhibitor is one that can cause ≥2 but <5 (AUC) value

A weak inhibitor is one that can cause ≥1.25- but <2 fold increase in the AUC values-fold increase in the AUC value

* For example: Ciprofloxacin and clarithromycin increased the anticoagulant effect of oral anticoagulants result in increased the risk of bleeding.

**4. Elimination interactions**

Most drugs are excreted in either bile or urine.

Interactions can occur when drugs interfere with

* Kidney tubule fluid pH
* Active transport systems
* Blood flow to the kidney
* Drug transporter proteins
* Biliary excretion

**Changes in urinary pH**

In passive reabsorption only the non ionized form is lipid soluble and able to diffuse back through the tubular cell membrane

At alkaline pH, weakly acidic drugs (pKa 3.0– 7.5) exist as ionized lipid-insoluble mol. and will be excreted.

Weak bases (pKa 7.5– 10) are excreted in acidic urine.

Strong acids and bases completely ionized and their clearance is unaffected by pH changes.

* For example: Urine alkalinisation and urine acidification clinically used in salicylate and amphetamine poisoning)

**Changes in active renal tubule excretion**

Drugs using same active transport system in the kidney tubules compete with one another for excretion.

* For example: Probenecid increased plasma conc. of penicillin by delaying real excretion as a result of inhibits the renal secretion of many other anion drug via organic anion transporters

**Change in real blood flow**

Blood flow through kidney is partially controlled by the production of renal vasodilatory prostaglandin

* For example: is the synthesis of such prostaglandin is inhibited by indometacin, the renal execration of lithium is reduced with the subsequent rise in plasma level

**Biliary excretion and the enterohepatic shunt**

Some drugs are excreted in the bile either change or conjugated form

* for example: as the glucuronide to make them more water soluble

Some of the conjugates are metabolized to the parent compound by the gut flora and are then reabsorbed. This recycling process prolongs the stay of the drug within the body. Antibiotics kill flora so leads to therapeutic failure of such drugs

* For example: This mechanism has been postulated as the basis of an interaction between board spectrum antibiotics and oral contraceptive

**Drug transporter protein**

Drug and endogenous substance cross the biological membrane not only by passive diffusion but also by carrier- medicated process known as transporter.

P-glycoprotein is a large cell membrane protein that is responsible for the transport of many substrate may result in increased or decreased concentration of drug.

* For example: Verapamil cause the P-glycoprotein inhibition Leading to digoxin toxicity

**Pharmacodynamic interactions**

“Pharmacodynamic interactions are those where the effects of one drug are changed by the presence of another drug at its site of action”.

This may result in

* an enhanced response (synergism),
* an attenuated response (antagonism) or an abnormal response.

**Antagonistic interactions**

A drug with an agonist action at a particular receptor type will interact with antagonists at that receptor

* For example: the bronchodilator acttion of β2-adrenoreceptor agonist such as salbutamol will be antagonised by β2-adrenoreceptor antagonist such as propranolol result in Therapeutic failure of agonist .

**Additive or synergistic interactions**

Two drugs with similar pharmacological effects are given together, the effects can be additive

* For example: NSAID, warfarin, clopidogrel if administered together may result in ncreased risk of bleeding.

**Consequences of drug interaction**

The consequences of drug interactions may be:

* Major: Life threatening.
* Moderate: Detritions of patients status.
* Minor: Little effect.

**How to overcome drug interactions**

* **Be knowledgeable about the actions of the drugs being used:** The knowledge of properties and the primary and secondary pharmacological actions of each of agent used or being considered for use is essential if the interaction potential is to be assessed accurately.
* **Consider therapeutic alternatives:** in most cases, two drugs that are known to interact can be administered concurrently as long as adequate precautions are taken (e.g., closer monitoring of therapy or dosage adjustments to compensate for altered response). However in those situations in which another agent with similar therapeutic properties and lesser risk of interacting is available, it should be used.
* **Avoid complex therapeutic regimen when possible:** The number of medications used should be kept to minimum. Therapeutic duplications in which agents are given that have overlapping pharmacological actions should be avoided unless clinically necessary. In addition, use of medication or dosage regimens that permit less frequent administration may help avoid interactions that result from an alteration of absorption (e.g. when a drug is administered in close proximity to meals).
* **Educate the patient:** Patients often know little about their illness, let alone the benefits and problems that could result from drug therapy. Individuals who are aware of, and understanding, this information can be expected to be in great compliance with the instructions for administering medications and more attentive to the development of symptoms that could be early indicator of drug related problems. Patients should be encouraged to ask questions about their therapy and to report any excessive or unexpected responses.
* **Monitor therapy:** The risk of drug related problem warrants close monitoring, not only for possible occurrence of drug interactions but also for adverse events occurring with individual agent and noncompliance. Any change in patient behavior should be suspected as being drug related until that possibility is excluded.

**Role of health care professional in avoiding drug interactions**

* Maintain complete and current patient medication records
* Supervise and monitor drug therapy to detect and prevent drug interactions.
* Should be vigilant in monitoring for potential drug interactions
* Advising patients regarding drugs proper use, foods or beverages to avoid when taking certain medications and about disease conditions.
* keep up-to-date on potential drug-food interactions of medications, especially today’s new drugs, so that they may counsel properly to the patient.
* By observing the preceding guidelines and recommendations and by strengthening communication with patient and other health care professionals.

**Clinical resources of drug interactions**

* The Drug interactions tools helps you check for interacting drugs, their effects, clinical significance, provide instant access to drug-drug, drug-food, drug-ethanol, drug-tobacco, drug-pregnancy effects .
* Provides clear, concise drug information ,including dosing ,warning ,precautions, severity as well as clinical practice guidelines .
* With the correct information at the point of care, significant number of adverse drug events can be prevented .
* The seven resources were
* Lexicomp interactions module
* Micromedex Drug interactions
* Clinical pharmacology Drug interaction report
* Facts & comparisons answers
* Stockley’s Drug interactions
* Drug interactions Analysis and management
* Drug interaction Facts

**Conclusion**

* Most potential drug interactions can be recognized by applying principles of clinical pharmacology and good clinical care. Increased vigilance by clinicians at the time of changing drugs improves the chances of identifying unwanted drug interactions before they significant harm.Knowing a few drugs well and makin g judicious use of available information is more effective for manging drug interaction.