DRUG INTERACTIONS

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Defination

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

- Concomitant use of several drug in presence of another drug is often necessory for achiving a set of goal or in the case when the patient is suffering from more than one disease.

Risk factors

- Poly pharmacy Multiple prescribers Multiple pharmacies
- Genetic make up
- Specific population like e.g,
- females , elderly, obese, malnouresed , criticaly ill patient ,
- trasplant recipient

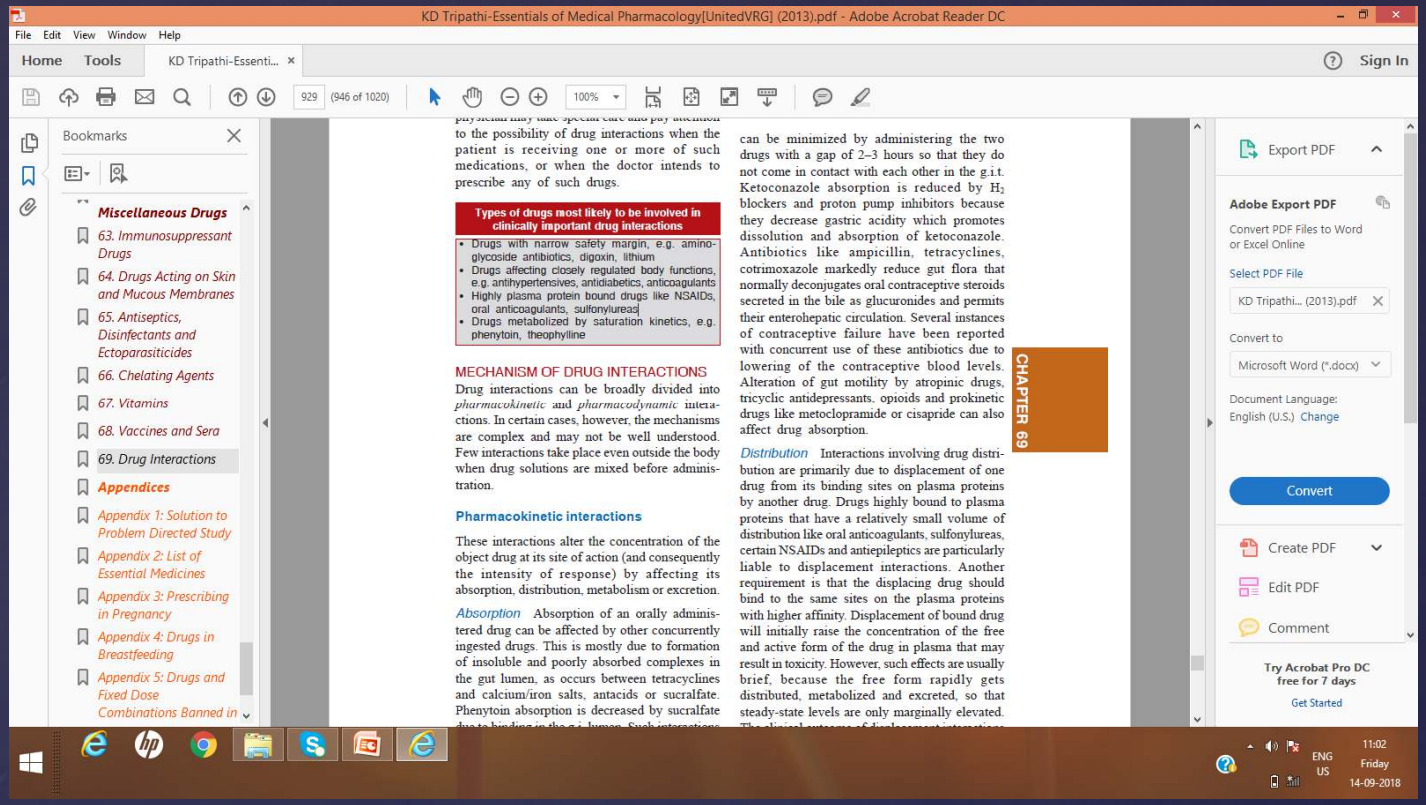
- Specific illness E.g. Hepatic disease,
  Renal dysfunction,
- Narrow therapeutic index drugs

  Cyclosporine, Digoxin, Insulin, Lithium , Antidepressant, Warfarin

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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Miscellaneous Drugs
63. Immunosuppressant Drugs
64. Drugs Acting on Skin and Mucous Membranes
65. Antiseptics, Disinfectants and Ectoparasiticides
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to the possibility of drug interactions when the patient is receiving one or more of such medications, or when the doctor intends to prescribe any of such drugs.
Types of drugs most likely to be involved in clinically important drug interactions
Drugs with narrow safety margin, e.g. aminoglycoside antibiotics, digoxin, lithium
Drugs affecting closely regulated body functions, e.g. antihypertensives, antidiabetics, anticoagulants
Highly plasma protein bound drugs like NSAIDs, oral anticoagulants, sulfonylureas
Drugs metabolized by saturation kinetics, e.g. phenytoin, theophylline
MECHANISM OF DRUG INTERACTIONS
Drug interactions can be broadly divided into pharmacokinetic and pharmacodynamic interactions. In certain cases, however, the mechanisms are complex and may not be well understood. Few interactions take place even outside the body when drug solutions are mixed before administration.
Pharmacokinetic interactions
These interactions alter the concentration of the object drug at its site of action (and consequently the intensity of response) by affecting its absorption, distribution, metabolism or excretion.
Absorption Absorption of an orally administered drug can be affected by other concurrently ingested drugs. This is mostly due to formation of insoluble and poorly absorbed complexes in the gut lumen, as occurs between tetracyclines and calcium/iron salts, antacids or sucralfate. Phenytoin absorption is decreased by sucralfate
can be minimized by administering the two drugs with a gap of 2–3 hours so that they do not come in contact with each other in the g.i.t. Ketoconazole absorption is reduced by H_2 blockers and proton pump inhibitors because they decrease gastric acidity which promotes dissolution and absorption of ketoconazole. Antibiotics like ampicillin, tetracyclines, cotrimoxazole markedly reduce gut flora that normally deconjugates oral contraceptive steroids secreted in the bile as glucuronides and permits their enterohepatic circulation. Several instances of contraceptive failure have been reported with concurrent use of these antibiotics due to lowering of the contraceptive blood levels. Alteration of gut motility by atropinic drugs, tricyclic antidepressants, opioids and prokinetic drugs like metoclopramide or cisapride can also affect drug absorption.
CHAPTER 69
Distribution Interactions involving drug distribution are primarily due to displacement of one drug from its binding sites on plasma proteins by another drug. Drugs highly bound to plasma proteins that have a relatively small volume of distribution like oral anticoagulants, sulfonylureas, certain NSAIDs and antiepileptics are particularly liable to displacement interactions. Another requirement is that the displacing drug should bind to the same sites on the plasma proteins with higher affinity. Displacement of bound drug will initially raise the concentration of the free and active form of the drug in plasma that may result in toxicity. However, such effects are usually brief, because the free form rapidly gets distributed, metabolized and excreted, so that steady-state levels are only marginally elevated.
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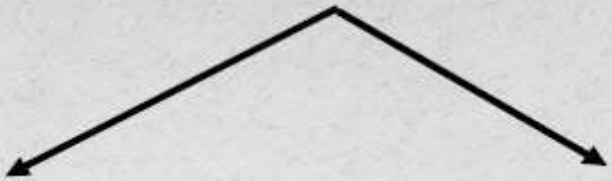
Mechanisms of drug interactions



Pharmacokinetics

Pharmacokinetics involve the effect of a drug on another from the point of view that includes absorption, distribution, metabolism and excretion

Pharmacodynamics

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
  - 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.

DRUG ABSORPTION

- Absorption of an orally administered drug can be affected by other concurrently ingested drugs.
- Due to formation of insoluble and poorly absorbed complexes in gut lumen.
- Eg: between tetracycline and calcium salts.

- Phenytoin absorption –decreased by sucralfate due to binding in gi lumen.

Interaction minimised –two drugs with gap of 2-3 hours.

Ampicillin,tetracycline :reduce gut flora:alter enterohepatic circulation.

Contraceptive failure of oral contraceptives.

- With oral anticoagulants-inhibition of gut flora-decreased vit k production in gut-risk of bleeding

f) Displaced protein binding

Displacement of one drug from its binding site on plasma proteins by another drug with high affinity.
Drugs with high plasma protein binding and small Vd :liable to displacement interactions.

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

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

- Inhibiting efflux transporter p-glycoprotein

increased blood levels of digoxin

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.

E.g., 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

ENZYME INDUCTION

Precipitant drug		Object drug
Phenobarbitone,		Protease inhibitor
Phenytoin		OCPs
Carbamazepine	:	Corticosteroids
Rifampicin		Sulfonylureas
		Antidepressants
		Warfarin,Metronidazole

Induction of metabolism:loss of efficacy of object drug

Avoid concurrent use or increase dose of object drug with monitoring.

Precipitant drug	Object drug
Erythromycin	Terfenadine
Clarithromycin	Astemizole
Ciprofloxacin	Phenytoin
Norfloxacin	Warfarin
Metronidazole	Theophylline
	Carbamazepine
Ketoconazole	Sulfonylureas
Itraconazole	Diazepam

ENZYME INHIBITION

Renal excretion:

- **Active tubular secretion**

▪**It occurs in the proximal 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.

- Probenecid- competitively blocks active transport of organic acids by OATP.

Penicillin- predominantly secreted by renal tubules.its reabsorption is minimal.

Net effect of probenecid is inhibition of penicillin excretion.more sustained blood levels.

Probenecid inhibits urinary excretion of cephalosporins,sulfonamides,methotrexate and indomethacin.

- Barbiturate poisoning:Since barbiturates are weak acids, enhanced renal elimination occurs through alkalinization of the urine- sodium bicarbonate 1 mEq/kg i.v.
- Diuretics act by lowering water and sodium levels; this causes more reabsorption of lithium in the proximal tubules so that the removal of lithium from the body is less, leading to increased blood levels of lithium.
- Diuretics,ACE inhibitors,NSAIDS found to raise steady state blood levels of Li by promoting its tubular reabsorption.

Pharmacodynamic interaction

- Modificatioon of action of one drug at the target site by another drug ,independent of its change in concentration.

Results in enhanced response (synergism),

Antagonism or abnormal response.

Precipitant drug	Object drug	interaction
Aspirin and other NSAIDS,Clopidogrel	Warfarin ,Heparin	Enhanced risk of bleeding due to antiplatelet action and gastric mucosal damage
Aspirin and other NSAIDS	ACE inhibitors Beta blockers	Reduced antihypertensive action due to inhibition of renal PG synthesis.
Aspirin and other NSAIDS	Furosemide	Reduced diuretic action due to inhibition of renal PG synthesis
Aspirin	Spironolactone	Reduced K+ conserving action due to decreased tubular secretion of canrenone

Precipitant drug	Object drug	interaction
Chlorpromazine,Imipramine and other TCA	Morphine,Codeine Pethidine	Enhanced CNS and respiratory depression
Chlorpromazine, Haloperidol and Metoclopramide	Levodopa -carbidopa	Antagonism of antiparkinsonian effect
Levodopa-carbidopa	ACE inhibitors,Prazosin ,vasodilators	Excessive postural hypotension.reduce dose of anti hypertensives
TCA s	Adrenaline(added to local anaesthetic)	Potentiation due to neuronal uptake inhibition-rise in BP.
Diuretic	Digoxin	Hypokalemia caused by diuretic increases digoxin toxicity

Precipitant drug	Object drug	interaction
Alcohol, opioids	Diazepam	Additive CNS and respiratory depression,motor impairment
Propranolol	Lidocaine	Reduced hepatic clearance of lidocaine.
Lidocaine	Quinidine and other anti arrhythmic drugs	Exaggerated cardiac depression.precipitation of arrhythmia
Sildenafil,Tadanafil	Nitrates	Nitrates-increase generation of c GMP.Potentiation-precipitous fall in B.P.
Clindamycin	Erythromycin,Clarithromycin,Chloramphenicol,Azithromycin	Mutual antagonism of antibacterial action due to proximal binding sites on bacterial ribosome

Drug interactions before administration

Certain drugs react with each other and gets inactivated if their solutions are mixed before administration.

- Penicillin G or ampicillin mixed with gentamicin or another aminoglycoside antibiotic
- Thiopentone sodium when mixed with succinylcholine or morphine
- Heparin when mixed with penicillin/ gentamicin/hydrocortisone
- Noradrenaline when added to sodium bicarbonate solution.

In general, it is advisable to avoid mixing of any two or more parenteral drugs before injecting.

Pharmacodynamic interaction

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

X., Propranolol + verapamil → Synergistic or additive effect

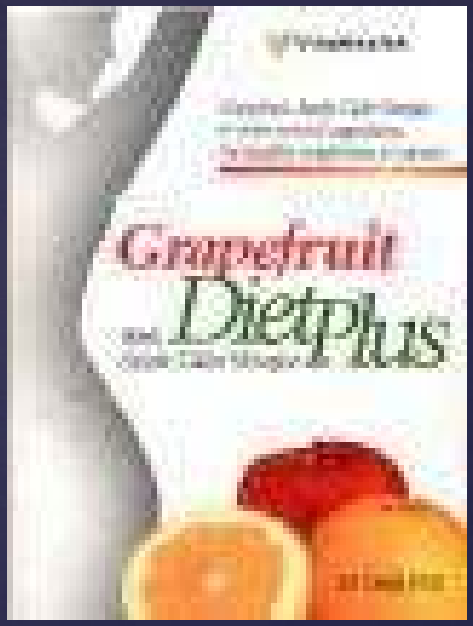
Additive effect : 1 + 1 =2

Synergistic effect : 1 +1 > 2

Potentiation effect : 1 + 0 =2

Antagonism : 1-1 = 0

Drug-Food interactions



- Grapefruit juice and Terfenadine Grapefruit juice and
- cyclosporin Grapefruit juice and felodipine
- Grapefruit contains : furanocoumarin compounds that
- can selectively inhibit CYP3A4


THANKS
TO
ALL