Cairo University
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Special Studies in Pharmacology

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Principles of Drug Interactions

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Definition:

A drug-drug interaction can be defined as the phenomenon that occurs when the pharmacological actions or pharmacokinetics of a drug are altered by prior administration or co-administration of a second drug.

The drug interactions may be dangerous (Adverse) or beneficial.

Adverse drug interactions:

Adverse drug interactions involve a variation in the therapeutic effects of drug, or an effect not observed when the drug is administered alone.

The adverse interactions are usually resulting from drugs with a narrow therapeutic index, metabolized by the hepatic mixed-function oxidase system and those drugs that are used chronically.

For example:

- The concurrent administration of cardiac glycosides and potassium-wasting diuretics increased digoxin toxicity.
- The toxicity of anticoagulant warfarin - by non-steroid anti-inflammatory drugs (NSAIDs) concurrently administered with warfarin.

Beneficial drug interactions:

Drugs are combined to achieve a synergistic effect or to limit the occurrence of side- effects. These are used clinically in veterinary medicine.

For example:

- Combination between sulpha drug and trimethoprim.
- The toxic effect of one drug is decreased by administration of another e.g. atropine administration to treat poisoning with organophosphorus compound.

Clinical Importance of Beneficial interactions:

- Potentiate & enhancement of drug effects.
- Broader the spectrum of activity.
- Reduce the recommended dose of each drug.

- Decrease drugs residues. Minimize the side effects.

Types of Drug Interactions

1. Drug interactions in vitro (In Vitro incompatibilities)

Those interactions include mixing of two drugs before administration, or the addition of a drug to intravenous infusion fluids.

- Chemical alteration to the active ingredients has occurred due to chemical reactions either without visible change in appearance of the drug, or change in color and turbidity is occurred when physically incompatible compounds are mixed. These reduce the therapeutic potency of drugs.

Example: Precipitation following the mixing of thiopentone & suxamethonium.

- When drugs are administered by i.v infusion, some drugs may be incompatible with infusion fluids.

Table (1): Incompatibility of drugs with intravenous fluids

Drugs	Incompatible i.v. fluids
Ampicillin sodium	Dextrose sol. & dextran.
Adrenaline	Sodium bicarbonate
Benzyl penicillin	Dextrose sol.
Heparin sodium	Dextrose sol.
Oxytetracycline	Sol. containing Ca^2 or Mg^2, dextrose.

2. Drug interactions in vivo

Drug interactions inside the body are classified on the basis of their mechanism into

a. Pharmacodynamic interactions:

In which one drug induces a change in a patient's response to a drug without altering the drug's pharmacokinetics (change in drug action without altered its plasma conc.)

The concurrent use of two or more drugs with opposing or similar pharmacological

actions is a form of Pharmacodynamic interactions.

For example:

1. Aminoglycoside antibiotics (streptomycin, neomycin, gentamicin, and kanamycin), clindamycin and polymyxin produce skeletal neuromuscular blockade.

▪Thus combination of aminoglycosides & non-depolarizing neuromuscular blockers (curare, gallamine) leads to excessive muscle relaxation.

✓ The use of non-depolarizing neuromuscular blocking agents in patients being treated with those antibiotics is not recommended.

2. General *anesthetics* including ether, halothane, methoxyflurane and enflurane potentiate the effect of non-depolarizing neuromuscular blockers.

✓Thus in patients anaesthetized with these agents, *reduced does of neuromuscular blockers should be used.*

3 - Cardiac glycosides:

The concurrent administration of cardiac glycosides and potassium-wasting diuretics increased toxic effects of glycosides.

b- Pharmacokinetic interactions:

In which one drug may alter the absorption, distribution, metabolism or excretion of another drug.

1- Drug interactions altered Absorption

1.1. Altered absorption after oral administration: A large number of drugs are available for oral administration; thus most interactions involving altered drug absorption occur in GIT and affected by several mechanisms.

a- Chemical reaction: can occur within GIT to form a non-absorbable complex by chelation of di- or trivalent cations such as Ca^{2+}, Mg^{2+}, Al^{3+}, Fe^{3+}.

● Oral administration of tetracycline or enrofloxacin and the concurrent ingestion of food (especially milk products), antacids or laxatives containing multivalent cations reduce absorption of tetracycline and enrofloxacin.

● Tetracycline administration with oral iron preparations reduces iron absorption.

b- Presence of adsorbents, such as kaolin & charcoal:

● Absorption of drugs from GIT is reduced by the presence of adsorbents because the active drug is adsorbed onto the kaolin or charcoal.

c- Changing gastrointestinal pH:

● PH of GIT has strong effect on absorption of orally administered drugs.

● Increase in GIT pH → decrease absorption of weak acids.

● Alkalis administration → reduces absorption of oral acetylsalicylic acid.

d- Alteration in gastric emptying:

● Drugs which delay gastric emptying decrease the rate of absorption of other Co- administered drugs from the small intestine.

● Metoclopramide is used to increase the rate of gastric empty & thus reduce the time to peak effect of other drugs administered concurrently.

e- Presence of food in stomach:

● Presence of food in stomach reduces the rate of gastric emptying & slows the absorption of drugs (e.g. penicillin and tetracycline).

● Such drugs should be given either half an hour before or 2 hours after meal.

● In contrast, Griseofulvin absorption is enhanced by fatty meals.

f- Alteration of gut flora:

● Antibiotics inhibit the gut flora that synthesizes vitamin K and so potentiate the action of oral anticoagulants.

1.2. When drugs are administered by <u>i.m. or S.C. injection</u>:

● Adrenaline addition to drug formulations delays absorption.

● Combination of insulin with protamine, and of penicillin with procaine.

II. <u>Interactions affecting drug Distribution</u>

A- Displacement of Protein Binding Sites:

Drugs that are bound to plasma albumin are exposed for displacement from albumin

binding sites by another highly bound co-administered drug.

● For example: the toxicity of anticoagulant warfarin- by non-steroid anti-inflammatory drugs (NSAIDs) concurrently administered with warfarin. When (NSAID) drug administered, it displaces warfarin from its albumin binding sites, the displaced drug markedly increases level of free drug to exert toxic effects.

b- Displacement of Receptor Binding sites:

● Quinidine displaces digoxin from binding sites in muscle increasing the serum concentration of digoxin & also promotes the renal excretion of digoxin.

III- <u>Interactions affecting drug Metabolism</u>

***a*- Enzyme Induction:**

● Some drugs able to stimulate (induce) the production of drug-metabolizing enzymes especially mixed function oxidases; the cytochrome P450 that are responsible for oxidation of many drugs as warfarin, and phenytoin.

● Drug interactions involving a loss of therapeutic activity result from the consequent increase in the rate of metabolism.

● Clinically, Phenobarbital is the most well known enzyme inducer and when administered with phenytoin for treatment of epilepsy, this will lead to therapeutic Failure if the dose of phenytoin is not increased.

● Phenobarbital also reduces therapeutic efficacy of Chloramphenicol, Griseofulvin, cyclosporine, doxycycline, metronidazole, theophylline and verpamil.

b- Enzyme Inhibition:

● Enzyme inhibition of drug- metabolizing enzymes generally decreases the rate of metabolism of the object drug; resulting in increased serum concentration of this drug and toxicity if the drug has a narrow therapeutic index.

●Chloramphenicol inhibits cytochrome P450–dependent monoxgeneses. Thus Chloramphenicol prolongs the duration of Phenobarbital induced anaesthesia.

IV- <u>Interactions affecting drug Excretion</u>

a- Reduction in urinary elimination:

- Altered active transport in the tubules (e.g., probenecid -- penicillin; methotrexate)
- Probenecid blocks the excretion of penicillin, cefazolin, enrofloxacin.
- Aspirin block the excretion of methotrexate & thus cause serious effects.

***b*- Change in urine pH:**

- influence the elimination of weak acids and weak bases because their passive reabsorption requires that they be un-ionized.
- Acetazolamide or sodium bicarbonate (urinary alkalinizer) will increase the excretion of weak acids; e.g.: urinary Alkalinizer increases the excretion of sulfonamides and prevents the development of crystal urea.

Reducing the Risk of drug interactions

Many drug interactions can be avoided if adequate precautions are taken.

1. Monitoring therapy and make adjustment to the drug dose regimen.
2. Avoid multiple-drug therapy and complex therapeutic regimens
3. Use individualized therapy.
4. Hepatic &kidney functions must be tested firstly.
5. Knowledge of the pharmacology of the drugs used in therapy.