Drug Interaction

Drug Interaction are said to be occur when the pharmacologic activity of a drug is altered by the concomitant use of

- ✓ Another drug, (Drug-Drug Interaction)
- ✓ By the presence of food, (Drug-Food Interaction)
- ✓ Disease, (Drug-Disease Interaction)
- ✓ Enzymes (Drug-Enzymes Interaction)

Drug-Drug Interactions

- Drug-drug interactions can be defined as the modulation of the pharmacologic activity of one drug by the prior or concomitant administration of another drug.
- occurred when the pharmacological effect of two or more drug given together.

When one drug alters the effects of another drug

e.g. Drug A causes Drug B to have …

- Increased or reduced effect
- Slower or more rapid effect

Susceptible patients

- Increase with the number of drugs received by the patient
- Specific patients group;
  - Elderly: they are likely to be taking multiple drugs and may have impaired renal and hepatic function
  - Critically ill patients: they have impaired organ functions which may affect elimination of drugs from the body
  - Any other concomitant disease

Mechanism of Interaction

- Pharmacokinetic Interactions: are those in which ADME of the object drug are altered. The resultant effect is altered plasma concentration of the object drug.
- Pharmacodyanamic Interactions are those in which the activity of the object drug at its site of action is altered by the precipitant. Such interaction may be direct or indirect. The resultant effect of all the pharmacodyanamic interaction altered the drug action without a change in plasma concentration

Pharmacokinetic Drug Interactions

1. Interactions Affecting Absorption
   - Activated charcoal acts as an adsorbent agent within git – useful for poisoning, affect the absorption of drug.
   - Tetracycline / Quinolones and Calcium --- reduced serum level of tetracycline or quinolones
   - Metoclopramide: increase the rate of GI emptying, accelerate abs of many drugs PCM, diazepam, propanolol, lithium. Abs low from stomach but higher from small bowel.

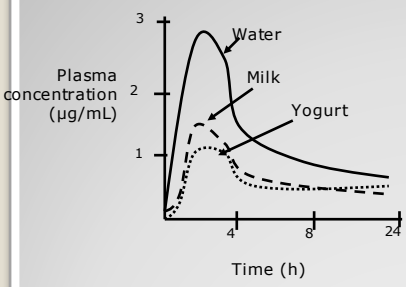

Fig: Effect of dietary calcium on the absorption of ciprofloxacin

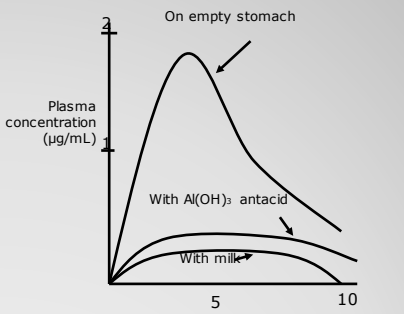

Fig: Effect of antacid and milk on absorption of tetracycline

2. Interaction Affecting Distribution

- One drug changes the way in which another drug is distributed around the body.
- The main mechanism behind this process is protein binding displacement.
- Clinically imp for highly bound drug. E.g. Warfarin. Displacement of only small fraction can change the effect by several times. (Aspirin /cimetidine)
- Quinidine can displace digoxin from its binding site.

3. Interaction Affecting Metabolism

- One drug changes the rate of metabolism of another drug
- Most clinically significant interaction involves effect in metabolism

Drug biotransformation:

- Phase I reaction: Oxidation, reduction, hydrolysis etc, mostly mediated by CYP450 enzymes, esp CYP3A4 and CYP2D6
- Phase II reaction: conjugation of drugs or its phase I metabolite with substances such as glucoronic acid, sulphuric acid, acetic acid etc to form polar, highly ionized organic acid, which is easily excreted in urine or bile.

1. Enzyme Induction

- leads to decreased therapeutic response to the affected drugs, except in the case where active metabolites are generated.
- Enzyme induction primarily affects phase I metabolism, although some phase II metabolism may also be effected.
- Enzyme inducers: antiepileptics such as barbiturates, phenytoin, carbamazepine, griseofulvin, dichlorphenazone.
- Cigarette smoking and chronic alcohol use can also lead to induction of drug metabolizing enzymes.

2. Enzyme Inhibition

- slows down the metabolism of object drug.
- Blood concentrations of object drug increase above normal therapeutic levels -Increased chance of toxicity
- Interaction of this type affects drugs with narrow therapeutic index. E.g. theophylline + ciprofloxacin – doubling in plasma conc. of theophylline
- The ability to inhibit enzymes may be related to specific chemical structure, e.g. Inhibitors ketoconazole, itraconazole, metronidazole, omeprazole.

4. Interaction Affecting Excretion

- Clinically significant renal excretion interaction occurs when an appreciable amount of drug or its active metabolites are eliminated in the urine.
- Excretion pattern can be affected by alteration in GFR, renal blood flow, tubular secretion and urine pH.

1. Altered Active Tubular Secretion

- Probenecid increases the serum concentration and prolongs the activity of penicillin derivatives, primarily by blocking their tubular secretion.

2. Changes in Urine pH

- Antacids increased passive reabsorption of basic drugs (Amphetamine, quinidine) and increased toxicity

3. Changes in Renal Blood flow

- Quinidine appears to reduce the renal clearance of digoxin, resulting in higher serum concentration of digoxin.
- NSAIDs decrease the renal clearance of lithium and thus increased the risk of toxicity.

Pharmacodynamics drug interaction

- Effects of one drug is changed by the presence of another drug at the site of action.
- One drug alters the sensitivity or responsiveness of tissues to another drug.
- Alteration is caused by competition for same receptor site; similar or antagonistic drug actions.
- Interaction may be synergistic or antagonistic.

Synergistic interactions

Interaction causes an increase in the effects of one or both of the drugs

A. Additive

- Two drug having same effects if given, the resultant effect is the sum of individual drug responses.
- Effect of Drug A + B = effect of drug A + effect of drug B

Examples:

- codiene+ paracetamol– as analgesic
- Nitrous oxide + ether – as general anaesthetic
- Amlodipine + atenolol – as antihypertensive
- Glimepride + metformin – as hypoglycaemic
- Ephedrine + theoplylline – as bronchodilator

B. Potentiation

- The effect of combination is greator than individual resultant effect of the components.

- Effect of Drug A + B > effect of drug A + effect of drug B

Examples:

- Combination of sulphonamide and trimethoprim results in potentiation of antibacterial effect.
- Levodopa + carbidopa – inhibition of peripheral metabolism of levodopa
- Antihypertensive drugs (ACEi and diuretics)

Antagonistic interactions

- one drug decreases or inhibits the action of another.

Effect of drugs A+B < effect of drug A + effect of drug B

- Based on MOA, antagonism may be

A. **Physical Antagonism**: Based on the physical property of the drugs, e.g. charcoal adsorbs alkaloids and can prevent their absorption-used in alkaloidal poisonings.

B. Chemical antagonism The two drugs react chemically and form an inactive product, e.g.

•• KMn04 oxidizes alkaloids-used for gastric lavage in poisoning.

•• Chelating agents (Cal. disod. edetate) complex toxic metals (As, Pb).

•• Nitrites form methaemoglobin which reacts with cyanide radical.

C. Interaction through physiological function

- Two drugs act on different receptors or by different mechanism, but have opposite effects on the same physiological function i.e. pharmacological effects in opposite directions. Eg.
- Glucagon and Insulin on blood glucose level
- Histamine and adrenaline on bronchial muscles
- Hydrochlorothiazide and triameterene on urinary K+ excretion.

Antagonistic interactions

D Interaction through receptor

- Antagonist interferes with binding of the agonist with its receptor.
- bronchodilator action of selective beta 2 adrenoceptor agonist such as salbutamol will antagonized by beta-adrenoreceptor antagonist (propanolol).
- Morphine and Naloxone
- Self Competitive and non competitive Antagonism