PHARMACOKINETIC DRUG INTERACTIONS

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Contents

INTRODUCTION

- A Drug interaction is an interaction between a drug and some other substance, such as another drug or a certain type of food, which leads to interaction that could manifest as an increase or decrease in the effectiveness or an 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 Penicillines when administered with Probenecid.
- The drug whose activity is effected by such an interaction is called as a “Object drug”.
- The agent which precipitates such an interaction is referred to as the “Precipitant”.

- PHARMACOKINETIC DRUG INTERACTIONS: Altered concentration, pharmacokinetic drug interactions occur when one drug changes the systemic concentration of another drug, altering ‘how much’ and for ‘how long’ it is present at the site of action.

- PHARMACODYNAMIC DRUG INTERACTIONS: Altered effect, pharmacodynamic drug interactions occur when interacting drugs have either additive effects, in which case the overall effect is increased, or opposing effects, in which case the overall effect is decreased or even ‘cancelled out’.

PHARMACOKINETIC DRUG INTERACTIONS

- Pharmacokinetics is ‘what the body does to the drug’.These interactions occur when one drug alters the concentration of another drug (the object) with clinical consequences.
- Pharmacokinetic interactions occur when the absorption, distribution, metabolism or elimination process of the object drug is altered by the precipitant drug and hence such interactions are also called as ADME interactions.
- The resultant effect is altered plasma concentration of the object drug.

CLASSIFICATION OF PHARMACOKINETIC DRUG INTERACTIONS

- Absorption interactions
- Distribution interactions
- Metabolism interactions
- Excretion interactions

DRUG ABSORPTION INTERACTIONS

- Absorption interactions are those where the absorption of the object 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:
- Faster or slower drug absorption.
- More or, less drug absorption.

- Most clinically significant interactions occur due to the following factors:

a) Changes in gastrointestinal pH

b) Changes induced by chelation

c) Changes in gastrointestinal motility

CHANGES IN GASTROINTESTINAL pH

- Absorption in the gut is governed by the gut pH, lipid solubility and pka of the drug.
- 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.
- However the alteration in pH has certain clinical implications as it can result in a significant reduction in the absorption of Ketoconazole and Itroconazole which are insoluble in water and are only ionized at low pH, hence gastric acidity plays an important part in this interaction.

CHANGES INDUCED BY CHELATION

- The various possible drug interactions that occur due to alterations in drug absorption the most clinically significant interactions occur due to chelation or formation of insoluble complexes.
- Clinically important interactions relate to use of Tetracyclines as well as ciprofloxacin that can form insoluble chelates with Ca, Al, and iron, resulting in its reduced antibacterial effects.
- This interaction can however be avoided if the interval between the medications is at least 2-3 hours.
- Chelation also seems to play an important part in reducing the bioavailability of Penicillamine caused by some antacids.

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.
- Drugs with anticholinergic properties like Propantheline or those altering bowel motility like Diphenoxylate may affect the absorption of other drugs.
- Eg: Propantheline increases the absorption of slow dissolving Digoxin by 30% as the reduced gut motility allows a slow dissolving Digoxin formulation more time to pass into solution making a greater amount available for absorption but this effect is not seen with fast dissolving tablets.
- Metoclopramide on the other hand produces the opposite effects on motility and digoxin absorption.

DRUG DISTRIBUTION INTERACTIONS

- Drug distribution interactions are those where the distribution pattern of the object drug is altered.
- The major mechanism for distribution interaction is alteration in protein-drug binding.
- Many drugs interact by displacement of each others binding to plasma proteins.
- Acidic drugs are known to have an affinity to bind to plasma proteins, hence when two or more are given concomitantly, competitive binding for the same site or receptor may displace one drug from the protein binding site increasing the amount of the displaced free drug in plasma and various tissues setting up an interaction leading to an enhanced potential for toxicity.

- Eg: Concomitant administration of warfarin with Phenylbutazone or other highly protein bound drugs leads to increased levels of warfarin.
- The drugs most likely to lead to clinically significant interactions are those that are: 90% or more protein bound, those bound to tissues or having a small volume of distribution, having a low therapeutic index, low hepatic extraction ratios, or those that are administered I.V.
- Drugs that are more likely to displace other drugs from protein binding sites include NSAID's, Phenylbutazone, salicylic acid, and sulfonamides.

METABOLISM INTERACTIONS

➢ Stimulation of metabolism

- Certain drugs stimulate the activity of hepatic microsomal enzymes. This effect is referred as enzyme induction.
- The increased activity is due to enhanced enzyme synthesis results in increased amounts of drug metabolizing enzyme.
- Enzyme induction will result in increased metabolism and excretion and reduced effect of agent which is metabolised by the hepatic enzymes.
- Eg : Warfarin and phenobarbital
- Phenobarbital increases the rate of metabolism of warfarin resulting in decrease anticoagulant activity.

➢ Inhibition of metabolism

- If one drug inhibits metabolism of another drug it result in prolonged action or intensified activity.
- Alcohol-disulfiram inhibit the activity of alcohol dehydrogenase, thus inhibiting oxidation of acetaldehyde , an oxidation product of alcohol. This result in accumulation of acetaldehyde and development of the characteristic unpleasant effect of disulfiram.

DRUG ELIMINATION REACTIONS

- Drug elimination reactions are those where the excretion pattern of the object drug is altered.
- The major routes for elimination of drugs remain the kidney and bile, but there are no significant drug - drug interactions through bile elimination, but only drug-disease ones.
- Some drugs are excreted from the body unchanged in the active form, usually in the urine or via the biliary tract in the faeces.
- Drugs that are chiefly excreted by the kidneys can get involved in drug interactions by different mechanisms such as competition at active transport sites, or alterations in glomerular Filtration, passive renal tubular reabsorption or active secretion and urinary pH.

- Changes in renal drug clearance may occur due to effects on renal tubular function or urine pH.
- For example, probenecid reduces the renal clearance of anionic drugs such as methotrexate and penicillin.
- Major mechanisms of excretion interactions are:

✓ Alteration in renal blood flow

✓ Alteration of urine pH

✓ Competition for active secretions

✓ Forced diuresis

- Alteration in renal blood flow- eg: NSAIDs (reduce renal blood flow) with Lithium.
- Alteration of urine pH- eg: Antacids with Amphetamine
- Competition for active secretion- eg: Probenecid and Penicillin

References

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THANK YOU