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Drug Interaction

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ABSTRACT

All pharmacists working in a clinical setting whether dispensing medicine or advice require a well-grounded knowledge of drug interactions to prevent harm to patients from medicine combination. The mechanisms by which most interactions develop are well documented and related tom the basic processes by which a drug acts and are acted upon in the body.

Keywords: Pharmacists, Clinical, Medicine, Drug, Patient.

INTRODUTION

A drug- drug interaction may be defined as the phenomenon that occurs when the effects or pharmacokinetics of a drug are altered by prior administration or co-administration of a second drug. Pharmacists play a valuable role in the screening for interactions and advising on management when interactions occur. This may beat patient's bed side as a part of the dispensing process or during the sale of a nonprescription medicine.

Types of drug interactions

Drug interactions are frequently characterized as either pharmacokinetic or pharmacodynamics interactions.

Pharmacokinetic interactions are those in which one drug alters the rate or extent of absorption distribution or elimination (metabolism or excretion) of another drug. This is most commonly measured by a change in one or more kinetic parameters such as maximum serum concentration, area under the concentration -time curve, half-life, total amount of drug excreted in urine etc.

Pharmacodynamics interactions are those in which one drug induces a change in a patient's response to a drug without altering the object drugs. Pharmacokinetics that is, one may see a change in drug action without altered plasma concentration. An example of this change is the increase in the toxicity of digoxin produced by potassium wasting diuretics [1].

Pharmacological interaction that is concurrent use of two or more drugs with similar or opposing pharmacological actions (eg: use of alcohol with an antianxiety drug and a hypnotic or antihistamine) are a form of pharmacodynamics interactions.

Mechanism of pharmacokinetic interaction altered absorption

Most interaction involving altered drug absorption occurs on the gut, the absorption of a drug from the GI tract may develop in some situation the absorption of drug. May reduced and its therapeutic activity compromised. In others absorption may be delayed but the same amount of drug is absorbed eventually.

Alteration of pH

It is recognized that the non-ionized form of the drug the (more lipid soluble form) will be absorbed more readily than the ionized form. Example: Ketoconazole – antacid.

Antacids Decrease the tablet dissolution of Ketoconazole (acidic) Therefore, the drug must be separated by at least 2 hour in the time of administration.

Alteration of motility: Cathartics by increasing GI motility may increase the rate at which another drug passes through the GI tract which results in decreased absorption of drugs.
Example: Metoclopramide.

Effect of food: Effect of food in influencing drug absorption sometimes is due to its action in slowing gastric emptying. However food also may affect absorption by binding with drugs decreasing the access of drugs to site of absorption, altering the dissolution rate of drugs or altering the PH of GI contents.
Example: Drug-Food interactions, Grapefruit juice and Terfenadine, Grapefruit juice and Cyclosporine, Grapefruit juice and Felodipine.
Grapefruit contains: Furanocoumarin compounds that can selectively inhibits CYP3A.

Alteration of metabolism in the GI tract: The absorption of certain agents is influenced by the extent to which they are metabolized in the GI tract.

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.
Eg: 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.

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 inhibition: It is the decrease of the rate of metabolism of a drug by another one. This will lead to the increase of the concentration of the target drug and leading to the increase of its toxicity. Inhibition of the enzyme may be due to the competition on its binding sites, so the onset of action is short may be within 24 hour. When an enzyme inducer (e.g. carbamazepine) is administered with an inhibitor (verapamil), the effect of the inhibitor will be predominant [2].

Alteration of GI flora: Changes in the microbial flora of the GI tract caused by antibiotics may alter the production or metabolism of certain agents, with a resulting change in the amount of agent being absorbed and available to produce a clinical response
Eg: Digoxin – Antibiotics.
40% or more of the administered digoxin dose is metabolized by the intestinal flora. Antibiotics kill a large number of the normal flora of the intestine Increase digoxin concentration and increase its toxicity.

Alteration of distribution: Displacement from protein binding sites: An interaction of this type may occur when two drugs that are capable of binding to proteins are administered concurrently. Although, they may bind at different sites on the protein molecule. The binding characteristics of one of the drug may be altered (noncompetitive displacement).
Probably, more significant situations in which the drugs are capable of binding to the same sites on the protein (competitive displacement).
Eg: Displaced protein binding. It depends on the affinity of the drug to plasma protein. The most likely bound drugs is capable to displace others. The free drug is increased by displacement by another drug with higher affinity. Phenytoin is a highly bound to plasma protein (90%), Tolbutamide (96%), and warfarin (99%). Drugs that displace these agents are Aspirin, Sulfonamides, and phenylbutazone.

Stimulation of metabolism

Many drug interactions have resulted from the ability of one drug to stimulate the metabolism of another, by increasing the activity of hepatic enzymes that are involved in the metabolism

of numerous therapeutic agents.

Eg: Warfarin – Phenobarbital, Oral contraceptives, Smoking, Alcohol, Levodopa – pyridoxine.

Inhibition of metabolism

One drug has initiated the metabolism of another usually resulting in a prolonged and intensified activity.

Eg: Alcohol – Disulfiram, Theophylline- Macrolide antibiotics

Alteration of excretion: Most drugs and their metabolites are excreted through the kidneys and the most important clinical implication of altering the renal excretion involves the use of drugs that are excreted in the form of active metabolite.

Renal excretion

Active tubular reabsorption: It occurs in the proximal tubules. The drug combines with a secretion specific protein to pass through. When a drug has the proximal tubules. 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.

Eg: Probenecid decreases tubular secretion of methotrexate.

Passive tubular reabsorption: Excretion and reabsorption of drugs occur in the tubules by passive diffusion which is regulated by concentration and lipid solubility. Ionized drugs are reabsorbed lower than non-ionized ones

Eg: Sodium bicarbonate increases lithium clearance and decreases its action.

Antacids Increases salicylates clearance and decreases its action.

Alteration of urinary P^H Eg: Salicylates- Acidifying and alkalizing agents, Amphetamines – Alkalizing agents.

Alteration of active transport: Eg: Penicillins – Probencid**,** Methotrexate - NSAID's, Lithium - NSAID's

Alteration of drug transport: P-glycoprotein functions as a transport system that may act as a barrier for certain agents and as a pump that facilitates the transport of certain agents, across membranes.

Eg: Digoxin – Quinidine/ Verapamil, Loperamide – P-glycoprotein.

Pharmacodynamics interactions

Mechanism: These occur when a drug has an additive or antagonistic effect on the pharmacological action of another medicine.

Pharmacological synergism: Synergism occurs when two drugs with a similar pharmacological or side effect are given together to produce an additive effect.

Eg: CNS depressants, Alcohol – other CNS depressants, Drugs having anticholinergic activity, Drugs exhibiting hypotensive effects, NSAID's.

Pharmacological antagonism: Interactions resulting from the use of two drugs with opposive effects should be easier to detect.

Eg: NSAID's – thiazide diuretics, Tricyclic antidepressants-antiepileptic.

Interaction at receptor site

Eg: MAOI'S – sympathomimetic agents, MAOI'S- Tricyclic antidepressants, MAOI'S- selective serotonin reuptake inhibitors.

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