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A REVIEW ON MECHANISM OF DRUG INTERACTIONS AND ITS MANAGEMENT IN CLINICAL PRACTICE

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ABSTRACT

Drug interactions occur when two or more drugs prescribed together drug action are modified by the diet, environmental factors, disease, drug excipients and results in shows harmful effects. Drug interactions can exhibit pharmacokinetic and pharmacodynamic responses increases or reduce the action of the original drug. Pharmacokinetic drug interactions are influenced by alterations in drug absorption, distribution, metabolism or excretion process this can decrease or increase the activity of the interacting drug. Pharmacodynamic interactions occurred with when drug interact with receptor and shows agonist or antagonist responses. The drug interactions responses may be major, moderate, minor can alter the individual drug actions. The severity of drug interactions may create death, disability, life threatening conditions to the patients. Drug interactions can be managed through avoiding the drug combinations, dosage adjustment, educating the heath care professionals and patients about drug interactions severity and dosage adjustment, drug modification practices can promote effective treatment outcomes. Early identifications of risk factors and implementing the software based advanced screening techniques to identify drug interactions and the establishment of drug information centers in the hospitals can prevent the progression of drug harmful effects to the patients.

Keywords: Pharmacokinetics, Pharmacodynamics, Drug interactions, Drug information centers, Drug combinations

INTRODUCTION

Drug interactions classification includes antagonism, synergism, potentiation, and interaction with metabolism. Antagonism means that one drug blocks the effect of another. A drug-drug interaction may increase or decrease the effects of individual and combined drugs. Synergism is defined as when two or more drugs work together against one target; produce an effect that is greater than the individual effect of the two combined drugs. Potentiation is defined as drug increases the effects of drug B, often by increasing the levels of drug B in the systemic stream.

Mechanisms of drug interactions:

Pharmacodynamic interactions one drug alters the response of another drug it may be agonist or antagonist action **[1-2]**.

Drug interactions are classified into three categories, it includes:

- Pharmacokinetic
- Pharmacodynamic
- Physicochemical

Physicochemical drug interaction: It may occur because of an incompatibility between chemical structural moieties.

Pharmacokinetic drug interactions:

Pharmacokinetic drug interactions occur when one drug alters the absorption, distribution, metabolism and excretion of another drug **[3-4]**.

Absorption:

It is the process where the movement of drug from the site of administration into the vascular stream. The absorption mechanism is proceeding with active transport, passive diffusion and facilitated transport mechanisms etc.

The oral route of drug administration absorption alter by the presence of various factors such as

- Altered gastric pH
- Chelation mechanism
- Adsorption
- Altered gastric emptying and intestinal motility
- Altered transport, and protein binding mechanisms

Effect on Absorption:

- Antacid - Penicillin G: Penicillin G being acid sensitive, its absorption from the stomach will be a function of the pH of the stomach.
- Antacid-Phenobarbital: Phenobarbital remains in a non-ionised form in an acidic medium and hence its absorption is decreased when antacid is given. Antacid administration will raise the pH of the stomach.

- Antacid-Pseudoephedrine: Being a basic drug, the absorption of pseudoephedrine will be enhanced with the simultaneous administration of antacids as the drug remains in a non-ionised form.
- Antacid - Enteric coated medicines: If enteric coated medicines are given with antacids, they will disintegrate and cause irritation and vomiting e.g. Bisacodyl.

Effect on transport system:

- **Food - Antibiotics:** The presence of food slows the process of stomach emptying and affects the dissolution rate. Hence food may influence the absorption of many drugs. Antibiotics like penicillins, tetracyclines, erythromycin and lincomycin are recommended to be given 1 hr before or 2 hr after a meal to permit maximum absorption.
- **Griseofulvin**: Phenobarbital: Phenobarbital may increase the secretion of bile and increase peristalsis. This would decrease the transit time in the upper portion of the GI tract where griseofulvin is absorbed most efficiently. This Phenobarbital reduces the absorption of griseofulvin.

Complex formation:

Complexation should be considered from a broader perspective and may involve drug-drug, dug-additive or even drug-container interactions. Complexes may be soluble or insoluble and may affect drug absorption.

Tetracycline - Metals: It is well established that the absorption of tetracyclines is reduced in presence of certain metals like calcium, aluminium, magnesium, bismuth and iron. Antacids containing the slats of these metals would also reduce the absorption of tetracyclines. As milk contains calcium it may also reduce the absorption of tetracyclines. The inhibition of tetracycline salts due to complexation with iron salts.

Changes in pH

Basic drugs are more soluble in acidic fluids, and acidic drugs are more soluble in basic fluids. Therefore, compounds that create an environment with a specific pH that decreases the solubility of compounds need divergent pH for absorption.

Chelation and Adsorption

Chelation involves the formation of a ring structure between a metal ion and an organic molecule forms an insoluble compound that is unable to cross the intestinal mucosa because of the lack of drug dissolution. Adsorption is the process of ion binding or hydrogen binding. Example: penicillin G, cephalexin adsorbs cholestyramine. This process decreases antibiotic exposure, so that the concomitant administration of adsorbents and antibiotics should be avoided.

Changes in gastric emptying

The presence or absence of food can affect the absorption of anti-infectives by various mechanisms. High-fat meals can significantly increase the extent of absorption of fat-soluble compounds such as griseofulvin, cefpodoxime etc. Prolong period of the stomach causes excessive degradation of acid-labile compounds such as penicillin and erythromycin. Because the primary location of drug absorption is the small intestine that changes in gastric emptying have major effects on drug response.

Distribution

The two main plasma proteins are responsible for transporting drugs to the tissues. If the two drugs are having highly plasma protein bounding, one drug can displace the other from the protein binding sites increases the concentration of unbound drugs and finally increase the efficacy of the drug.

Distribution can be affected by:

- Loss of albumin and α1-acid glycoprotein
- Displacement from tissue binding sites
- Chelation of drug from tissues
- Competition for plasma protein binding

Drug interactions affecting distribution:

Protein binding and displacement

Albumin contains both basic and acidic groups and binds to basic and acidic drugs. Acidic drugs (i.e., penicillins, sulfonamides) are strongly bound to albumin, and basic drugs (i.e., erythromycin) are weakly bound to albumin at a larger number of sites. Basic drugs may also preferentially bind to alpha-1-acid glycoprotein. When a protein displacement interaction occurs that increases the free drug in plasma and rapidly distribute throughout the body. An increase in unbound drug concentration in metabolism and elimination sites will augment the rates of elimination **[5-8]**.

Drug interactions affecting drug metabolism

The principal site of drug metabolism takes place in the liver. Metabolism in general converts lipophilic compounds into ionized metabolites for renal elimination. Drug-metabolism occurs in two ways that are synthetic (Phase I) and synthetic (Phase II) reactions. Phase I reactions include oxidation, reduction, and hydrolysis and occur in the membrane of hepatocyte endoplasmic reticula. Phase II reactions are associated with conjugation reactions.

Mechanisms of Induction

Induction occurs rapidly which is determined by the half-life of the substrate and also by the rate of isozyme turnover.

Phase II Drug Metabolism

The term Phase II metabolism represent synthetic reactions occurring after Phase I processes. Phase II metabolism process consists of various isozymes that include uridine 5-diphosphate (UDP)-glucuronosyl-transferases, glutathione –*S*- transferase, acetyltransferases, sulfotransferases, and methyl transferases.

Elimination

Change in drug elimination

Drug metabolites are eliminated by the kidney through three different processes: glomerular filtration, passive tubular re-absorption, and active tubular secretion. Drug interactions can occur at the level of re-absorption.

Glomerular Filtration

Rates of glomerular filtration can be affected by changes in renal blood flow, cardiac output, and extent of protein binding. Highly protein-bound drugs increase glomerular filtration and finally increase drug elimination.

Tubular Secretion

The most common renal drug interactions occur at the transport site of tubular secretion. Many organic anionic, cationic drugs and metabolites compete with each other for secretion. Eg. Sulfonamides and zidovudine.

Tubular Reabsorption

Reabsorption of drugs from the tubular lumen proceeds with passive diffusion and active transport processes. Only non-ionized compounds are passively reabsorbed from the renal tubule, and urinary pH can modify the reabsorption of weak organic acids and bases. Renal clearance of weak organic bases increase with urine acidification (salicylates and ascorbic acid) and decrease with urine alkalinization (i.e., by antacids, calcium carbonate)

Pharmacodynamic drug Interactions:

Pharmacodynamic interactions occur when two drugs have equal pharmacological effects e.g. alcohol and tricyclic antidepressants **[9-10]**.

These interactions can be classified as either:

Antagonistic

when the effects oppose each other. E.g. Neostigmine indirectly antagonizes the effect of NDMRs by increasing the level of ACh at the neuro muscular junction.

Additive effect

The combined effect is produced by the action of more than two agents are being equal to the sum of their individual effects. E.g. Midazolam with propofol reduces the effect.

Non-competitive antagonism:

Non-competitive antagonism occurs when the agonist and antagonist act on completely different receptor locations to produce antagonism e.g. acetylcholine and papaverine.

Competitive antagonism:

It involves the competition between agonist and antagonist for the same receptors and the extent to which the antagonist opposes the pharmacological action of the agonist which is determined by relative number of receptors occupied by the two receptors.

Synergistic effect:

An interaction between two or more drugs which causes the total effect of the drugs to be more than the sum of the effects of the individual drug. Eg: Co-administration of remifentanil and propofol has a synergistic effect in the maintenance of anaesthesia.

Physiological antagonism: It involves that two endogenous substances antagonize the effect of each other by acting at different receptor sites. Eg. Adrenaline and histamine

Drug interactions can be further categorized into 3 groups:

1. Drug-drug interactions
2. Drug-food interactions
3. Drug-disease interactions
4. Drug-herb interactions

Drug-drug Interactions

It includes when two or more drugs react with each other. Drugs with a narrow therapeutic range cause the incidence of serious drug interactions **[11-13]**. It was depicted in **Table 1**.

Drug-food interactions

These interactions occur when drugs react with foods, dietary supplements and interfere with drug absorption. Alcohol with metronidazole causes skin flushing, headache, and palpitations. Grapefruit juice enhances the effect of drugs like simvastatin, nifedipine and ciclosporin and the consumption of grapefruit juice should best be avoided. Dairy products contain calcium that reduces the absorption of biphosphonates, levothyroxine. E.g. ciprofloxacin and tetracycline.

Drug-disease interactions: It can occur when a drug worsens a medical condition. For example, a nasal decongestant containing pseudoephedrine increases blood pressure.

Drug-herb interactions: It was showed in **Table 2**.

Table 1: Drug-drug Interactions

Interacting Drug	Interacting Drug	Mechanism of Interaction
Warfarin	NSAIDs	Drug displacement
Erythromycin	Cisapride	Inhibition of cisapride metabolism
Erythromycin	Theophylline	Inhibition of theophylline metabolism

Table 2: Drug-herb interactions [14]:

Herb	Source	Interactions
Ginkgo yinxingye	Ginkgo biloba	warfarin (cause bleeding)
Garlic dasuan	Allium sativum	warfarin (cause bleeding)
Salvia danshen	Salvia miltiorrhiza	warfarin (cause bleeding)
Ginger jiang	Zingiber officinale	sulfaguanidine (Enhance absorption)
Licorice gancao	Glycyrrhiza uralensis	glycosides (Increased sensitivity)
Tang-kuei danggui	Angelica sinensis	warfarin (Causes bleeding)
Ginseng renshen	Panax ginseng	Antidepressants (Cause manic episodes)
Astragalus huangqi	Astragalus embranaceus	Cyclosporine (Impair immuno-suppressive effects)
St. John's wort tianjihuang	Hypericum perforatum	Serotonin-uptake inhibitors (Cause mild serotonin syndrome)

Drug interaction severity [15-17]:

Minor: Drug interactions clinical effects are limited. Medication change is usually not required.

Moderate: Drug interactions result in potential deterioration of the patient's condition. The patient should be monitored for the clinical manifestations of the interaction and medical intervention or a change in therapy is required.

Severe: The drug interaction between medications causes life-threatening or permanent damage.

Patient related risks for drug-drug interactions

- Age
- Presence of multiple diseases
- Multiple medication use
- Narrow therapeutic index medications
- Pharmacokinetics
- Allergies
- Genes
- Poor diet
- Gender
- Past history of drug interactions
- Drug doses
- Combined therapy

Clinical abnormality of Drug Interactions:

- Life-threatening
- Death
- Permanent impairment of organs
- Disability
- Congenital anomaly
- Hospitalization

Sources for identification of drug interactions [18]:

Clinically identification of drug interactions can be obtained from the following sources:

- Stockley drug interactions text book
- Martindale - the complete drug reference

- National Medicines Information Centre
- British national formulary

Management of drug interactions [19-21]:

- Educating health care practitioners and patients on potential interactions to prevent drug related problems.
- Implementing advanced software screening techniques for the identification of drug *i*nteractions in health care.
- Avoid prescribing of drug combinations
- Adjustment of dosage forms
- Regular monitoring of drug therapy
- Continuous review of new prescription drugs and over-the-counter drugs.
- Identification of patient demographic details and clinical information to provide the right medication to patients.
- Regular interaction with patients to prevent the development of drug related problems.

CONCLUSION:

Drug interaction is a pharmacological response that occurs when two or more drugs acting simultaneously. The drug effect may change associated with various patient related risk factors. The severe drug interactions outcome leads to an increase in the toxicity of the drug. Drug interactions can be managed through avoiding the prescribing of drug combinations, regular analysis of drugs, dosage adjustment, educating the heath care professionals and patients on prevention and management of drug interactions and the drug modification practices could promote effective treatment outcomes **[22-23]**. Early identification of risk factors and implementing the software based advanced screening techniques to identify the drug interactions and the establishment of drug information centers in the hospitals can lower the harmful drug effects to the individual patients.

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