Chapter ... 5

DRUG INTERACTIONS

♦ **LEARNING OBJECTIVES** ♦

After completing this unit, reader should be able to:

- ❖ Know drug interaction and its types.
- ❖ Describe the mechanism involved in drug interaction.
- ❖ Know management of drug interaction.

5.1 INTRODUCTION

A drug interaction has occurred when the administration of one drug alters the clinical effects of another. The result may be an increase or decrease in either the beneficial or harmful effects of the second agent. Although the number of potential interacting drug combinations is very large only a small number are relevant in clinical practice.

- **Drug-drug interaction:** A reaction between two or more drugs. This can involve prescription medications, over-the-counter medicines (OTC), and herbs, vitamins, and supplements. An example of this is someone who takes a diuretic; a drug that attempts to rid the body of excess water and salt and also takes ibuprofen. The ibuprofen may reduce the diuretic's effectiveness because ibuprofen often causes the body to retain salt and fluid.
- **Drug-food interaction:** When food or beverage intake alters a drug's effect. If someone taking certain statins to lower cholesterol drinks a lot of grapefruit juice, this can cause too much of the drug to stay in the body. This may increase their risk for liver damage or kidney failure.
- **Drug-alcohol interaction:** Certain medications that should not be taken with alcohol. Often, combining the two can cause tiredness and delayed reactions, and can also increase your risk for negative side effects.
- **Drug-disease interaction:** The use of a drug that alters or worsens a condition or disease the person has. For example, certain decongestants people take for colds can increase blood pressure. This is a potentially dangerous interaction for people with high blood pressure (hypertension).

- **Drug-laboratory interaction:** When a medication interferes with a laboratory test. This can result in inaccurate test results. For instance, certain antidepressants (tricyclic antidepressants) have been shown to interfere with skin prick tests used to determine allergies someone may have.

5.2 DRUG-DRUG INTERACTION CLASSIFICATION

DDIs can be classified as Pharmaceutical and Pharmacological interaction according to where the interaction occurs: outside or inside of the body. Most pharmaceutical drug interactions, often called incompatibilities, occur outside the body whereas pharmacological interactions occur within the body. Pharmaceutical interactions generally occur before drugs are actually administered to the patient and whereas pharmacological interactions, which occur inside the body.

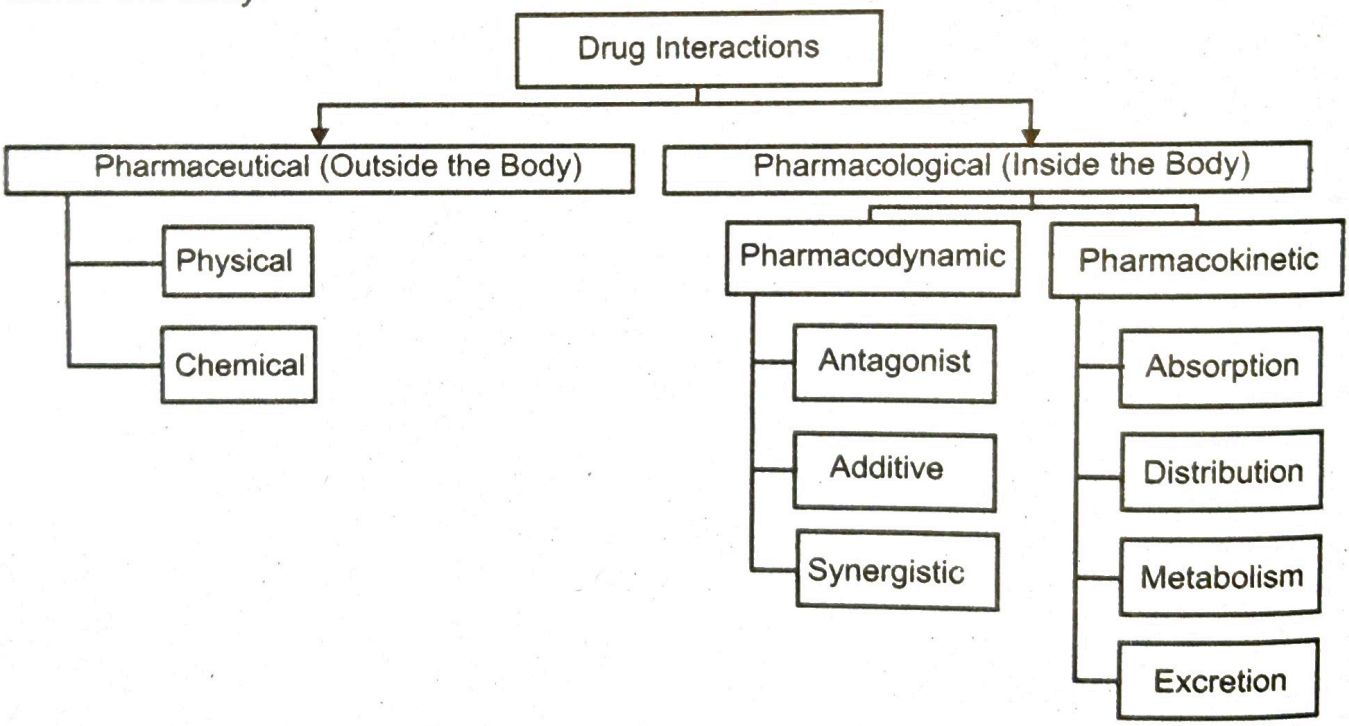

Fig. 5.1: Classification of Drug-Drug Interactions

5.3 PHARMACEUTICAL INTERACTIONS

Pharmaceutical drug interactions can be divided in to chemical and physical reactions. A chemical reaction is occurs due to the incompatibility between two drugs administered concurrently. For example, Phenytoin (Dilantin) and Lorazepam (Ativan), become ineffective if mixed together in the same IV bag or syringe. Physical reaction occurs when physically altering a drug formulation such as by crushing a sustained-release tablet could result in the drug being released more quickly and/or in a larger amount. Alcohol or food given with some sustained release products may cause similar problems.

5.4 PHARMACOLOGICAL INTERACTIONS

Pharmacological interactions are most commonly occurring DDIs. Pharmacological interactions are classified as Pharmacodynamic interactions and Pharmacokinetic

interactions. Pharmacokinetic interactions result from alterations in a drug's absorption, distribution, metabolism, or excretion characteristics. Pharmacodynamic interactions are a result of the influence of combined treatment at a site of biological activity and yield altered pharmacological actions at standard plasma concentrations. Although drug interactions occur through a variety of mechanisms, the effects are the same: the potentiation or antagonism of the effects of drugs.

5.5 PHARMACOKINETIC INTERACTIONS

Pharmacokinetics is defined as what the body does to a drug, or more formally, the movement of drugs through the body including the processes of absorption, distribution, metabolism, and excretion (ADME).

Inhibition of Absorption: Drugs that act as binding agents such as Cholestyramine and Colestipol can impair the bioavailability of other drugs. This will result in a reduction in the therapeutic effect of the object drug. The effect can be profound with some combinations such as Cholestyramine and furosemide. Some drugs such as Fluoroquinolone antibiotics (e.g., Cipro) are susceptible to chelation with cations such as aluminium, magnesium, and iron. Other drugs such as Itraconazole, Ketoconazole, Glipizide, Glyburide, Cefpodoxime, and Cefuroxime have pH dependent absorption. The amount of these drugs that is absorbed from the gut may be increased or decreased by drugs that increase stomach pH.

Enzyme Inhibition Increasing Risk of Toxicity: Most drugs are metabolized to inactive or less active metabolites by enzymes in the liver and intestine. Inhibition of this metabolism can increase the effect of the object drug. If the increase in effect is large enough, drug toxicity may result. This is one of the most common mechanisms by which clinically important drug interactions occur. Since only a few different cytochrome P450 isozymes are involved in drug metabolism, competition between two drugs for these isozymes will occasionally occur. This competition may result in one drug interfering with the metabolism of another drug.

For example, inhibitors of CYP1A2 can increase the risk of toxicity from clozapine or theophylline. Inhibitors of CYP2C9 can increase the risk of toxicity from Phenytoin, Tolbutamide, and oral anticoagulants such as Warfarin. Inhibitors of CYP3A4 can increase the risk of toxicity from many drugs, including Carbamazepine, Cisapride, Cyclosporine, Ergot alkaloids, Lovastatin, Pimozide, Protease inhibitors, Rifabutin, Simvastatin, Tacrolimus, and Vinca alkaloids.

Enzyme Inhibitors Resulting in Reduced Drug Effect: A small number of drugs are not active in the form administered to patients. These drugs are known as prodrugs and require activation by enzymes in the body before they can produce their effect. Inhibition of the metabolism of these prodrugs may reduce the amount of active drug formed, and decrease or eliminate the therapeutic effect. For example, the analgesic and toxic effects of codeine appear to result from its conversion to morphine by CYP2D6. Thus, CYP2D6 inhibitors can impair the therapeutic effect of Codeine. CYP2D6 inhibitors may similarly affect the analgesic effect of Hydrocodone.

Table 5.1: Potential Mechanisms of Drug Interactions Involving Absorption and Distribution

Absorption	Distribution	Metabolism	Excretion
• Altered gastric pH • Chelation of compounds • Adsorption of compounds • Altered gastric emptying • Altered intestinal motility • Altered intestinal blood flow • Altered active and passive intestinal transport • Altered intestinal cytochrome P450 isozyme activity • Altered intestinal P-glycoprotein activity	• Altered protein binding	**Phase I (Non-synthetic)** • Genetic polymorphisms • Inhibition of activity • Suppression of activity • Induction of activity **Phase II (Synthetic)** • Genetic polymorphisms • Inhibition of activity • Induction of activity	• Glomerular filtration • Tubular secretion • Tubular reabsorption

Enzyme Induction Resulting in Reduced Drug Effect: Some drugs called "enzyme inducers"—are capable of increasing the activity of drug metabolizing enzymes, resulting in a decrease in the effect of certain other drugs. Examples of enzyme inducers include Aminoglutethimide, Barbiturates, Carbamazepine, Glutethimide, Griseofulvin, Phenytoin, Primidone, Rifabutin, Rifampin, and Troglitazone. Some drugs, such as ritonavir, may act as either an enzyme inhibitor or an enzyme inducer, depending on the situation. Drugs metabolized by CYP3A4 or CYP2C9 are particularly susceptible to enzyme induction. In some cases, especially for drugs that undergo extensive first-pass metabolism by CYP3A4 in the gut wall and liver, the reduction in serum concentrations of the object drug can be profound.

Enzyme Induction Resulting in Toxic Metabolites: Some drugs are converted to toxic metabolites by drug metabolizing enzymes. For example, the analgesic acetaminophen is converted primarily to non-toxic metabolites, but a small amount is converted to a cytototoxic metabolite. Enzyme inducers can increase the formation of the toxic metabolite and increase the risk of hepatotoxicity as well as damage to other organs.

Altered Renal Elimination: For some drugs, active secretion into the renal tubules is an important route of elimination. For example, digoxin is eliminated primarily through renal excretion, and drugs such as Amiodarone, Clarithromycin, Itraconazole, Propafenone, and Quinidine can inhibit this process. Digoxin toxicity may result.

5.6 PHARMACODYNAMIC DRUG INTERACTIONS

The term "pharmacodynamic interactions" refers to interactions in which drugs influence each other's effects directly. As a rule, for example, sedatives can potentiate each other. The same is true of alcohol, which can potentiate the sedative effects of many drugs.

Additive Pharmacodynamic Effects: When two or more drugs with similar pharmacodynamic effects are given, the additive effects may result in excessive response and toxicity. Examples include combinations of drugs that prolong the QT interval resulting in ventricular arrhythmias, and combining drugs with hyperkalemic effects resulting in hyperkalemia.

Antagonistic Pharmacodynamic Effects: Drugs with opposing pharmacodynamic effects may reduce the response to one or both drugs. For example, drugs that tend to increase blood pressure (such as non-steroidal anti-inflammatory drugs) may inhibit the antihypertensive effect of drugs such as ACE inhibitors. Another example would be inhibition of the response to benzodiazepines by the concurrent use of theophylline.

Table 5.2: Examples of Pharmacodynamic Interactions

Substance I	Substance II	Possible effect
Additive interactions		
NSAIDs	SSRI, phenprocoumon	Increased risk of bleeding
NSAIDs	Glucocorticoids	Increased risk of gastric bleeding
ACE inhibitors	Spironolactone, amiloride	Hyperkalemia
SSRIs	Triptans	Serotonin syndrome
Tricyclic antidepressants	Low-potency neuroleptics	Increased anticholinergic effects
Quinolones	Macrolides, citalopram	QT-interval prolongation, torsade de pointes
Antagonistic interactions		
Acetylsalicylic acid	Ibuprofen	Reduced effects
ACE inhibitors	NSAIDs	Reduced effects
Levodopa	Classical neuroleptics	Reduced effects
Phenprocoumon	Vitamin K	Reduced effects

SSRI, selective serotonin reuptake inhibitor; NSAID, nonsteroidal anti-inflammatory drug

QUESTIONS

1. Define drug interaction.
2. Write the types of drug interaction.
3. Write the mechanism of drug interaction with examples.

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