# UNIT 16 DRUG INTERACTION

**Structure**

16.1 Introduction
Objectives
16.2 Types of Drug Interaction
16.3 Pharmacokinetic Interaction
Drug Interactions involving Absorption
Drug Interactions involving Distribution
Drug Interactions during Metabolism
Drug Interactions during Excretion
16.4 Pharmacodynamics Interaction
16.5 Summary
16.6 Terminal Questions
16.7 Answers

## 16.1 INTRODUCTION

In the previous unit you have studied about the various types of poisoning and their treatment with antidotes and chelating agents. You have also learnt about the treatment of addiction cases. In this unit you shall study about the various pharmacokinetic and pharmacodynamic drug-drug interactions that may affect the drug absorption and subsequently their therapeutic efficacy.

**Objectives**

After studying this unit, you should be able to:

- explain the rational for co-administration of two or more drugs;
- explain the various phenomenon that can take place when two or more drugs are administered together;
- enumerate the different types of drug interactions that can take place in a biological system;
- explain the mechanism of drug antagonism and synergism with examples; and
- explain the importance of drug interactions in therapeutics with two or more examples.

## 16.1 INTRODUCTION

Drug interactions may be defined as an alteration in duration and/or onset of action of the pharmacokinetic and/or pharmacodynamic of one drug produced by another drug. The multiple drug therapy produces a combined effect, which may be antagonistic or synergistic in nature. In antagonism the effects of one drug are reduced or abolished by the second drug, and in synergism the effects

may be additive or potentiative in nature. Both these effects may be harmful or useful to the patient in a particular disease. The drug interactions may be divided into:

i) *Pharmacokinetic,* which occur at the level of absorption, distribution, metabolism and excretion of one drug by another.

ii) *Pharmacodynamics,* which occur at the site of drug action involving the receptors.

## 16.3 PHARMACOKINETIC INTERACTIONS

The drug may interact with another drug at any point during their absorption, distribution, metabolism and excretion.

### 16.3.1 Drug Interactions Involving Absorption

Important drug interactions include antacids which contain calcium, magnesium or aluminium that interfere with absorption of tetracycline by forming a 'chelate' with the metals; carbonates prevent absorption of iron; cholestyramine interferes with the absorption of certain drugs like warfarin, thyroxine and digitalis glycosides. Some important drug interactions at the site of absorption are shown in Table 16.1.

**Table 16.1: Drug interactions at the sites of absorption**

i) **Interaction due to the formation of chelate complex**

| | | |
|---|---|---|
| Antacids | Tetracycline, isoniazid, atenolol, chlorpromazine penicillamine, digoxin, ranitidine | Decreased absorption |
| Antacids | Bishydroxycoumarin | Increased absorption |
| Cholestyramine | Warfarin, digitoxin, cephalexin and chlorothiazide | Decreased absorption |
| Activated charcoal | Tolbutamide, theophylline Phenytoin, digoxin, carbamazepine | Decreased absorption |
| Activated charcoal | Piroxicam, theophylline | Increased absorption |
| Mineral oil | Fat soluble vitamins | Decreased absorption |
| Iron preparation | Methyldopa | Decreased absorption |

ii) **Interaction due to the alteration in gastric pH**

| | | |
|---|---|---|
| Antacids | Cimetidine | Decreased absorption |
| Cimetidine | Tetracycline | Decreased absorption |

iii) **Interaction due to increase in gastric motility**

| | | |
|---|---|---|
| Metoclopramide | Digoxin, cimetidine | Decreased absorption |
| Metoclopramide | Chlorothiazide, acetaminophen | Increased absorption |

iv) **Interaction due to decrease in gastric motility**

| | | |
|---|---|---|
| Antacids | Isoniazid, phenytoin, propranolol and benzodiazepines | Decreased absorption |
| Amitriptyline | Bishydroxycoumarin | Increased absorption |

v) **Interaction due to alteration of gut**

| | | |
|---|---|---|
| Cimetidine | Lidocaine, propranolol, verapamil, imipramine | Increased absorption |

### 16.3.2 Drug Interactions Involving Distribution

After absorption into blood many drugs are bound to plasma proteins, the portion of the drug which is being transported in the bound form is inactive (pharmacologically) and only the free part or molecule that diffuse into the tissues produce their effect. The most important drug interaction caused by displacement from plasma proteins occur with coumarin anticoagulants. Phenylbutazone displaces warfarin from its binding site thereby causing bleeding. Tolbutamide is displaced by dicumarol resulting in severe hypoglycemia (See Table 16.2).

**Table 16.2: Interactions caused by displacement of drugs from plasma protein binding sites**

| **Drug displaced** | **Displacing agent** |
|---|---|
| Coumarin | Diazoxide, ethacrynic acid, phenylbutazone, NSAIDs |
| Tolbutamide | Dicumarol, phenylbutazone |
| Phenytoin | Tolbutamide, NSAIDs |
| Diazepam | Heparin |

NSAIDs = Nonsteroidal antiinflammatory drugs.

### 16.3.3 Drug Interactions during Metabolism

This type of interaction occurs when the metabolism of a drug is inhibited or decreased by another drug.

Certain drugs induce the hepatic microsomal enzyme system i.e. enzyme induction, which decreases the effectiveness of other drugs, for example, if phenobarbital is suddenly discontinued without lowering the dosage of coumarin, severe hemorrhage can occur. Some important drug interactions during metabolism are shown in Table 16.3 and 16.4.

**Table 16.3: Drugs that induce the metabolism**

| **Drug (inducing part)** | **Drug induced** |
|---|---|
| Chloral hydrate | Bishydroxycoumarin |
| Phenobarbital | Bishydroxycoumarin, digitoxin, phenylbutazone, phenytoin |
| Phenytoin | Carbamazepine, theophylline, oral contraceptives |

**Table 16.4: Drugs inhibit the metabolism of other drugs**

| **Drug causing inhibition** | **Drug inhibited** |
|---|---|
| Bishydroxycoumarin | Tolbutamide |
| Disulfiram | Phenytoin, theophylline, warfarin |
| Isoniazid | Phenytoin |
| Phenylbutazone | Tolbutamide, phenytoin |

### 16.3.4 Drug Interaction during Excretion

The renal drug clearance is influenced by alterations in glomerular filtration rate and tubular reabsorption or secretion rate.

The tubular secretion of penicillin is inhibited by probenecid, so that the blood concentration and its half life (therapeutic effects) is prolonged with the simultaneous use of these two drugs. Phenylbutazone can block the renal tubular reabsorption of uric acid, leading to uricosuria.

Quinidine inhibits the tubular secretion of digoxin which consequently raises the plasma digoxin concentration, which may be associated with toxicity. Certain other drugs also increase the digoxin concentration like verapamil, amiodarone, spironolactone etc.

Ammonium chloride increases urinary volume with acidification of urine. The excretion of amphetamine is decreased in relatively alkaline urine and has proved useful in 'the treatment of amphetamine intoxication'.

## 16.4 PHARMACODYNAMIC INTERACTIONS

Pharmacodynamic interactions take place at the site of drug action. When two or more drugs with similar pharmacological effects are administered together, an additive or synergistic effect is usually seen. These type of interactions are of two types:

The ***direct pharmacodynamic interactions*** occur when two drugs either act on the same site or on two different sites with a similar effect. When two drugs act on same site, they are either antagonist or synergist. For example:

**Antagonism:** Reversal of the effect of opiates with naloxone. Reversal of anticholinergic effects with tricyclic antidepressants and physostigmine.

**Synergism:** Increased anticoagulation of warfarin with clofibrate, corticosteroids, tetracycline, vitamin K and naloxone.

The ***indirect pharmacodynamic interactions*** are unrelated to the effects of the object drug, for example:

- Drugs which alter potassium content may have effect on the therapeutic effect of cardiac glycosides, which are enhanced by potassium depletion e.g., potassium-sparing diuretics, corticosteroids and purgatives.
- Diuretics like frusemide may attenuate the effects of oral hypoglycemic drugs.
- Drugs like salicylates, dipyridamole, phenylbutazone decrease the ability of platelets to aggregate, and thus impairing the haemostasis if warfarin induced bleeding occurs.
- The nonsteroidal antiinflammatory drugs like aspirin, indomethacin and phenylbutazone causes ulceration in gastro-intestinal tract which provides a site for bleeding in patients on anticoagulants.

The pharmacodynamic interactions are relatively common in practice, but they can be minimized if the interactions are anticipated and appropriate precautions are taken by avoiding irrational and unnecessary drugs combination.

**Table 16.5: Some clinically important drug interactions**

| **Drug affected** | **Drug interacting** | **Effect** |
|---|---|---|
| ***Gastrointestinal system*** | | |
| Carbenoxolone | Amiloride, spironolactone | Inhibition of ulcer healing. |

| Drug affected | Drug interacting | Effect |
|---|---|---|
| Cimetidine | Antacids | Reduced absorption if taken simultaneously. |
| Metoclopramide | Anticholinergic drugs such as atropine, propantheline, narcotic analgesics | Antagonism – they have opposing effects on gastrointestinal activity. |
| ***Cardiovascular system*** | | |
| Antiarrhythmic drugs | Any combination of two or more | Increased myocardial depression. |
| Lignocaine, mexiletine, | Diuretics: Bumetanide, | Antagonised by |
| Lignocaine | Cimetidine, propranolol | Increased risk of lignocaine toxicity. |
| Verapamil | β-adrenoceptor blocking drugs | Asystole, hypotension. |
| Digoxin & other cardiac glycosides | Diuretics: Bumetanide, furosemide, thiazides | Increased toxicity. |
| | Cholestyramine, colestipol | Reduced absorption. |
| | Phenobarbitone, rifampicin | Inhibition (Digitoxin only) |
| Diuretics | Indomethacin Carbenoxolone, corticosteroids, estrogens | Antagonism. |
| Aldosterone antagonists | Captopril, potassium supplements, | Hyperkalaemia. |
| ***Respiratory system*** | | |
| Theophylline | Cimetidine, erythromycin, influenza vaccine, oral contraceptives | Potentiation. |
| | Carbamazepine, phenytoin, rifampicin | Plasma concentration of theophylline may be reduced. |

| Drug affected | Drug interacting | Effect |
|---|---|---|
| ***Antihypertensive drugs*** | | |
| Captopril | Antiinflammatory analgesics such as indomethacin, phenylbutazone, corticotrophin, estrogens, oral contraceptives | Reduced effects. |
| | Alcohol, antidepressants, hypnotics, sedatives, tranquillizers, fenfluramine, levodopa, vasodilators such as nitrates, nifedipine, verapamil | Potentiation. |
| | Potassium supplements, potassium sparing diuretics. | Hyperkalaemia. |
| β-blockers | Indomethacin | Antagonism of antihypertensive effect. |
| | Nifedipine | Severe hypotension and heart failure occasionally. |
| | Sympathomimetic amines | Severe hypertension reported. |
| ***Infections*** | | |
| Aminoglycosides e.g. gentamycin etc., | Ethacrynic acid, furosemide, skeletal muscle relaxants | Increased ototoxicity, Increased neuromuscular blockade. |
| Cephalosporins | Furosemide, gentamycin | Increased nephrotoxicity. |
| Dapsone | Probenecid | Reduced excretion: Increased side effects. |
| Griseofulvin | Phenobarbitone | Impairs absorption. |
| Ketoconazole | Antacids, anticholinergic drugs, cimetidine, ranitidine | Decreased absorption. |

| Drug affected | Drug interacting | Effect |
|---|---|---|
| Metronidazole | Alcohol | 'Antabuse' reaction. |
| Tetracycline | Antacids, dairy products, oral iron, sucralfate, zinc sulphate | Reduced absorption. |
| ***Malignant disease & immunosuppression*** | | |
| Azathioprine, Mercaptopurine | Allopurinol | Potentiation: Increased toxicity. |
| Cyclosporin | Ketoconazole | Increased plasma concentration of cyclosporin. |
| Methotrexate | Aspirin, phenylbutazone, probenecid | Delayed excretion: Increased toxicity. |
| | Cotrimoxazole, pyrime-thamine | Increased anti-folate effect/ |
| ***Central nervous system*** | | |
| A. *Analgesics* | | |
| Aspirin | Metoclopramide | Potentiation. |
| Ketoprofen, | Probenecid | Probenecid |
| Paracetamol | Cholestyramine, metoclopramide | Reduced absorption. |
| B. *Antiepileptics* | | |
| Carbamazepine | Cimetidine, eryth- romycin, isoniazid | Potentiation. |
| Ethosuximide | Carbamazepine | Reduced plasma concentration of ethosuximide. |
| Phenobarbitone, primidone | Phenytoin, sodium valproate | Increased sedation, increased blood levels of phenobarbitone. |
| C. *Psychotropic drugs* | | |
| Hypnotics & sedatives | Alcohol, antidepressants, antihistaminics, narcotic analgesics | Potentiation. |

| Drug affected | Drug interacting | Effect |
|---|---|---|
| Tricyclic depressants | Alcohol | Potentiation of sedative effect. |
| | Oral contraceptives | Reduced effect. |
| | Phenothiazine derivatives | Increased side effects. |
| Imipramine | Cimetidine | Potentiation. |
| Lithium | Diuretics, NSAIDs , | Potentiation. |
| | Acetazolamide, Sodium bicarbonate | Increased lithium excretion. |
| | Haloperidol | Increased risk of extrapyramidal effects. |
| ***Endocrine system*** | | |
| Antidiabetic drugs | Alcohol | Antabuse like reaction. |
| | β-Blockers, MAO inhibitors | Potentiation. |
| | Corticosteroids, corticotrophin, diazoxide, oral contraceptives | Antagonism |
| | | Acidosis. |
| ***Gynaecology*** | | |
| Oral contraceptives | Barbiturates, carbamazepine, dichloralphenazone, phenytoin, primidone, rifampicin. | Reduced effect. |
| | Oral antibiotics such as ampicillin, tetracycline | Reduced effect. |

**SAQ 1**

a) Drug interactions can be divided into _____ and _____ interactions.

b) Activated charcoal _____ the absorption of digoxin.

c) Reversal of the effect of opiates with naloxone is an example of drug _____.

d) Cholestyramine _____ the absorption of digoxin and other cardiac glycosides.

e) Rifampacin blunts the action of antiepileptic drugs by increasing their _____.

g) Co-administration of metformin and alcohol can lead to the development of _____.

h) Antacids and dairy products _____ the absorption of tetracycline.

## 16.5 SUMMARY

- Drug interactions may be defined as an alteration in duration and/or onset of action of the pharmacokinetic and/or pharmacodynamic of one drug produced by another drug.
- Pharmacokinetic interactions occur at the level of absorption, distribution, metabolism and excretion of one drug by another.
- Pharmacodynamic interactions occur at the site of drug action involving the receptors.
- Drug interactions can either lead to Antagonism (decrease in drug action) or Synergism (increase in drug action).

## 16.6 TERMINAL QUESTIONS

1. What do you understand by the term Drug Interactions?
2. What are the different types of drug interactions?
3. Explain the phenomenon of drug Antagonism and Synergism.

## 16.7 ANSWERS

**Self Assessment Question**

1. a) Pharmacodynamic and Pharmacokinetic
   b) Decreases
   c) Antagonism
   d) Decreases
   e) Metabolism
   f) Lactic acidosis
   g) Decrease

**Terminal Questions**

1. When two or more drugs are administered together, they can either lead to alteration in duration and/or onset of action or alter the pharmacodynamic of each other. This is known as drug interaction.

2. This produces a combined effect, which may be antagonistic or synergistic in nature. In antagonism the effects of one drug are reduced or abolished by the second drug, and in synergism the effects may be additive or potentiative in nature. Both these effects may be harmful or useful to the patient in a particular disease. The drug interactions may be divided into:

   i) *Pharmacokinetic,* which occur at the level of absorption, distribution, metabolism and excretion of one drug by another.

   ii) *Pharmacodynamics,* which occur at the site of drug action involving the receptors.

3. When two or more drugs are administered together, they may alter the effectiveness of each other. This is known as drug interactions. When the alterations occur at the Pharmacodynamic level, they are known as antagonism or synergism.

   **Antagonism:** In this, one drug reduces the effectiveness of the other drug either by acting at the same receptor or by acting on some other physiological mechanism that opposes the drug effect. The net result is a decrease in drug actions. Antagonism can be summarized as follows:

   Combined effect of (A+B) < Effect of A + Effect of B

   Example: Reversal of the effect of opiates with naloxone (opiate antagonist).

   Reversal of anticholinergic effects with physostigmine.

   **Synergism:** In this, the net result of drug interaction is an increase in drug action. It can either be **additive**:

   Combined effect of (A+B) = Effect of A + Effect of B

   Or it can be **potentiated**:

   Combined effect of (A+B) > Effect of A + Effect of B

   Example: Increased anticoagulation of warfarin with clofibrate, corticosteroids, tetracycline, vitamin K and naloxone.