CHAPTER 1
INTRODUCTION

1.1. DEFINITION & BACKGROUND OF DRUG-DRUG INTERACTIONS

Patient’s safety and quality of life were considerably improved by the recent developments in pharmacotherapy. A huge number of drugs were available and their indications were increasing day by day as a result of such developments. Along with beneficial therapeutic effects drugs may also cause undesirable consequences. Development of drug-drug interactions (DDIs) is one among those consequences [1,2,3]. A drug-drug interaction can be defined as “a modification of the effect of a drug when it is co administered with another drug”. The effect can be enhanced or reduced pharmacological action of either substance or it may be an adverse effect which is not normally associated with either drug [4,5].

In the year 1895, the phenomenon of drug interaction was recognized by two physiologists Oliver and Schaefer. They observed that adrenal extract caused arrhythmias in dogs, anaesthetized with chloroform [6]. The clinical result of a drug-drug interaction may manifest as synergism, antagonism or idiosyncratic. They often result in increased risk of hospitalization, prolonged hospital stay, high treatment costs and even sometimes results in increased risk of death [7-13]. During the period 1999-2003, majority of the drugs were withdrawn from the US market which were associated with significant drug-drug interactions [14,15]. From the scientific, regulatory and health care communities, drug-drug interactions have received a great attention worldwide [16,17].

1.2. EPIDEMIOLOGY

Adverse events (AEs) associated with the use of drugs became a major public health problem in the last century involving both the patients and health care professionals [18,19]. Varying rates of potential DDIs that range from 5% to 8% was mostly carried out by the pharmacoepidemiologic studies in United States and Europe [16]. In United States, approximately 3% of the hospital admissions were done due to
drug interactions \cite{18,19}. About 1.3% of the all hospital admissions in Australia were due to adverse drug events (ADEs) in the year 2005. Another recent study revealed that 3% of the potential drug related problems were due to drug interactions in Australia \cite{20,21}. According to the Harvard Medical Practice study, about 20% of the AEs in a hospital inpatient setting were drug related and among them 8% were considered to be due to DDIs \cite{23,24}. Approximately 6-30% of the adverse drug events were due to DDIs which shows a direct adverse impact on the patient’s health outcomes and considerable economic burden on the health care system \cite{4}.

1.3. **CAUSES OF DRUG INTERACTIONS**

The activity of a drug can be influenced by many factors and majority of these factors are directly related to the drug regimen, time of administration, route of administration and duration of therapy. Other factors related to the patient like gender, age, genes, cardiac dysfunction, hepatic and renal impairment. Drug absorption, metabolism and excretion can be mainly influenced by the age factor. These functions get slow down with advancing age which may result in drug interactions. Existing literature revealed that geriatrics are more prone to drug-drug interactions when compared to the other age groups. Gender and genetics may also influence the occurrence of DDIs. To certain type of drugs males and females may respond differently especially in case of hormones. Drug absorption and metabolism can be influenced by genetic makeup in some individuals and they require additional dose to get the therapeutic effect. In some cases, the drug can be retained for a longer period of time in the body. Drug-drug interactions can often be influenced by disease states too. When compared to normal patients, patients with hepatic and renal impairment may respond differently for different drugs. The drugs react with the other drugs that have been already taken by the patients in such situation. Drugs can be much more slowly metabolized in the patients with hepatic impairment. Drugs have more chance to interact with the other drugs because the drugs remain in circulation for longer time in this case \cite{6}.

Polypharmacy, treatment duration and disease severity may also influence the risk and severity of drug-drug interactions \cite{25,26}. In Greek the word poly means
“much” or “many”. When patient uses multiple drugs (>2), then it is said to be polypharmacy \cite{27,28}. The incidence of potential DDIs is close to 40% in patients consuming 5 drugs and exceeds up to 80% in patients consuming more than 7 drugs \cite{30,31,32}. Polypharmacy increases the possibility of drug-drug interactions and adverse drug reactions (ADRs) that may result in poor compliance, increased risk of hospitalization and medication errors (MEs) \cite{33,34}. Critically ill patients are at an increased risk for drug interactions due to the complex pharmacotherapy. Pharmacological characteristics of the drugs and the pharmacokinetic profile are the other determinant factors for the occurrence of drug-drug interactions \cite{35-40}.

1.4. REASONS FOR THE INCREASED PREVALENCE OF DRUG-DRUG INTERACTIONS

1.4.1. Drug potency

At present, drugs of high potency are introduced in the treatment plans. Majority of these high potency drugs do not have only one specific type of activity but they also influence the other physiological systems. Thus, these drugs in various ways may simultaneously affect the body.

1.4.2. Concurrent use of over the counter drugs and prescription drugs

Common over the counter (OTC) drugs like antacids, laxatives, vitamins and analgesics are known to be interacting with prescription drugs. Absorption of the majority of drugs can be decreased by the antacids.

1.4.3. Patient’s non-compliance

In India, non compliance is a major problem especially in geriatrics. They tend to take either double dose or skip the dose all together when they forget the drug regimen. Drug interaction can occur in both the situations and in order to manage the current situation another drug can be taken by the patient and that drug may sometimes aggravate/ worsen the current situation.
1.4.4. Abuse and Misuse of drugs

Sometimes, some patients may prescribe themselves and even increase or decrease their dose without considering the actual regimen. This type of behavior is mainly observed in the patients who usually use analgesics, sleeping pills and antidepressants. Here the problem lies within the self-medication. In order to get better sleep, some patients often take the sleeping pills at increased dose without consulting the prescriber. They don’t reveal this matter to the prescriber which may result in serious drug-drug interactions.

1.4.5. Other reasons

At present, most of the patients want to take a second opinion regarding their disease and treatment and in this process they consult two or three different physicians and could be prescribed with different prescriptions. The patients do not reveal regarding the previously prescribed drugs by the previous doctor to the current prescriber and some patients may often take all the drugs together which are prescribed by both the doctors. This situation may also result in serious drug-drug interactions.

1.5. MECHANISM OF DRUG INTERACTIONS

Pharmacokinetic (PK) and Pharmacodynamic (PD) Interactions

The nature of the drug-drug interactions can be pharmacokinetic or pharmacodynamic. When a drug alters the absorption, distribution, metabolism and the clearance of another drug it is said to be pharmacokinetic interaction and when a drug’s specific performance is altered by the other drugs then it is called as pharmacodynamic interaction.

1.5.1. PHARMACOKINETIC INTERACTIONS

(1) Drug interactions due to alteration in absorption process

Interactions involving alterations in the absorption of drugs from GI tract assume much significance because majority of the drugs are administered orally. In case of the absorption of drugs from gastro intestinal tract (GIT), there can be many
alterations. The changes in the therapeutic activity can be resulted due to the alteration of overall absorption. The desired therapeutic effect can often be delayed due to delayed absorption. The drugs which show delayed absorption may remain longer time in the body and often resulted in degradation of the drug.

(i) Alteration of pH

Majority of the drugs in use are either weak bases or weak acids. At gastric pH, these drugs exhibit different degrees of ionization. By passive diffusion, the absorption of a drug is dependent on the pKa of the drug, pH of the fluid at the site of absorption and partition coefficient of the drug. When compared to the ionized form of the drug, unionized form of the drug is better absorbed. The absorption rate of certain drugs can be altered due to the administration of antacids with those drugs due to the change in pH. When tetracycline is coadministered with antacid, the bioavailability of tetracycline is reduced due to slow dissolution because of antacid.

(ii) Alteration due to complexation

With metallic ions, majority of the drugs form stable complexes and these complexes entrap drug molecules and take them out of circulation which results in their reduced availability to the body and thus making them less effective. With calcium, aluminium, magnesium and iron, tetracycline readily form complexes that results in decreased absorption. Hence, milk and milk products which are high in calcium should not be given with tetracycline. The same effect on tetracycline can also be observed with antacids containing calcium or aluminium salts.

(iii) Alteration due to change in motility and/or gastric emptying time

In the past, castor oil was used to stimulate GI motility for emptying of the stomach and this practice decreases the absorption of drugs. Drugs which are slowly absorbed and the drugs which required prolonged contact with the stomach lining are affected more when compared to other drugs.
(iv) Other factors that affects absorption

a. Inhibition of enzymes: Absorption of drugs can be affected by the inhibition of enzymes especially the GI enzymes.

b. Malabsorption states: Decreased absorption of nutrients and vitamins from the GI tract can be caused due to certain drugs like Colchicine, Neomycin acid Cholestyramine which may result in malabsorption problems.

(2) Alteration of Distribution

Once the drug is absorbed from the site of administration, it gets distributed in the body and this distribution could be in the blood components or in the extravascular components. Majority of the drugs are almost totally or partially bound to tissue and plasma proteins after the absorption process. The most common component of blood plasma is the albumin to which a drug gets bound easily. The portion of the drug is therapeutically not active when it is bound to plasma albumin or to tissue protein. But it serves as a reservoir from which the usually much smaller unbound active fraction can be replenished as “free drug”. Equilibrium exists between the ‘bound’ and ‘unbound’ fraction of the drug. The albumin drug complex serves as a reservoir and the binding of drugs to plasma albumin is reversible. When two drugs try to bind to the same site, competition exists because there are only a limited number of protein binding sites. The other drug which is coadministered can be displaced by the drug that has the greater affinity for the binding site from plasma or tissue proteins. The therapeutic effect can be increased due to increase in the unbound active fraction of the other drug. For the common binding site, this type of drug-drug interaction is called “displacement” interaction. The drug that is displaced is known as the “displaced drug” and the drug that displaces the other drug from the binding site is known as “displacer”. Warfarin and Phenylbutazone are extensively protein bound especially to albumin. Warfarin displacement occurs due to greater affinity of Phenylbutazone for the binding site. This results in hemorrhage because the “free” Warfarin gets released in to the blood stream and beyond the desired level the anticoagulant activity suddenly increases.
(3) Alteration of metabolism

Metabolic transformation process converts lipophilic substances into polar hydrophilic entities for easy excretion and this process is often called as biotransformation. This process mainly occurs in liver and to some extent in the plasma. In the biotransformation of drugs, microsomal enzymes catalyze many of the metabolic processes in the liver and these processes occurs in two phases that includes Phase-I reaction and Phase-II reactions. Functionalisation reactions like oxidation, reduction and hydrolysis comes under the category of phase-I reactions whereas conjugation or true detoxification reactions comes under the category of phase-II reactions. The hepatic Cytochrome P450 (CYP450) enzyme system or microsomal mixed function oxidases are generally involved in phase-I metabolism and these are the most important enzymes involved in drug metabolism. These enzymes become more significant when certain drugs affect or interact with these enzymes which results in altering the metabolism of the drug. By the drugs, these enzymes can either be inhibited or induced (activated).

a. Enzyme induction

In the liver microsomes, various drugs have the capacity for increasing the synthesis and activity and this process of enhancing drug metabolizing ability of the enzymes especially the microsomal enzymes by various drugs and chemicals are called enzyme induction. Chemical entities responsible for this process are called as inducers. Coumarin anticoagulants like Warfarin can be metabolized by Phenobarbital at a greater rate which results in bleeding.

b. Enzyme inhibition

A few drugs have the ability to inhibit the enzyme activity in which the normal rate of metabolism is slowed down which increases the half life of the drug. Due to this, drug can be accumulated in the body, which in turn results in adverse drug reactions. The metabolic inactivation of Phenytoin can be inhibited by Isoniazid which leads to slowing down of the metabolism of the drug that result in accumulation leading to toxicity.
(4) **Alteration in Excretion process**

For the excretion of drugs, kidney is the major organ. From the body, drugs can be eliminated either as metabolites of the parent drug or as unchanged especially in case of highly acidic and highly polar drugs. Excretion of one drug through the kidney may be altered by concurrent administration of another and may result in an increased or decreased rate of excretion of either one or both the drugs. In excretion, this interference can be used to therapeutic advantage.

**i) Interference with urinary excretion**

By blocking the tubular excretion, Probenecid inhibits Penicillin transport system. The blood levels of Penicillins can be maintained at a higher level for a prolonged period.

**ii) Alteration of urinary pH**

A drug that alters the pH of urine can affect the renal excretion of other drug significantly. These other drugs get either reabsorbed or excreted to a greater extent when urinary pH is changed and consequently their therapeutic activity is affected. Acidic drugs like Aspirin, Nitrofurantoin show increase in renal clearance when urinary pH is alkaline. In alkaline conditions, the therapeutic efficacy of these drugs goes down.

**1.5.2. PHARMACODYNAMIC INTERACTIONS**

As a result of concurrent administration, as distinguished from drug incompatibility these interactions occur. The combined drug effects may be either “Homergic” or “Hetergic”. When two drugs produce the same effect it is “Homergic” and when only one of the pair of drugs produced altered effects, it is “Hetergic”.

**1) Drugs having opposing pharmacological effects**

It can be easy to detect the interactions that may result from the use of two drugs which have opposing pharmacological effects. The use of a sedative to decrease
the stimulant effect of ephedrine, which is being used in asthmatic condition, is one of the examples for this type.

(2) Drugs having similar pharmacological effects

Aminoglycoside antibiotics have the tendency to affect ears leading to ototoxicity. Along with these antibiotics if the patient is prescribed with a powerful diuretic like Furosemide this ototoxicity can be further aggravated. The additive effect of these drugs becomes detrimental.

(3) Alteration of electrolyte levels

The electrolytes of the body can be depleted by the diuretics especially the potassium ions. This affects the action of some drugs like Digitalis and Lithium. Diuretics like Furosemide can cause loss of potassium. Arrhythmias can be caused due to the depletion of potassium when the drug Digitalis is prescribed for cardiovascular disorders along with diuretics. Potassium sparing diuretics like Spiranolactone can be prescribed as the drug of choice in order to prevent this type of interactions.

(4) Alteration of receptor site interactions

Particular drugs affect the affinity of certain drugs. The interaction between the Warfarin and D-Thyroxine is this type of pharmacodynamic interaction. The effect of Warfarin can be enhanced by D-Thyroxine by increasing its affinity for the receptor site.

(5) Other pharmacodynamic interactions—Alteration of GI flora by antibiotics

GI flora can be altered by some antibiotics and this may leads to the depletion of vitamin K which results in decreased coagulant effect.

1.6. BENEFICIAL EFFECTS OF DRUG-DRUG INTERACTIONS

Drug-drug interactions are not always hazardous to human health. They have beneficial therapeutic effects and clinical advantages too. Protamine Sulphate binds with heparin to form an inactive complex. In case of overdose of heparin, Protamine Sulphate can be used for the management [6,41,42,43].
1.7. ROLE OF CLINICAL PHARMACIST IN THE MANAGEMENT OF DRUG-DRUG INTERACTIONS

Detection, management and prevention of drug-drug interactions are the professional responsibilities of the clinical pharmacists in the clinical scenario [6]. Clinical pharmacist should make the patients aware about the drug-drug interactions and their consequences. Before a patient takes a new drug, reviewing drug therapy for potential interactions can occur as a part of drug review process. Before initiating a treatment, the patient must be asked regarding the OTC medication taken including vitamin supplements [44]. Some drug combinations may often result in drug-drug interactions. Hence, those combinations must be avoided by replacing with an alternative drug. By adjusting the dose of an object drug sometimes it is possible to prescribe the two interacting drugs safely. If the object drug is administered at least 2 hours before or 4 hours after the precipitant drug, drug-drug interactions can be avoided for those involving binding in the gastrointestinal tract. Some interactions can be managed through close clinical and laboratory monitoring for the evidence of the interaction in some cases when it is essential to administer interacting drug combinations. If necessary, the drugs can be discontinued or appropriate dosage changes can be made in this way. In order to make a valuable contribution in patient management, the clinical pharmacists have to be expertise in this area that ensure the patients’ quality of life.

Patients with multiple pathologies, hepatic and renal impairment are at a high risk of developing drug-drug interactions [1]. Due to inherent toxicity, non-linear pharmacokinetics or potent enzyme inducing or inhibiting ability of some drugs pose a higher risk. For the screening of drug-drug interactions, ready reference system like pocketbooks, tables, standard references or computer based programs can be more helpful. A large number of drug-drug interactions of questionable clinical significance were identified by the computerized drug interaction screening systems. Hence, a standard and unbiased computerized screening system must be preferred.

To avoid potential interactions, patient education plays a vital role. Providing reliable advice on interaction management can greatly add benefit to the patient’s
safety and well being. Simple warning message printed on the tablet bottle label or patient information leaflets can be more useful. For example if a patient is prescribed with Ciprofloxacin, he/she must be advised not to take with iron. The above advice can be verbal or written based on the patient’s level of understanding. With newly introduced drugs, additional care and monitoring is essential as clinical exposure and experience to potentially interacting drugs will be limited. The clinical pharmacist must be very cautious when a newly introduced drug is combined with other drugs with a high risk of potentially serious adverse effects [45-51].