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Review Article

A Review on Drug Interactions

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Abstract

In present article we have discus the drug interactions as a one of the growing and interesting research oriented topic in which a person can identify in-vitro in-vivo interactions of drug with all body components and foreign particles. One can understand the drug interaction inalteration in the duration or magnitude (or both) of the pharmacological effect of one drug produced by another drug when more than one drug is administered simultaneously the combined effect may be antagonistic or synergistic in antagonism the effect of one drug is reduced or abolished by the other, whereas in synergism the effect may be additive or supra-additive (potentiation).There are many other physical and chemical aspects are also responsible for the drug interactions. There are some important objectives of the work, drug interactions are important aspect of pharmaceutical point of view many drug interaction are important to understand the biopharmaceutical interaction in body as well as outside the body, for such more understaning review article emphasizes basics of drug interactions.

Keywords: Drug food interactions, Mode of actions, Classification.

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Introduction

Drug interaction occurs on simultaneous use of two or more drugs. When two drugs are taken in close sequence to each other, they may interact either to increase or diminish the intended effect of one or both drugs, or they may produce an unintended and potentially harmful effect. unfortunately drug interaction may be recognized only when severe toxicity occurs e.g. a hypertensive crisis may occur when a monoamine oxidase inhibitor (MAOI) like tranyl cypromine, and an indirectly acting sympathomimetic drug like methamphetamine are used together; severe haemorrhage may occur if warfarin and salicylate are combined. The term *drug interaction* is defined as an alteration in the duration or magnitude (or both) of the pharmacological effect of one drug produced by another drug when more than one drug is administered simultaneously the combined effect may be *antagonistic or synergistic* in antagonism the effect of one drug is reduced or abolished by the other, whereas in synergism the effect may be additive or supra-additive (potentiation). The term poly pharmacy covers the practice of multiple drug therapy in the management of disease. Judicious use of drug interaction (rational poly pharmacy) can be of considerable benefits to the patients, to produce the synergistic effect which is not produced by one drug alone. [1]

Fig. 1: Differnet medication may involve in drug interaction

To minimize the side effect of drugs, drug interaction refers to modification of effect to one drug by another drug when they are administered simultaneously or in quick succession the modification is always quantitative ,i.e. the response is either increased or decreased in response , but sometimes it is qualitative i.e. abnormal or different type of response is produce. The Possibility drug interaction occurs when patient concurrently takes more than one drug, and chance increase with the number of drug increases. Many medical conditions are treated with combination of drugs. The component of combination selected such that they complement each other's action. E.g. an antibiotic is used along with an analgesic to treat the painful infective conditions. [2] many drug may alter the metabolic detoxification of other drugs and thereby change pharmacological response these interactions drug plays an vital to the patient's therapy may be affected, leading perhaps to a synergistic or antagonistic effect and producing and undesirable or toxic side effect.[3]

Objectives of drug interaction studies

There are some important objectives of the work, drug interactions are important aspect of pharmaceutical point of view many drug interaction are important to understand the biopharmaceutical interaction in body as well as outside the body. Many drug interactions are important to study the pharmacokinetic and pharmacodynamic studies of drug interaction. There are some pharmacodynamics interaction as physical interactions and chemical interaction. In these study we understand about the physical interaction such as some interaction occurs if they physically mixed with each other they shows some interaction which are undesirable for the therapeutic aspects. Some interactions are chemically important if drug molecules were mixed with each other they interact chemically which causes the undesirable chemical changes. Pharmacokinetic aspects are also of importance in which we understand about the absorption, distribution, metabolism, and excretion of the drug. Many drugs show interactions during absorption. Some interactions occur during the distribution of the drug, metabolism of drug and excretions of the drug which can be minimize and understand by the drug interaction studies. We can also predict about the mechanism of drug interactions interaction, how they interact during absorption, metabolism, distribution, and excretion of drug. We can avoid the unwanted drug interaction by these studies. Other objectives of these studies are to understand the drug interaction, to understand the mechanism of the drug interaction that how that interacts, by these studies we can also studies about the causes and reason of drug interaction. Some drug interactions are important and beneficial too, we can find out some beneficial effect of the drug. Some drug interaction harmful which can also be minimizing by these studies. Drug interaction studies are also important to avoid predictable unwanted effect of the drug interactions; it helps us to overcome the antagonism of the response as well as to avoid the harmful effect of the drug interaction. These studies are also useful to avoid the side effects of the drug due to the drug interaction such as antagonism of the effect. We can also potentiate the effect of the drug by understanding the synergistic effect of two drugs. These studies also important to avoid the side effects of the drug due to the drug interaction. Some life threatening conditions are avoided by these studies.

Classification of drug interaction

The term ***drug interaction*** is defined as an alteration in the duration or magnitude (or both) of the pharmacological effect of one drug produced by another drug when more than one drug is administered concurrently the combined effect may be *antagonistic or synergistic* in antagonism the effect of one drug is reduced or abolished by the other, whereas in synergism the effect may be additive or supra-additive (potentiation).*Chemical antagonism* refers to uncommon situation where the two drugs combine in solution. *Pharmacokinetic antagonism* refers to the situation in which the antagonist effectively reduces the concentration of the active drug at its site of action. *Physiological antagonism* is a term used loosely to describe the interaction of two drugs whose opposing action in the body tend to cancel the effect of each other .Drug interaction may occur outside the body (in vitro) or inside the body (in vivo). [4]

1) Outside the body (In vitro)
a) Physical interaction.
b) Chemical interaction.
2) Inside the body (In vivo)
a) Pharmacokinetic interaction
b) Pharmacodynamic interaction
1) Outside the body
These interactions may occur during formulation and mixing of drugs and the term incompatibility often used to designate these in vitro reactions.

Table 1: Some Important Drug-Food Interactions [1-4]

Drug	Food item	Effect
Anticoagulants	Food rich in vit-k	Decrease anticoagulant effect due to enhanced hepatic synthesis of clotting factor
Antihypertensive diuretics	Licorice	Cause hypokalemia
Digoxin	Milk products	Slowed absorption and decrease effect
Paracetamol	Carbohydrates	Slow drug absorption
Erythromycin	Acidic fruit juice	Decompose the drug and reduce effect

Physical interaction
This term used when the physical state of both the drug is altered when the chemical are mixed e.g. amphotericin precipitate when mixed with normal saline instead of five percent dextrose; the anticoagulant effect of heparin, a negatively charged acid is antagonized by protamine, a positively charged base used.

Chemical interaction
this term applies when the component of drug mixture interact to form chemically altered drug, e.g. drugs mentioned below are chemically incompatible in solution; methicillin and kanamycin; aminophylline and chlorpromazine; dopamine and sodium bicarbonate. In most cases chemical incompatibilities are manifested by precipitation and color change. Occasionally in vitro interaction can occur without any observable change.

2) Inside the body
Most of the interaction occurs inside the body can be categorized as either pharmacokinetic or pharmacodynamics interaction**.**

Pharmacokinetic interaction
In this category the change in response to the first drug is the result of an alteration of the drug at receptor site, and it is produced by other drug.
Interaction during gastrointestinal absorption, Interaction during distribution (plasma protein binding), Interaction during metabolism, Interaction during excretion

a) Interaction during gastrointestinal absorption
Many drug influence absorption during from gastrointestinal tract. Which include dissolution rate of the ingested drug, gastric emptying time, gut motility and blood flow, Drugs are absorbed mainly in their non-ionized form from the gut .gastric emptying time and gut motility are important factor which determine the rate and extent of absorption of drug.

Table 2: Drug interaction during absorption [1-4]

Interacting drug	Result of interaction
Antacid with anticoagulant (dicoumarol and warfarin)	Antagonism of anti coagulant effect
Antacid with anti-infective (sulphonamide, nilidixic acid)	Reduction of anti-infective drugs
Mineral oil and fat soluble vit-(A,D,E,K)	Mineral reduces the absorption of vitamins.

b) Interaction during distribution (plasma protein binding)

When certain drugs are absorbed into the blood circulation, most of them attach themselves to plasma protein. The portion of drug which is transported in the bounded form is pharmacologically inactive, and only the free molecule that diffuse into the tissue exert their effect. The presence of second drug of higher affinity for protein, competes with the first drugs for the protein binding site, and displaces the first drug.

Table 3: Dispalcement of drug from plasma protein binding [1-4]

Drug Displaced (Lower Binding Affinity)	Displacing Agent (Higher Binding Affinity)
Acetaminophen	Phenylbutazone,phenytoin,salicylates
Methotrexate	Salicylate, sulphonamides
Pamaquine	Quinacrine
Sulphonamides	Phenylbutazone, warfarin
Warfarin	Oxyphenbutazone phenytoin

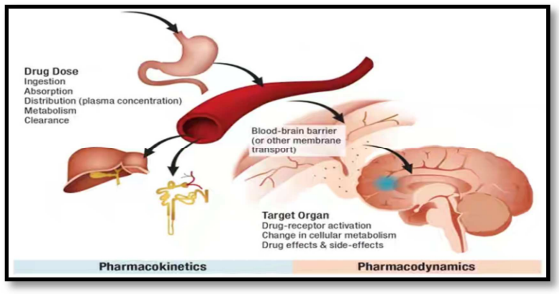

Fig. 2: Pathway of pharmacodynamics and pharmacokinetic interaction

c) Interaction during metabolism

The conversion of drug to its metabolite is termed as biotransformation, and it usually occur in the liver. These reactions are usually mediated by enzymes, so that drug capable of altering the enzymatic process involved in drug metabolism can lead to drug interaction**.**

Enzyme induction, liver microsomal enzymes are involve in the drug metabolism can be stimulated by drugs including barbiturates, hydantoins, etc. this is termed as *enzyme induction* and result in reduced therapeutic activity to those drug that are metabolized by the microsomal enzyme.

Table 4: Drug that induce the metabolism of other drug [1-4]

Inducer	Drugs affected
Alcohol	Tolbutamide
Chloral hydrate	Warfarin, bishydroxycoumarin
Haloperidol	Warfarin
Phenylbutazone	Steroid hormones
Phenytoin	Steroid hormone

Enzyme inhibition, compound that interfere with the activity of inactivating enzymes can increase the action of other drug or endogenous substance, e.g. monoamine oxidase inhibitor(MAOIs) inhibit the normal functioning of endogenous enzyme monoamine oxidase (MAO), elevate of biogenic level of amines and may produce hypertensive crises in the presence of pressor amine.

d) Interaction during excretion

Interaction during excretion may involve any of the renal excretory processes. i.e. glomerular filtration, tubular reabsorption, or active tubular secretion. Most interaction occurs due to change in pH or competition for active tubular mechanism.

Table 5: Inhibition of drug metabolism [1-4]

Drugs	Metabolic inhibitors
Bishydroxycoumarin	Chloramphenicol, phenylbutazone
Pethidine	Oral contraceptives
6-mercaptopurine	Allopurinol
Tolbutamide	Alcohol, chloramphenicol
Hexobarbital	Metyrapone, progesterone

Pharmacodynamics interaction

Pharmacodynamics interaction occurs at the site of drug action. They usually lead to altered effect to affected organ. Mostly drugs effects are the result of binding of the drug to the specialized areas on or within the cells, known as receptor site. The magnitude of the effect depends on the concentration of the free drug at its receptor site. The free drug or active metabolites concentration at the receptor site depends on the amount of drug in the body, which in turn regulated by,

- Physical and chemical properties of the drug.
- Altered gastrointestinal absorption or competition for protein binding site (or receptor).
- Altered drug metabolism.
- Change in acid-base equilibrium.
- Alteration of haemodynamic or renal tubular functions.

1) Interaction in the CNS

The aminoglycoside antibiotics (streptomycin, kanamycin, gentamycin) and the potent loop diuretic frusemide when used simultaneously may cause severe toxicity. The aminoglycosides are also increase and prolong the action of muscle relaxants.

2) Interaction in the bronchial tree

Bronchial relaxation occurs when the formation of cyclic 3’5’-AMP (c-AMP). The formation of this messenger is increased when adenylcyclase in stimulated by catecholamine. Alternatively, the breakdown of c-AMP can be inhibited by aminophylline. Thus the combination of the two may be useful in the treatment of bronchial asthma.

3) Interaction in the heart

Interaction at this site mainly involves the beta-blocker and cardiac glycosides. The beta-blocker can produce a profound bradycardia, and delayed auriculoventricular conduction. These actions are mainly due to the unopposed action of the vagus nerve, and can be overcome by administering atropine concurrently.

Drug interactions before administration

Some drugs interact with each other and get inactivate if their solutions are mixed before administration.

1. Penicillin G or ampicillin mixed with gentamicin or another aminoglycoside antibiotic.
2. Thiopentone sodium when mixed with succinylcholine or morphine.
3. Heparin when mixed with penicillin/ gentamicin/ hydrocortisone.
4. Noradrenaline when added to sodium bicarbonate solution.

Drug interaction – Risk factor

1. Poly pharmacy
2. Multiple prescriber
3. Multiple pharmacies
4. Genetic makeup
5. Specific illness (e.g. hepatic disease, renal dysfunction)

Mechanism of drug interactions

Drug interactions are of two types pharmacokinetic or pharmacodynamic. Pharmacokinetic interactions result from alterations in a drug’s absorption, distribution, metabolism, or excretion characteristics. Pharmacodynamics interactions are a result of the influence of combined treatment of drugs at a site of biological activity and yield altered pharmacological effects 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. The mechanisms by which changes in absorption, distribution, and excretion occur have been understood for decades. However, only recently has technology allowed for a more thorough understanding of drug-metabolizing isoforms and influences thereon [5-9].

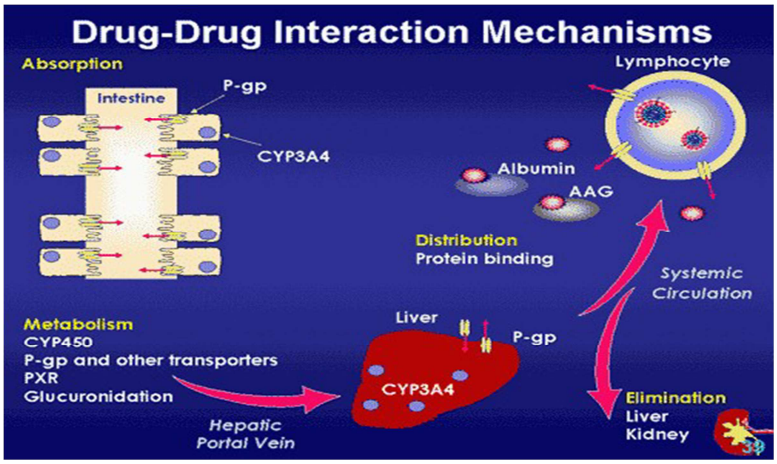

Figure.3. drug-drug interaction mechanism

Mechanisms of drug interactions involving absorption and distribution

Absorption

- 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 isozymes activity
- Altered intestinal P-glycoprotein activity

Distribution

- Altered protein binding

Drug interactions affecting absorption

Mechanisms of absorption of drug include passive diffusion, convective transport, active transport, facilitated transport, ion-pair transport, and endocytosis. Some drug combinations can affect the rate or extent of absorption of anti-infective by interfering with one or more of these mechanisms. Generally, a change in the extent of a medication's absorption of greater than 20% may be considered clinically significant. [10-11]

Changes in pH

The rate of drug absorption by passive diffusion is limited by the solubility, or dissolution, of a drug in gastric fluid. Compounds that create an environment with a specific pH may decrease the solubility of compounds needing an opposing pH for absorption. However, drug solubility does not completely ensure absorption because only un-ionized molecules are absorbed. Although acidic drugs are soluble in basic fluids, basic environments can also decrease the proportion of solubilized acidic molecules that are in an un-ionized state. Therefore, weak acids (P*Ka*= 3–8) may have limited absorption in an alkaline environment, and weak bases (p*Ka* = 5–11) have limited absorption in an acidic environment.

These interactions can be clinically significant. For example, because the nucleoside analog didanosine is acid labile and requires a neutral-to-basic pH to be absorbed, all didanosine formulations are buffered. However, medications known to require an acidic environment for dissolution, such as ketoconazole, itraconazole, and dapsone, have demonstrated significantly decreased absorption when given concomitantly. Antacids, histamine receptor antagonists, and proton pump inhibitors all raise gastric pH to varying degrees. Antacids transiently (0.5–2 hours) raise gastric pH by 1–2 units, H2-antagonists dose-dependently maintain gastric pH above 5.0 for many hours, and proton pump inhibitors dose-dependently raise gastric pH above 5.0 up to 19 hours. The concomitant administration of these compounds leads to significant alterations in the extent of absorption of basic compounds such as certain azole antifungals and β-lactam antibiotics. However, because of large inter individual variability in the extent of altered gastric pH, significant interactions may not occur in all patients. [12]

Chelation and Adsorption

Drugs may form insoluble complexes by chelation in the gastrointestinal tract. Chelation involves the formation of a ring structure between a metal ion (e.g., aluminum, magnesium, iron, and to a lesser degree calcium) and an organic molecule (e.g., anti-infective medication), which results in an insoluble compound that is unable to permeate the intestinal mucosa because of the lack of drug dissolution. A number of examples of the influence on anti-infective exposure by this mechanism exist in the literature, involving primarily the quinolone antibiotics in combination with magnesium- and aluminum-containing antacids, sucralfate, ferrous sulfate, or certain buffers. These di- and trivalent cations complex with the 4-oxo and 3-carboxyl groups of the quinolones, resulting in clinically significant decreases in thequinolone area under the concentration–time curve (AUC) by 30 to 50% [13-16]. Adsorption is the process of ion binding or hydrogen binding and may occur between anti-infectives such as penicillin G, cephalexin, sulfamethoxazole, or tetracycline and adsorbents such as cholestyramine. Because this process can significantly decrease antibiotic exposure, the concomitant administration of adsorbents and antibiotics should be avoided. [17, 18]

Changes in gastric emptying and intestinal motility

The presence or absence of food can affect the absorption of anti-infective by a variety of the mechanisms. High-fat

meals can significantly increase the extent of absorption of fat-soluble compounds such as griseofulvin, cefpodoxime, and cefuroxime axetil. Prolonged stomach retention can cause excessive degradation of acid-labile compounds such as penicillin and erythromycin. Because the primary location of drug absorption is the small intestine, changes in gastric emptying and gastrointestinal motility may have significant effects on drug exposure. Rapid gastrointestinal transit effected by prokinetic agents such as cisapride, metoclopramide, and domperidone may decrease the extent of absorption of poorly soluble drugs or drugs that are absorbed in a limited area of the intestine. [19-20]

Cytochrome P450 isozymes

Gastrointestinal CYP isozymes, responsible for Phase I oxidative metabolism are most highly concentrated in the proximal two-thirds of the small intestine. Two intestinal CYP isoforms, CYP3A4 and CYP3A5 (CYP3A4/5), account for approx. 70% of total intestinal P450 protein and are a major determinant of the systemic bioavailability of orally administered drugs. For example, the benzodiazepine midazolam is a specific CYP3A4/5 substrate with no affinity for P-glycoprotein. An investigation of oral and intravenous midazolam plasma clearance in 20 healthy young volunteers revealed an incomplete correlation between the two measures (r = 0.70). The large variability in midazolam oral clearance not accounted for by hepatic metabolism most likely represents the contribution of intestinal CYP3A4/5. Therefore, it appears that at least 30–40% of the clearance of many CYP3A compounds may be significantly influenced by CYP3A4/5 located in enterocytes. Because the activity of intestinal CYP3A4/5 can also be influenced by variety of environmental factors the potential for drug interactions to occur during drug absorption is great. [21-22]

Some of the most significant effects of drug interactions occurring at the intestinal isozymes level involve the potential suicide inhibition of CYP3A4/5 with grapefruit Juice. Generally, this interaction results in a minimum threefold increase in the extent of absorption and toxicity of the concomitantly administered agent, but can also result in decreased efficacy of prodrugs needing CYP3A for conversion to active moieties. The concern of this interaction is strictly limited to orally administered agents because the active components of grapefruit juice are either inactivated in the gut or are present in such minute quantities in the portal circulation that no effect on hepatic metabolism occurs. [23-26]

Drug interactions affecting Distribution

Protein binding and displacement

Drug interactions affecting distribution are those that alter protein binding. Generally, the importance of drug displacement interactions has been overestimated, with the extrapolation of data from in vitro investigations without consideration for subsequent physiological phenomena. The lack of well-designed studies has prevented precise quantification of the influence of protein binding on anti-infective therapeutic efficacy in vivo. However, redistribution and excretion of drugs generally occurs quickly after displacement, and the effects of any transient rise in unbound concentration of the object drug are rarely clinically important [27].Albumin constitutes the main protein fraction (~5%) in blood plasma. As albumin contains both basic and acidic groups, it can bind basic and acidic drugs. Acidic drugs (i.e., penicillin's, sulfonamides, doxycycline, and clindamycin are strongly bound to albumin at a small number of binding sites, and basic drugs (i.e., erythromycin) are weakly bound to albumin at a larger number of sites. Depending on relative plasma concentrations and protein-binding affinities, one drug may displace another with clinically significant results. This interaction is much more likely to occur with drugs that are at least 80 to 90% bound to plasma proteins, with small changes in protein binding leading to large relative changes in free drug concentration.

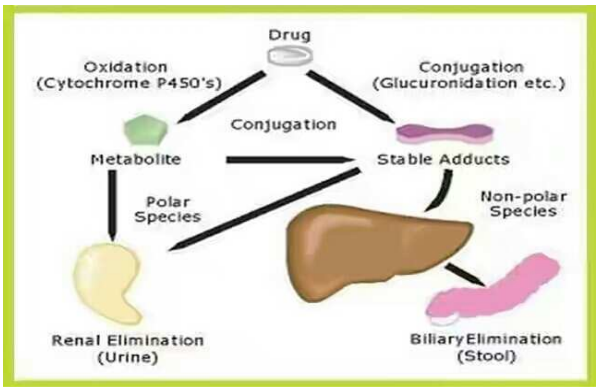

Figure.4. metabolism of drug

Drugs that are poorly bound to plasma proteins may also be displaced, but the relative increase in free drug concentration is generally of less consequence. When a protein displacement interaction occurs, the increased free drug in plasma quickly distributes throughout the body and will localize in tissues if the volume of distribution is large. An increase in unbound drug concentrations at metabolism and elimination sites will also lead to increased rates of elimination.Therefore, many clinically significant drug interactions that have been attributed to protein binding have often involved a second, unrecognized mechanism of interaction. Generally, interactions between basic drugs and albumin are not clinically significant. In subjects with normal concentrations of albumin and anti-infective concentrations of less than 100 μg/mL, the degree of protein binding will be relatively constant. At higher anti-infective concentrations, available binding sites may theoretically become saturated and the extent of binding subsequently decreased. Clinically significant

displacement interactions for α-1-acid glycoprotein have not been described. This is most likely caused by the large volume of distribution of these drugs, with plasma containing a very small proportion of the total amount of drug in the body. [28-29]

Drug interactions affecting drug metabolism

The principal site of drug metabolism is the liver. Metabolism generally converts lipophilic compounds into ionized metabolites for renal elimination. Drug-metabolizing activity can be classified according to non-synthetic (Phase I) and synthetic (Phase II) reactions. Phase I reactions include oxidation, reduction, and hydrolysis and occurring the membrane of hepatocyte endoplasmic reticula. Phase II reactions result in conjugation (i.e., glucuronidation, sulfation) and occur in the cytosol of the hepatocyte. The majority of oxidative reactions are catalyzed by a super family of mixed-function mono-oxygenizes called the CYP enzyme system. Although CYP isozymes are located in numerous tissues throughout the body, the liver is the largest source of CYP protein. Many significant pharmacokinetic drug interactions involve the hepatic CYP isozymes.

Mechanisms of inhibition

Enzyme inhibition can result in sudden catastrophic drug interactions. Several mechanisms of inhibition exist, and many drugs can interact by multiple mechanisms. Reversible inhibition is most common. Reversible inhibition occurs when compounds quickly form weak bonds with CYP isozymes without permanently disabling them. This can occur both competitively (competition for the same binding site between inhibitor and substrate) and noncompetitively (inhibitor binds at a site on the enzyme distinct from the substrate). The magnitude of this type of inhibition depends both on the affinity of substrate and inhibitor for the enzyme and on the concentration of the inhibitor at the enzyme site. Affinity is represented by an inhibitor constant *Ki*, which is the concentration of inhibitor required to decrease the maximal rate of the reaction to half of the uninhibited value. For example, potent reversible CYP3A inhibitors generally have *Ki* values below 1 *M* (e.g. ketoconazole, Iitraconazole, ritonavir, and indinavir), although drugs with *Ki* values in the low micro molar range can also demonstrate competitive inhibition (e.g., erythromycin and nelfinavir). Compounds with *Ki*'s greater than 100 *M* for the CYP3A subfamily tend not to produce clinically significant inhibition.

CYP inhibition can also occur as a result of a slowly reversible reaction. When an Inhibitor binds to a CYP isozyme and undergoes oxidation to a nitrosoalkane species; it can form a slowly reversible complex with the reduced heme in the CYP isozymes. This interaction has been documented between the macrolide antibiotics and CYP3A and explains why clinically significant interactions (i.e. erythromycin and terfenadine) can occur with compounds that have modest *Ki* values. It is postulated that irreversible, mechanism-based inhibition (or suicide inhibition) Occurs with the CYP-mediated formation of a reactive metabolite. This metabolite can covalently and irreversibly bind to the catalytic site residue and permanently inactivate the enzyme for subsequent reactions. The extent of the clinical importance of this reaction depends on the total amount of CYP isozymes present, the total amount of inhibitor to which the isozymes is exposed, and the rate of new isozymes synthesis. [30-31]

Mechanisms of induction

An increase in CYP activity through induction is less of an immediate concern than inhibition because induction occurs gradually rather than rapidly and generally leads to compromised therapeutic goals rather than profound toxicity. Because the time-course of enzyme induction is determined by the half-life of the substrate as well as the rate of isozymes turnover, it is often difficult to predict this time-course specifically. Clinically significant induction results from a more than 50-fold increase in the number of enzyme molecules. This generally occurs through an increase in P450 synthesis by either receptor-

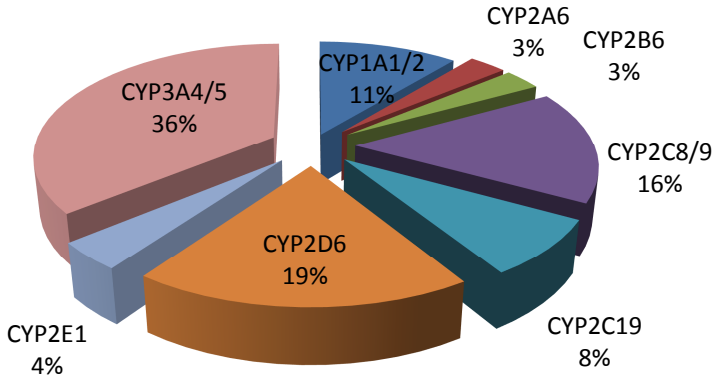

Fig. 5: Proportion of drugs metabolized by P450 isozymes

mediated transcriptional activation or mRNA stabilization. However, protein stabilization leading to decreased rates of P450 degradation has also been noted. Induction of the CYP1 family by cigarette smoke, charcoal-broiled foods, indoles (found in broccoli, cauliflower, cabbage, Brussels sprouts, kale, watercress), and omeprazole occurs primarily by substrate binding to the Ah-receptor (dioxin receptor). This complex subsequently binds with a receptor nuclear translocator, enters the hepatocyte nucleus, and binds with regulatory deoxyribonucleic acid (DNA) sequences to enhance gene transcription and stabilize mRNA.The CYP2 family is

induced by a variety of structurally diverse compounds. Although the mechanism of CYP2 gene induction is not well understood and a specific receptor has not been identified, transcriptional CYP2C gene activation and mRNA stabilization were demonstrated to occur with the azole antifungal agents ketoconazole, clotrimazole, and miconazole. A transcriptional mechanism for CYP3 induction has been identified. Investigators have established that a human orphan nuclear receptor, termed the pregnane X receptor (PXR), binds to a response element in the CYP3A4promoter region. PXR is activated by a range of drugs known to induce CYP3A4 expression (i.e., rifampicin, clotrimazole, etc.). PXR is expressed most abundantly in the liver but is also present in the small intestine and colon. CYP3A can also be induced by posttranscriptional message stabilization and protein stabilization with the following anti-infective: macrolides, imidazole antifungal agents, and rifampin. The specific mechanisms for this are currently unknown but most likely involve interaction with a cyclic adenosine 5′-monophosphate- dependent phosphorylation process involved in protein denaturation. [32-33]

Genetic polymorphisms

Polymorphisms are generated by nonrandom genetic mutations that occur in at least 1% of a population and give rise to distinct subgroups within that population that differ in their ability to metabolize xenobiotics. Clinically significant polymorphisms have been documented for CYP2D6, CYP2C9, and CYP2C19. Extensive or rapid metabolizers (generally the largest proportion of a population) have heterozygous or homozygous dominant alleles, poor metabolizers possess variant homozygous autosomal recessive alleles, and ultra-extensive metabolizers exhibit gene amplification of autosomal dominant alleles. Poor-metabolizer phenotypes can be at high risk for toxicity from drugs that require CYP inactivation and at high risk for therapeutic inefficacy from prodrugs that need CYP activation. However, they are at low risk for drug interactions that involve enzyme inhibition or induction because their activity is preemptively compromised and cannot be induced. In addition, because of the large variability (e.g., 40-fold or greater) in enzyme activity documented in extensive metabolizers, drug interactions may not manifest in all subjects with this phenotype. Inhibition of drug-metabolizing enzymes may result in more significant effects in those with high initial enzyme activity, and induction of drug metabolizing enzymes may result in more significant effects in those individuals with low initial enzyme activity. [34-36]

Drug interactions affecting excretion

Renal elimination of drugs involves glomerular filtration, tubular secretion, and tubular reabsorption. Five mechanisms of drug–drug interactions can occur at the site of renal elimination.

Glomerular filtration

Rates of glomerular filtration can be affected by changes in renal blood flow, cardiac output, and extent of protein binding. With highly protein-bound drugs (e.g., >80%), a significant increase in the unbound fraction can lead to an increase in glomerular filtration and subsequent increased drug elimination. Conversely, with transporter saturation and renal elimination at maximal, elimination rates may decrease significantly with increased free drug [37-38].

Tubular secretion

The most common renal drug interactions occur at the transport site of tubular secretion. Sharing the same proximal tubular active transport system, many organic anionic and cationic drugs and metabolites compete with each other for secretion. A classic example of this interaction, used long ago intentionally for therapeutic benefit, is the combination of probenecid and penicillin to increase antibiotic serum concentrations. Examples of other anti-infective that may exhibit interactions by this mechanism include the sulfonamides, penicillin, and zidovudine.

Tubular reabsorption

Reabsorption of drugs from the tubular lumen involves both passive diffusion and active transport processes. Only no ionized compounds are passively reabsorbed from the renal tubule, and thus manipulating urinary pH can alter the reabsorption of weak organic acids and bases. Renal clearance of weak organic bases (p*Ka* = 7–10) is increased with urine acidification P-Glycoprotein has been identified in the apical membrane of the proximal tubule and can transport a large variety of drugs into the lumen. A number of experimental drug interaction investigations have implicated the inhibition of renal p-glycoprotein to an increase in plasma drug concentrations. Quinolones, macrolides, and azole antifungals demonstrate affinity for renal P-glycoprotein and can potentially contribute to significant drug interactions. Although renal nucleoside transporters have been shown to mediate the secretion and reabsorption of purine and pyrimidine nucleoside analog drugs, their role in clinically significant drug interactions is unknown. [39-42]

Table 6: Important drug interactions

Sr. No.	Precipitant Drug	Object Drug	Interaction
1	Ampicillin, Amoxicillin Tetracyclines	Oral contraceptives	Interruption of enterohepatic circulation of the estrogen failure of contraception
2	Ampicillin, Amoxicillin Tetracyclines	Oral anticoagulants	Inhibition of gut flora decreased vit. K production in gut risk of bleeding; Monitor INR and reduce anticoagulant dose if needed.
3	Carbenicillin, Ticarcillin	Aspirin and other antiplatelet drugs	Cause additive platelet inhibition risk of bleeding; Avoid concurrent use.

Sr. No.	Precipitant Drug	Object Drug	Interaction
4	Ceftriaxone Cefoperazon	Oral anticoagulants	Additive hypoprothrombianaemia bleeding; Monitor INR and reduce dose of anticoagulant
5	Sulfonamides Cotrimoxazole	Phenytoin	Displacement + inhibition of metabolism phenytoin toxicity; Avoid concurrent use.
6	Sulfonamides Cotrimoxazole	Warfarin	Displacement + inhibition of metabolism + decreased production of vit-K in gut risk of bleeding; Monitor INR and reduce dose of warfarin.
7	Sulfonamides Cotrimoxazole	Sulfonylureas	Displacement + inhibition of metabolism hypoglycemia; Avoid concurrent use.
8	Sulfonamides Cotrimoxazole	Thiazide diuretics	Increased incidence of thrombocytopenia; Avoid concurrent use.
9	Metronidazole, Procarbazine, Tinidazole Griseofulvin, Cefotetan Cefoperazone, Ceftriaxone	Alcohol	Accumulation of acetaldehyde disulfiram –like or bizarre reactions; Warn the patient not to drink .alcohol
10	Metronidazole Tinidazole	Lithium salts	Decreased excretion Li toxicity; Monitor Li level and reduce lithium dose
11	Metronidazole Tinidazole	Warfarin	Inhibition of metabolism risk of bleeding; Avoid concurrent use
12	Ciprofloxacin Norfloxacin, Pefloxacin	Theophylline Warfarin	Inhibition of metabolism toxicity of object drug; Monitor and reduce dose .of object drug
13	Erythromycin, Fluconazole Clarithromycin Ketoconazole, Itraconazole Protease inhibitors	Terfenadine Astemizole Cisapride	Inhibition of metabolism by CYP3A4 rise in blood level of object drug dangerous ventricular arrhythmia; Concurrent use contraindicated.
14	Erythromycin, Fluconazole, Clarithromycin Ketoconazole, Itraconazole Protease inhibitors	Phenytoin, Carbamazepine Warfarin, Sulfonylureas Diazepam, Theophylline Cyclosporine HIV protease inhibitors	Inhibition of metabolism by CYP3A4 toxicity of object drug; Avoid concurrent use or readjust dose of object drug.
15	Erythromycin, Fluconazole Clarithromycin Ketoconazole, Itraconazole Protease inhibitors	Statins	Inhibition of metabolism, higher risk of myopathy; Avoid concurrent use.
16	Gemfibrozil,Nicotinic acid	Statins	Increased risk of myopathy; Caution in concurrent use.
17	Tetracyclines	Lithium salts	Rise in plasma Li level due to decreased excretion;Avoid use of tetracycline or monitor and reduce dose of lithium.
18	Iron salts, Calcium salts Antacids, Sucralfate	Tetracyclines Fluoroquinolones	Decreased absorption due to formation of complexes in GIT failure of antibiotic therapy; Stager drug administration by 2-3hours
19	Furosemide	Minocycline Aminoglycoside Antibiotics	Enhanced vestibular toxicity; Avoid concurrent use.Additive ototoxicity and nephrotoxicity; Avoid concurrent use.
20	Diuretics	Tetracycline	Antianabolic effect of tetracycline increases urea production which is retained by the diuretic; Avoid concurrent use.
21	Diuretics	Lithium	Decreased excretion –rise in Li level –toxicity; Reduce dose of lithium and monitor level.
22	Diuretics	Digoxin	Hypokalaemia caused by diuretic increases digoxin toxicity; Give K+ sparing diuretic /K+ supplements.
23	Tetracyclines, Clindamycin, Chloramphenicol, Macrolide antibiotics	Penicillins Cephalosporins	Bactericidal action of penicillins and cephalosporins may be antagonized by the bacteriostatic antibiotics; Avoid concurrent use.
24	Clindamycin	Erythromycin, Azithromycin Clarithromycin Chloramphenicol	Mutual antagonism of antibacterial action due to proximal binding sites on bacterial ribosomes; Avoid concurrent use

Sr. No.	Precipitant Drug	Object Drug	Interaction
25	Phenobarbitone Phenytoin Carbamazepine Rifampin	Metronidazole, Warfarin, Doxycycline,Sulfonyl ureas Chloramphenicol Protease inhibitors Corticosteroids Oral contraceptives Antidepressants	Induction of metabolism loss of efficacy of object drug; Avoid concurrent use or increase dose of object drug with monitoring.
26	NSAIDs	Ciprofloxacin and Other fluoroquinolones	Enhanced CNS toxicity, seizures; Avoid concurrent use.
27	Aspirin and other NSAIDs	Sulfonyl ureas Phenytoin,Valproate Methotrexate	Displacement and /or reduced elimination toxicity of object drug;Avoid concurrent use/ substitute NSAID with paracetamol
28	Aspirin and other NSAIDs	Warfarin Heparin	Enhanced risk of bleeding due to antiplatelet action and gastric mucosal damage;Avoid concurrent use
29	Aspirin and other NSAIDs	ACE inhibitors Beta-blockers Thiazide diuretics	Reduced antihypertensive effect due to inhibition of renal PG synthesis; Avoid concurrent use
30	Aspirin and other NSAIDs	Furosemide	Reduced diuretic action due to PG synthesis inhibition in kidney; Avoid concurrent use
31	Allopurinol	Ampicillin	Increased incidence of rashes; Avoid concurrent use
32	Chronic Alcoholism	Paracetamol	Hepatotoxic dose of paracetamols reduced; Doses < 3 g/day are safe.
33	Chlorpromazine, Haloperidol, Metoclopramide	Levadope–carbidopa	Antagonism of antiparkinsonian effect; Concurrent use contraindicated
34	Sildenafil Tadalafil	Nitrates	Marked potentiationprecipitous fall in BP; Concurrent use contraindicated
35	lidocaine	Beta-blockers	Enhanced bradycardia and hypotension

Result and Discussion

Drug interaction studies are important as per pharmaceutical considerations drug interaction have significant impact on the drug and its biochemical activity.by these studies we can understand drug interaction with respect to its chemical, physical, and biological aspects. we can find out the mechanism of interaction which can be useful in studying unwanted effects of drug interaction and we can also overcome these unwanted effects.Drug interaction studies are useful in determining the root cause of undesirable drug interaction, which help to avoid these side effects.

After understanding the drug interactions we can sort out some benefacial result which help us in further complications and also overcome the drug interaction related problems. Whatever the antagonistic effects were arising they can be avoided and harmfull effects were minimized.

These studies are also useful to understand the synergism, which help to potentiate the effect of drug. Some synergism effects may produce high degree of activity which may be unwanted. Some important drug interaction can also be overcome which may causes side effect.

Conclusion

The present article provides the use full information related to drug interaction in body or outside the body. It is very difficult to assess the true incidence and clinical significance of drug interactions. Article also provides the understanding the mechanisms underlying drug interactions is important for the prediction and avoidance of drug toxicity when initiating combination therapy. Although multiple in vitro methods are currently in use to assess drug interactions, not all have allowed the prediction of clinically significant events. As drug

interactions most commonly result from influences on drug-metabolizing enzymes. Many other physical and chemical aspects are also responsible for the drug interactions. Drug interaction may be due to poly pharmacy, multiple prescribers, multiple pharmacies, etc. Drug interaction studies help to overcome the side effects due to the drug interaction, and also useful in understanding the synergism.

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