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Review of Drug Interactions: A Comprehensive Update

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Authors' contributions

Preparation of this review was carried out in collaboration between both authors. Author MM suggested and designed the review. Author DS wrote the first draft of manuscript and managed the literature searches. Author MM overviewed and modified the manuscript, and completed and confirmed the literature searches. Both authors read and approved the final manuscript, and contributed to the revision of manuscript.

Review Article

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ABSTRACT

Prescribing multiple medications predisposes to possibilities of occurrence of drug interactions. Various different terminology and ways exist to classify or arrange drug interactions. Drugs interact with other drugs, foods, beverages and herbs; outside or inside the body. Knowledge of *In vitro* interactions is essential to avoid loss of activity of drugs before administration. Although every theoretical drug interaction may not manifest in practice, drug interaction is a prominent cause of adverse or undesired events related to drug administration. Amongst the herbs, St. John's wort has a potential of producing significant drug interactions due to its capacity to induce metabolism of number of drugs. *In vivo* interactions at pharmacokinetic level affect absorption, distribution, biotransformation or excretion of drugs. Induction or inhibition of cytochrome P450 (CYP450) enzymes forms a major basis of drug interactions. Induction of metabolism of a substrate drug leads to treatment failure. Inhibition of metabolism leads to serious interactions by aggravating toxicity of substrate drugs. As compared to induction, inhibition is a fairly rapid process, and number of precipitant drugs which inhibit the metabolism is much more than that of inducers. Role of drug transporters, especially P-glycoprotein (P-gp), in causation of drug interactions is being increasingly identified. P-gp affects absorption, distribution and excretion, and hence plays a major role in

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pharmacokinetic drug interactions. Additionally, P-gp works hand in hand with CYP450 enzymes. In pharmacodynamic interactions, the drugs synergise or antagonise the effect at the level of target of action. Clinically beneficial and reparative drug interactions are explored to obtain useful drug combinations. Extensive research has led to development of a large number of *In vitro* and *In vivo* methods to detect and predict drug interactions. Appropriate awareness and knowledge of possible drug interactions is crucial in prevention of drug interactions and their consequences.

Keywords: Drug interactions; transporter; P-glycoprotein; methods for detection; CYP450.

1. INTRODUCTION

In the modern era of medicine, it is surprising if one comes across a patient receiving just one or two medications at a time. Coexistence of multiple medical conditions as well as the need and practice of polypharmacy play role in occurrence of drug interactions. Drug interaction is an alteration in the nature or effect of drugs due to concurrent administration of one or more drugs, foods or beverages. Drug-drug interaction has been a known factor affecting response to drugs and a prominent cause of adverse drug reactions.

Enormous research has highlighted the epidemiological features of drug interactions. Although every theoretical or seemingly possible drug interaction may not manifest in actual practice, there have been reports of as high as 21% adverse drug event related hospital admissions to be due to drug interactions [1]. A meta-analysis involving 39 studies between 1966 and 1996 from US hospitals reported about 7% of hospitalisations to be due to drug interactions [2,3]. Retrospective analysis of data on prescriptions dispensed to 2.1 million Italian individuals from January 2004 to August 2005 identified 27 pairs of potentially interacting drugs [4]. Another large study in Australian veterans found that 1.5% of the subjects were dispensed potentially hazardous interacting drug pairs, and the potentially hazardous drug interactions were noted at a rate greater than 5% [1].

Antiretroviral medications have great potential for drug-drug interactions. Different studies between 2004 and 2009 from UK, US, Kenya, Switzerland and Netherlands in 3596 patients with AIDS-related disease showed a prevalence of clinically significant drug-drug interactions to be 23-40% [5]. In a study involving 153 patients receiving antiretroviral therapy, at least one clinically significant drug interaction was found in 41.2% of their regimens. In 34.6% of regimens, there was at least one drug interaction that required a dosage adjustment. The risk factors associated with clinically significant drug interactions included age older than 42 years, more than three comorbid conditions, treatment with more than three antiretroviral agents and treatment with a HIV protease inhibitor (PI). Clinically significant drug interactions were more prevalent with PI-based than non-nucleoside reverse transcriptase inhibitor (NNRTIs)-based regimens [6].

Incidence of prescription of drugs with potential for interactions has been reported to be around 4 to 5 percent among hospital inpatients. Most of these potential drug interactions may not occur or may go unrecognised. In a major surveillance programme revealing 3600 (4.3%) adverse drug reactions in 83,000 drug exposures, 234 (6.9%) were attributed to drug interactions [7].

2. FACTORS AFFECTING DRUG INTERACTIONS

2.1 Patient-Related Factors

The patient-related factors include drug clearance in a particular patient, age, genetic factors, gender, concurrent diseases, environmental factors and diet [8,9]. Drug interaction becomes more crucial in patients with extremes of age (too old and too young age), immune-compromised hosts, patients receiving medications pertaining to or affecting cardiovascular or central nervous systems, and also in patients with chronic diseases, multiple illnesses and in those having renal or hepatic impairment. The post-transplant patients, patients with severe illnesses, and those with AIDS-related disease also are more susceptible to occurrence of drug interactions [3,5].

At old age, altered drug disposition, presence of multiple illnesses and use of multiple medications increase the risk of drug-drug interactions. So also, it is obviously harder to remember taking several drugs at different times. This predisposes to inappropriate drug intake. The situation worsens particularly if over-the-counter (OTC) medications are also being taken [3,10]. In a study involving 287,074 veterans, the drugs commonly involved in potentially hazardous drug interactions were verapamil, methotrexate, amiodarone, lithium, warfarin, cyclosporine and itraconazole [1]. The manifestations of drug-drug interactions at old age include hallucinations and psychomotor agitation due to interaction between venlafaxine and propafenone, psychic disturbances due to interaction between sodium valproate and levetiracetam and occurrence of blood dyscrasia due to coadministration of phenobarbital and lamotrigine in a patient with epilepsy [11,12,13]. The other extreme of age is the childhood, and children clear most medications more quickly, and are therefore at increased toxicity risk if drug metabolism is altered. Risk of theophylline toxicity due to inhibition of its metabolism by macrolids is higher in children than in adults [3]. Diseases have an impact on drug interactions, because cytokines, drug transporters and enzymes may get modified during infectious and other processes. For example, P-glycoprotein transporter activity is decreased in patients following small bowel resection, and the CYP3A4 hepatic microsomal enzymes get affected due to liver cirrhosis [3].

2.2 Drug-Specific Factors

The drug-specific factors include specific kinetic and dynamic properties of drugs, number of drugs prescribed, and the dose, time, sequence, formulation and route of administration [8]. Multiple prescribers, widespread use of alternative medicines, and use of drugs more likely to be involved in drug interactions lead to increased possibility of a drug interaction [3,5]. Incidence of drug interactions increases with number of medications that the patient receives. It is reported that the risk of drug interaction increases substantially when number of co-administered medications exceeds four, and incidence of clinically significant drug interactions reaches up to 20% when number of drugs consumed is between 10 and 20 [14].

Prescribing and dispensing may involve potentially hazardous interacting drug pairs [1]. A study found that the common precipitant drugs prescribed in primary care practice were nonsteroidal anti-inflammatory drugs (NSAIDs) and antibiotics, in particular, rifampin [15]. Drugs with narrow therapeutic range or low therapeutic index (having small difference between therapeutic dose and toxic dose) are more likely to be the objects for serious drug interactions. Object drugs in common use involved in drug interactions included warfarin, fluoroquinolones, antiepileptics, oral contraceptives, cisapride and 3-hydroxy-3-

methylglutaryl coenzyme A-reductase inhibitors (HMG CoA-reductase inhibitors) [16]. It was suggested that drugs involved in so many potentially serious drug interactions should be viewed as “red flags”, which included warfarin, cyclosporine, erythromycin, azole antifungals (itraconazole, ketoconazole and fluconazole), PIs (HIV protease inhibitors) and HMG CoA-reductase inhibitors (statins) [14].

Past research, in addition, suggested that drug interactions are clinically relevant with drugs affecting closely regulated body functions (namely antihypertensive, antidiabetic and anticoagulant medications), and drugs having saturable kinetics, high first pass metabolism or a single inhibitable route of elimination [14].

Some more pharmacokinetic factors are relevant in causation of drug interactions. Drugs with high plasma protein binding, drugs predominantly metabolised by CYP3A4 isoform and the drugs which are inducers or inhibitors of cytochrome P450 (CYP450) enzyme system are in general more likely to be involved in drug interactions.

3. TRANSPORTERS, P-GLYCOPROTEIN, AND PHARMACOKINETIC INTERACTIONS

Modification of transport of drugs across cell membranes is liable to influence drug influx or efflux and affect absorption, distribution as well as elimination. The transporters play a crucial role in pharmacokinetic drug interactions. Increasing research has been changing the perspective of understanding pharmacokinetic processes. The two important superfamilies of transporters are solute carrier (SLC) transporters and human ATP-binding cassette (ABC) transporters [17].

SLC transporter superfamily is involved mainly in uptake of neurotransmitters across membranes of nerve endings as well as sodium, glucose and other substances. They transport organic and inorganic compounds including drugs, xenobiotics, vitamins, hormones, sugars, ions, metals, and proteins. Transport occurs as symport (cotransport) or antiport (exchange transport). Examples of SLC transporters include SLC6A2 or norepinephrine transporter (NET), SLC6A3 or dopamine transporter (DAT), SLC6A4 or serotonin transporter (SERT), vesicular monoamine transporter for dopamine and norepinephrine transport into adrenergic vesicles (VMAT), gamma amino butyric acid transporters (GAT1, GAT2, GAT3), sodium glucose transporters (SLGT1, SLGT2) in intestines and renal tubules, the organic anion transporting polypeptide (OATP – OATP1B1/1B3) and organic cation transporter (OCT) in liver canaliculi and renal tubules, and dipeptide and tripeptide transporters (PEP1 and PEP2) [17].

ATP-binding cassette (ABC) transporter superfamily utilises ATP for transport of molecules. This superfamily includes the most studied, P-glycoprotein (P-gp) efflux transporter, also known as multidrug resistance type 1 (MDR1) transporter or ABCB1, the product of the MDR1 gene. P-gp is involved in efflux of substances from cytoplasm to extracellular fluid or cell organelle in intestinal mucosa, renal tubules, bile canaliculi, choroidal epithelium, astrocyte foot processes around brain capillaries (blood brain barrier), and testicular and placental microvessels. It limits intestinal absorption as well as entry and penetration of substances in brain, testes, fetal tissues, and promotes their biliary and renal elimination. P-gp has high transport capacity and broad substrate specificity, and is a biological protective mechanism against mainly hydrophobic, amphipathic, uncharged or basic substances. The genetic polymorphism in MDR1 transporter can affect therapeutic drug levels. Role of P-gp

in neoplastic cells is significant in development of resistance by neoplastic cells to anticancer agents, and is coded by MDR1 gene. Verapamil has been shown to be an inhibitor of P-gp, and therefore has been studied for preventing or reversing resistance to anticancer drugs. Substrates of P-gp include several anticancer drugs (etoposide, teniposide, mitomycin, doxorubicin, paclitaxel, vinblastine and vincristine), some PIs (saquinavir, indinavir), fexofenadine, H2 blockers, antiarrhythmics, calcium channel blockers, digoxin, immunosuppressants, corticosteroids, antiemetics, antidiarrheal agents (loperamide), analgesics, antibiotics, anthelmintics, sedatives and antidepressants [18].

P-gp can be induced by substances such as rifampin, phenobarbital, grapefruit juice, and St. John's wort, and induction would lead to decreased effects of many drugs like statins, antihypertensives, and antihistamines [18]. P-gp is inhibited by many substances such as verapamil, nifedipine, felodipine, diltiazem, quinidine, amiodarone, erythromycin, clarithromycin, ritonavir, cyclosporin A, elacridar, valspodar, cortisol, omeprazole, pantoprazole, ketoconazole, itraconazole and tamoxifen. Induction or inhibition of P-gp is an established cause of various drug interactions at the level of absorption, distribution or elimination. Function of P-gp seems to be in parallel with that of the CYP450 enzyme system, especially CYP3A4 isoform [18].

Other ABC transporters include multidrug resistance-associated protein (MRP) transporter (responsible for excretion of some drugs and anticancer agents in urine and bile), multidrug resistance-associated protein 1 (MRP1, which has a physiologic role in leukotriene secretion), multidrug resistance-associated protein 2 (MRP2) and ABCG2, known as the breast cancer resistance protein (BCRP).

4. CLASSIFYING/ARRANGING DRUG INTERACTIONS

Classifying drug interactions is an exercise of looking at drug interactions in various ways, and there exist different parameters to classify drug interactions. Rather than using a relatively rigid term such as "classification", it will be wiser to say that following are some of the different ways of arranging drug interactions from various different perspectives. It also goes without saying that since every type uses a different basis or criterion for classifying; some types or examples of drug interactions may overlap or be repeated under different headings in this article.

1. (A) Food-Drug interactions
   (B) Drug-Herb interactions
   (C) Drug-Drug interactions

2. Drug-Drug interactions can be further arranged into:

   (A) *In vitro* (Pharmaceutical) drug interactions (Occurring outside the body)
   (B) *In vivo* (Pharmacological) drug interactions (Occurring inside the body)
      (a) Pharmacokinetic interactions: Those interfering with -
         (1) Absorption (2) Distribution (3) Biotransformation (4) Elimination
      (b) Pharmacodynamic interactions: Those producing -
         (1) Additive or synergistic effect (2) Antagonistic effect

3. (A) Clinically Desirable (Beneficial) drug interactions
   (B) Harmful drug interactions (Adverse drug interactions): Further arranged as -
      (a) Nonserious (b) Serious or Fatal

4. (A) “Clinically Significant” or “Clinically Manifesting” drug interactions
   (B) “Clinically Less Significant” or “Theoretical” or “Non-manifesting” drug interactions

5. (A) Highly Predictable” drug interactions
   (B) Predictable” drug interactions
   (C)Drug interactions that are “Not Predictable”
   (D) Unestablished drug interactions

6. (A) Drug interactions leading to treatment failure
   (B) Drug interactions leading to an increased pharmacologic effect
   (C) Drug interactions leading to toxic reactions/effects

7. Reparative drug interactions

8. Drug interactions with unknown mechanisms

In the following sections, various important drug interactions are discussed under different types of headings to clarify their mechanism and arrangement from a specific perspective. We have intentionally avoided the tabular representation, which many times may pose difficulties in following too long tables and may make it difficult to explain and elaborate the exact mechanism of a drug interaction.

5. DESCRIPTION OF DRUG INTERACTIONS

5.1 Food-Drug Interactions

Generally, food decreases absorption of most of the medications to some extent. Absorption and bioavailability of certain medications is very significantly hampered by food intake, for example, rifampin, which is therefore advised to be taken early in the morning on empty stomach [19,20].

Tetracyclines, sulfonamides, and fluoroquinolones chelate the calcium present in milk and milk products, resulting in diminished absorption of calcium as well as these antimicrobials [19,20].

Monoamine oxidase (MAO) inhibitors block breakdown of amines, especially tyramine present in certain foods. So when such foods are ingested, tyramine and other indirectly acting amines accumulate in nerve endings and release the stored norepinephrine, which precipitates hypertensive or hyperadrenergic crisis. Foods that contain tyramine/tyrosine/tryptophan or high content of other amines and are likely to interact with MAO inhibitors include some aged or processed cheeses, beer, Chianti and Alicante type wines, yeast extracts, avocados, chocolates, fava beans, pods of broad beans, beef or chicken liver, smoked or pickled meat or fish (herrings), dried fish, some processed or cured meats and sausage [7].

Food containing high carbohydrate content decreases absorption of iron, levodopa, penicillins, tetracyclines and erythromycin. Food in general, as well as acidic foods or various juices decrease didanosine absorption [7].

Warfarin is an oral anticoagulant and acts by inhibiting vitamin K-dependent clotting factors. Green leafy vegetables, namely, broccoli, spinach, kale, Brussels sprouts and cabbage are high in vitamin K content, and therefore their high intake can counter the effect of warfarin. Exactly opposite effect (increased effect of warfarin) is likely if onions, garlic or vitamin E-containing foods are consumed with warfarin, because these substances have anticlotting effects [7].

Grapefruit juice stimulates the P-gp transporter, and decreases the effect of statins, antihypertensives and antihistamines. Black licorice contains glycyrrhizin, which decreases the effect of antihypertensive drugs and diuretics [19,20].

There are interesting examples of particular types of food increasing the absorption of certain drugs. High-fat food increases absorption of griseofulvin, saquinavir, lovastatin and spironolactone. Acidic foods, juices and sodas improve ketoconazole absorption. Vitamin C present in orange and other citrus fruits, citrus juices and cranberry juice increases iron absorption by facilitating dissolution as well as conversion of ferrous to ferric form. High fiber diet adsorbs tricyclic antidepressants and reduces their absorption. Wheat bran and oatmeal adsorb digoxin and decrease its bioavailability [19,20].

Amongst beverages, alcohol is an important substance leading to serious drug interactions. Alcohol profoundly depresses central nervous system (CNS) and leads to serious additive effect with other CNS depressants, which include hypno-sedatives such as benzodiazepines, nonbenzodiazepines and barbiturates, and antiepileptic medications, classical antihistamines, anxiolytics, antidepressants and opioids. NSAIDs, corticosteroids and alcohol all lead to gastric irritation and bleeding. Acetaminophen, amiodarone and methotrexate may produce additive hepatotoxicity with alcohol. Insulin and sufonylureas produce inhibition of gluconeogenesis, and concurrent alcohol intake may lead to prolonged and profound hypoglycemia. Disulfiram or drugs such as metronidazole, cephalosporins, H2 blockers, chlorpropamide and macrolides inhibit acetaldehyde dehydrogenase and lead to accumulation of acetaldehyde, if the patient consumes alcohol. This is a serious interaction consisting facial flushing, nausea, vomiting, headache, hypotension, dizziness, sweating, confusion and exhaustion, classically described as alcohol intolerance [7].

5.2 Drug-Herb Interactions

Some potential interactions between drugs and herbal products are elaborated below.

Warfarin is known to have potential interactions with some herbs leading to an increased effect of warfarin. These include ginkgo (*Gingko biloba*), denshen (inhibits warfarin metabolism), garlic (inhibits platelet aggregation) and ginger (anticoagulant activity). Ginkgo decreases plasma concentrations of omeprazole, ritonavir and tolbutamide [21]. Clinical cases indicate interactions of ginkgo with antiepileptics, aspirin, diuretics, ibuprofen, risperidone, rofecoxib, trazodone and warfarin [22].

The effect of warfarin is decreased by green tea (contains vitamin K and hence opposes warfarin action), St. John’s wort (increases warfarin metabolism), dong quai (*Angelica sinensis*) (unknown mechanism) and alfalfa [18]. Devil's Claw (*Harpagophytum procumbens*) and Ginseng (*Panax ginseng*) also do have a potential to interfere with action of warfarin and phenelzine [22,23].

St. John's wort (*Hypericum perforatum*) is a known inducer of microsomal enzymes and due to induction it is likely to decrease the effects of PIs (protease inhibitor such as indinavir), NNRTIs (non-nucleoside reverse transcriptase inhibitors), antidepressants, transplant medications (such as cyclosporine) and warfarin. St. John's wort is also known to induce P-gp and may decrease serum digoxin levels [21]. St. John's wort used concurrently with selective serotonin reuptake inhibitors (SSRIs) has a risk of precipitating mental confusion, nausea, fatigue, and weakness. A review of 80 clinical trials and 128 case reports indicated that St. John's wort is an important herb involved in drug interactions. Clinical trials suggested that St. John's wort, via CYP450 and P-gp induction, reduces plasma concentrations (and/or increases the clearance) of alprazolam, amitriptyline, atorvastatin, chlorzoxazone, ciclosporin, debrisoquine, digoxin, erythromycin, fexofenadine, gliclazide, imatinib, indinavir, irinotecan, ivabradine, mephenytoin, methadone, midazolam, nifedipine, omeprazole, oral contraceptives, quazepam, simvastatin, tacrolimus, talinolol, verapamil, voriconazole and warfarin. Case reports or case series suggested the interactions of St. John's wort with adrenergic vasopressors, anaesthetics, bupropion, buspirone, ciclosporin, eletriptan, loperamide, nefazodone, nevirapine, oral contraceptives, paroxetine, phenprocoumon, prednisone, sertraline, tacrolimus, theophylline, tibolone, venlafaxine and warfarin [22].

Kava Kava (*Piper methysticum*) is likely to produce additive CNS depression when used with alprazolam [23]. It increases clearance of chlorzoxazone (a CYP2E1 substrate) and may also interact with levodopa and paroxetine [22]. Raw or processed garlic (*Allium sativum*) consumed in inadvertently large quantities decreases the effect of protease inhibitors (PIs). It also interacts with chlorpropamide, fluindione and warfarin. It reduces plasma concentration of chlorzoxazone [22]. Milk thistle (*Silybum marianum*) decreases effect of PIs or NNRTIs [23].

Cinchona bark (quinine) carries a risk of additive CNS toxicity in the form of ataxia and mental confusion if used concurrently with amantadine (an antiviral agent) and the risk of additive cardiotoxicity if used with astemizole (an antihistamine). Cinchona bark also leads to increased serum carbamazepine levels. Herbs having diuretic properties (broom, buchu, dandelion, juniper) have a potential of increasing serum lithium levels. Ayurvedic herbal shankhapushpi can decrease the effect of phenytoin, leading to occurrence of seizures. Wormwood can lower seizure threshold. Black cohosh can antagonise blood pressure lowering effect of some antihypertensives. Figwort may precipitate digoxin toxicity. Red clover, chamomile and many other herbs can interfere with action of anticoagulants [23]. Echinacea may affect clearance of caffeine (a CYP1A2 probe) and midazolam (a CYP3A4 probe). No interactions have been reported for saw palmetto (*Serenoa repens*) as per some studies, whereas some other studies mention that it may interact with anticoagulants and steroid hormones [22].

5.3 *In vitro* (Pharmaceutical) Drug Interactions (Occurring Outside the Body)

Certain drugs react with each other and get inactivated if they are mixed in a syringe or in an infusion. So the drug effect might be lost even before administration. Phenytoin precipitates in 5% dextrose solution [7]. Aminoglycosides (like gentamicin), macrolides (like erythromycin), tetracyclines and chloramphenicol are physically/chemically incompatible with most beta lactams (penicillins and cephalosporins) resulting in loss of antibiotic activity, wherein usually a beta lactam substance inactivates the other structures. Heparin cannot be mixed in a syringe with hydrocortisone, penicillins or aminoglycosides. Hydrocortisone may inactivate penicillins and aminoglycosides. Norepinephrine cannot be mixed with sodium

bicarbonate. Thiopental may produce a precipitate with succinylcholine, pancuronium, atracurium, ketamine or morphine when mixed in a syringe. Nonliposomal amphotericin B is prone to precipitate in electrolyte-containing solutions, and hence it is necessary to give it in 5% dextrose. Nitroglycerine can get inactivated by binding to a particular type of plastic of the containers or that of the infusion sets [7,24].

5.4 *In vivo* (Pharmacological) Drug Interactions

"*In vivo*" or "Pharmacological" interactions are those taking place within the body, and this section shall consider mostly the "drug-drug" interactions. These may take place by interference with pharmacokinetics or pharmacodynamics of drugs or sometimes both.

5.4.1 Pharmacokinetic Drug Interactions

Pharmacokinetic drug interactions take place due to alteration in absorption, distribution, biotransformation or elimination of one or more drugs, and may have clinical implications as mentioned below [25].

5.4.1.1 Drug interactions produced by affecting absorption

Drug interactions affecting the extent of absorption leading to subtherapeutic drug concentrations are clinically more important than those affecting only the rate of absorption [8].

Gastrointestinal absorption of drugs may be decreased by another drug by various mechanisms such as change in pH, motility or perfusion, adsorption, binding, chelation, other chemical reactions and affecting transporters or microbial flora [8].

Change in pH: Antacids and H2 blockers increase the gastric pH and decrease absorption of iron, ketoconazole, fluoroquinolones and tetracyclines, because these substances need acidic environment for absorption. Sucralfate needs to get polymerised to produce its effect, and polymerisation takes place at acidic pH. Antacids and H2 blockers raise the gastric pH. This blocks polymerisation of sucralfate as well as its effect. Stomach wash with sodium bicarbonate is helpful in acidic drug poisoning to increase the gastric pH, and thereby to increase ionisation and inhibit absorption of acidic poisons [24].

Gastrointestinal motility or perfusion: Altered gastrointestinal motility by anticholinergics, tricyclic antidepressants, opioids, and prokinetics (like metoclopramide or cisapride) affects drug absorption. Metoclopramide reduces the extent of absorption of digoxin by allowing less time for it. It also reduces bioavailability of cimetidine [24]. Anticholinergics lead to a slower absorption of most drugs, because they delay gastric emptying. This results in slower absorption and greater degradation of levodopa (less of it reaches the brain) [24].

Adsorption: Sucralfate adsorbs tetracyclines, phenytoin and H2 blockers, and thus decreases their absorption. Activated charcoal adsorbs the alkaloids, and prevents the further absorption of remaining unabsorbed poison from the stomach (termed "physical antagonism" because adsorption is a physical phenomenon).

Chemical reaction: Magnesium oxide reacts chemically with alkaloids, and tannic acid forms alkaloidal tannate. Thus, they are useful for stomach wash in alkaloidal poisoning to

prevent further absorption of alkaloids (termed “chemical antagonism” because the reaction is of chemical nature) [24].

Binding: Bile acid binding resins (bile acid sequestrants such as cholestyramine) bind to warfarin, digoxin and statins, and interfere with their absorption. There needs to be an interval of at least 4 hours between administration of statins and resins. Pectin-kaolin combinations and antacids markedly decrease digoxin absorption [8].

Chelation: Tetracyclines, sulfonamides, and fluoroquinolones chelate ions such as calcium, magnesium, aluminium and iron, and form insoluble complexes with them. This leads to reduced absorption of substances (milk and milk products, antacids and iron tablets) containing these ions. In this process, the absorption of the chelating substances (tetracyclines, sulfonamides or fluoroquinolones) is also hampered. Chelation is chemical antagonism [7].

Induction of efflux transporter: Rifampin stimulates intestinal P-gp. Increased P-gp facilitates digoxin elimination. So, if rifampin and digoxin are concurrently used, there is a decreased oral bioavailability of digoxin and decreased serum digoxin levels [24].

Inhibition of microbial flora: Intestinal microbial flora normally deconjugates the oral contraceptives secreted in bile as glucuronides and allows their enterohepatic circulation. However, concurrent use of broader spectrum antimicrobial agents such as ampicillin, amoxicillin, tetracyclines, chloramphenicol, sulfonamides, cotrimoxazole, fluoroquinolones or macrolides inhibit the intestinal flora, and reduce the enterohepatic cycling of oral contraceptives, leading to failure of contraception [8].

In some other cases, the gastrointestinal absorption of a drug may be increased by another drug.

Inhibition of efflux transporter: Grapefruit juice inhibits the P-gp and increases absorption of cyclosporine, alprazolam, midazolam, terfenadine, astemizole, cisapride, atorvastatin, calcium channel blockers (felodipine, nifedipine, amlodipine), carbamazepine and estrogens. Similarly when P-gp is inhibited by drugs such as clarithromycin or itraconazole, increased digoxin levels make the patient more susceptible to digoxin toxicity, particularly the CNS manifestations [8,24].

Gastrointestinal motility: Metoclopramide hastens absorption of drugs such as aspirin or diazepam by facilitating gastric emptying. Anticholinergics may increase the extent of digoxin and tetracycline absorption due to decreased motility and longer transit time in gastrointestinal tract [24]. Metoclopramide increases rate of absorption of theophylline, and can lead to three times higher incidence of headache and nausea [7].

Alteration in pH or ionisation: Vitamin C or citrus fruits increase iron absorption by favoring dissolution, and reduction of ferric to ferrous form [24].

A drug may bind to another drug and affect its absorption on parenteral administration. Combining two medications outside the body may not necessarily lead to loss of activity. They may remain compatible, and after entering human body, one of the drugs in combination may help the other by various mechanisms as described below. Insulin is combined with protamine or zinc outside the body to obtain neutral protamine Hagedorn (NPH) or protamine zinc insulin (PZI). Protamine and zinc are binding substances, and

inside the body they release insulin slowly over a long period of time, thus prolonging duration of action of insulin. Benzyl penicillin given with procaine produces a prolonged action. Similarly, penicillin in oil or in aluminium monostearate acts for a longer duration. In another example, a drug may affect the perfusion and thereby influence absorption of another drug. If lidocaine is used for local anaesthesia along with epinephrine, epinephrine produces vasoconstriction, decreases local blood flow, and decreases the rate of entry of lidocaine. So the duration of action of lidocaine gets prolonged ("Time synergism"). Combination also has an advantage of minimising the systemic absorption and systemic toxicity of the local anaesthetic. (Additionally, epinephrine minimises the bleeding at the surgical field) [7,8,24].

5.4.1.2 Drug interactions produced by affecting drug distribution

Mechanisms of drug interactions based on alteration in drug distribution include competition for plasma protein binding and displacement from plasma protein binding sites, displacement from tissue binding sites, alteration in local tissue barriers like P-glycoprotein transporter, change in perfusion (vasodilators and angiotensin-converting enzyme inhibitors), and change in volume of distribution (diuretics).

Plasma protein binding and displacement: Acidic and neutral drugs mainly bind to albumin. These include NSAIDs, sulfonamides (sulfamethoxazole), tolbutamide, warfarin, benzodiazepines, barbiturates, valproic acid, phenytoin, naproxen, penicillins, steroids and fibrates. Basic drugs mainly bind to alpha-1 acid glycoprotein. These include beta blockers (alprenolol), verapamil, quinidine, disopyramide, lidocaine, bupivacaine, tricyclic antidepressants, methadone and prazosin [24].

The bound form of a drug is inactive and the free form is active. As the free form is distributed and utilised, there is a constant turnover from the bound form to free form. Generally, the drugs having high plasma protein binding capacity act longer. When two drugs have a capacity to bind substantially to the same plasma protein binding site, there is a possibility of competition for the same site. In such situations, one of the drugs may displace the other from the plasma protein binding site. This leads to an inadvertent or unaccounted increase in concentration of the displaced drug. This excess free concentration of the displaced drug may lead to its enhanced effect and/or toxicity [8].

Warfarin, phenytoin, NSAIDs, sulfonylureas, and oral contraceptives are some of the known highly plasma protein binding agents, and are more liable to be involved in plasma protein binding and displacement drug interactions. Phenylbutazone displaces warfarin resulting in excess effect and bleeding. Salicylates, ketoprofen, indomethacin, naproxen and diclofenac can displace methotrexate causing methotrexate toxicity [26]. Ibuprofen binds to site II of albumin, while salicylates, diclofenac and naproxen bind to site I (which is also the site for binding of warfarin), hence ibuprofen is less likely to show a drug-drug interaction with warfarin [27]. Valproic acid displaces phenytoin resulting in phenytoin toxicity.

Even if the two drugs have a high plasma protein binding property, still the primary prerequisite for possibility of competition and/or displacement is the capacity of both drugs to bind to the same type of plasma protein (albumin or alpha-1 acid glycoprotein). It is interesting that although this primary prerequisite may be fulfilled, it does not necessarily mean that a significant effect takes place. For example, if the displaced drug shows increased concentration, but if it rapidly diffuses in tissues or gets rapidly metabolised or excreted, then its increased concentration may remain high transiently, but may not manifest

into a clinically significant drug interaction. The clinical significance is attained only in cases of highly bound drugs with limited volume of distribution. Hence overall impact of many displacement interactions may remain minimal. Such interactions may remain theoretical and may not clinically manifest [7,24].

Tissue binding and displacement: Interactions are possible if one drug displaces another from binding sites (other than receptors) in the tissues. Because of huge capacity of tissue binding sites, only transient increases in unbound drug concentration is the common result of such interactions. Quinidine, nifedipine, verapamil and amiodarone can increase digoxin concentration by this mechanism [7].

5.4.1.3 Drug interactions produced by affecting biotransformation or metabolism

These interactions are related to enzyme induction and enzyme inhibition. An important kinetic factor involved in possibility of a drug interaction is whether the two drugs are metabolised by the same isoform of subfamily of the cytochrome P450 enzyme system (CYP450) associated mainly with liver and gastrointestinal mucosa [28]. Cytochrome P450 enzyme system may be referred to as CYP450 or just CYP. The number (say 3) after CYP stands for the family, for example, CYP3. The capital alphabet (say A) after CYP3 describes the subfamily, for example CYP3A. The number after the alphabet (say 4) stands for the polypeptide (indicating the individual enzyme or individual isoform in the subfamily), for example, CYP3A4. CYP450 enzymes belong to probably the largest known gene superfamilies. CYP450 enzymes are hemoproteins localised to mitochondria or endoplasmic reticulum, and are involved in breakdown or detoxification of endogenous as well as exogenous substances like drugs and xenobiotics. Relative quantities of various CYP enzyme subfamilies or isoforms in humans in decreasing order are those of 3A, 2C19, 2D6, 2C8 and 2C9, 1A2, 2E1, 2B6 and 2A6 [29]. A single CYP enzyme isoform can metabolise many drugs, and a single drug also may be metabolised by more than one isoform. This unusual feature of extensively overlapping substrate specificity of CYP450 is one of the important reasons for occurrence of drug interactions. Metabolism of drugs can be stimulated or inhibited by concurrent therapy and the result of this phenomenon varies from negligible to dramatic [30]. Major metabolism of a large number of substances is under province of CYP3A subfamily and it is in relatively higher quantities in liver. This fact makes CYP3A more significant as far as induction- and inhibition-based drug interactions are concerned [29]. In humans, the CYP3A4 protein is encoded by the *CYP3A4* gene. Protein is indicated as CYP and the gene in italic letters as CYP [31]. This gene is part of a cluster of CYP450 genes on chromosome 7q21.1 [32,33]. CYP3A4 is responsible for metabolism of approximately half of the drugs, and hence this isoform is involved in many drug interactions of clinical significance [34].

Interactions based on enzyme induction: Enzyme induction is a process, in which a drug stimulates a particular isoform of CYP450, and there occurs a gene-mediated increase in number of molecules of the metabolising enzyme, and hence the drugs supposed to be metabolised by a particular isoform will be rapidly degraded. Drug that stimulates the enzyme is called an “inducer”. Induction is a complex, dose-related phenomenon requiring the inducer to reach a critical concentration to bind and activate transcription factors at an intranuclear receptor or regulation point from which upregulation of messenger RNA occurs with a subsequent increase in enzyme protein production [7]. Induction is a relatively slow process that may start after 3-4 days of exposure to an inducer. Maximal effect usually occurs after 7–10 days and requires an equal or longer time to dissipate after the inducer is stopped [8]. However, drugs like rifampin that have shorter half life produce the induction

more quickly, i.e. after only a few doses, because they reach the steady-state concentration more rapidly. Enzyme inducers can also increase the activity of phase II metabolism such as glucuronidation. Some of the common inducers are ethyl alcohol, barbiturates (phenobarbitone, primidone), carbamazepine, phenytoin, rifampicin, rifabutin, griseofulvin, efavirenz, nevirapine, bosentan, St. John's wort, smoking and dichlorodiphenyltrichloroethane (DDT). Inducers are classified on the basis of percent decrease in plasma area under curve (AUC) values of substrate drug. Strong inducers are those which produce 80% or more decrease in AUC of substrate. Examples of strong inducers of CYP3A4 include rifampin, phenytoin, carbamazepine and St. John's wort. Moderate inducers produce between 50% and 80% decrease in AUC of substrate and include phenobarbitone, nevirapine and efavirenz. Weak inducers produce between 20% and 50% decrease in AUC of substrate. Induction-based interactions can lead to significant manifestations [28]. Induction of estrogen metabolism may lead to failure of contraceptive effect and unexpected pregnancy. Similarly, therapeutic failure with digoxin and digitoxin is known. Failure of immunosuppressive action of cyclosporine can lead to organ transplant rejection. Patients receiving enzyme inducers may show failure of therapy to antimicrobial agents like metronidazole or doxycycline prescribed for some infections. Antiepileptic drug doses may fall short and seizures may be precipitated. Loss of anticoagulant effect of warfarin is known to lead to thrombosis. When the induction wanes, failure to recognise the need to reduce the warfarin dose may lead to bleeding. Methadone withdrawal reactions are known in patients on opioid substitution programmes, who receive inducers for another purpose [7].

Self induction: An agent inducing a particular isoform of CYP450 may itself be a substrate for the same isoform. This results in induction of metabolism of the inducing agent. This is called "self induction" or "auto induction". This simply means that a drug induces its own metabolism and leads to decreased effects, and development of tolerance (in case of barbiturates or carbamazepine), when the drug is used for longer periods. So also, the dose of such medications needs to be increased gradually and cautiously to avoid toxicity [7, 28].

Drug interactions based on enzyme inhibition: Enzyme inhibition is a phenomenon in which some particular drugs produce inhibition of enzymes responsible for breakdown of certain substrates. Drugs which produce inhibition of enzymes are called "enzyme inhibitors". As compared to induction, inhibition is a direct phenomenon of affecting a particular enzyme. Therefore, inhibition is often a fairly rapid process, and may begin as soon as sufficient tissue concentration of the inhibitor is achieved. However, if the half life of the affected drug is long, it may take a week or more to reach a new steady-state serum concentration. After stoppage of an inhibitor drug, the effect of inhibition lasts relatively for shorter duration [8]. Various mechanisms involved in inhibition of metabolism include competition and reversible binding to enzyme (quinidine), inactive complex formation with enzyme (macrolids), enzyme destruction (vinyl chloride), inhibition of synthesis of enzyme molecules of a particular isoform or competing for the same isoform [8,24].

Inhibitors are classified as strong, moderate or weak depending upon their effect on the substrate. Strong inhibitor is the one that causes more than 5-fold increase in plasma AUC values or more than 80% decrease in substrate clearance. Some example of strong inhibitors and the isoform inhibited are fluconazole (2C9), gemfibrozil (2C8), fluvoxamine and ciprofloxacin (both 1A2), bupropion, cinacalcet, fluoxetine, paroxetine and quinidine (all 2D6), and indinavir, ritonavir, nelfinavir and saquinavir as well as clarithromycin, itraconazole, ketonazole, nefazodone and telithromycin (all 3A4, 5, 7) [28]. Moderate inhibitor causes more than 2-fold increase in plasma AUC values or 50%-80% decrease in

clearance of substrate. Examples of moderate inhibitors with isoform they inhibit are trimethoprim (2C8), amiodarone (2C9), duloxetine, sertraline and terbinafine (all 2D6), aprepitant, erythromycin, fluconazole, grapefruit juice, verapamil and diltiazem (all 3A4, 5, 7). Weak inhibitor causes 1.25-2-fold increase in plasma AUC values or 20%-50% decrease in clearance. Cimetidine is a weak inhibitor at 1A2, 2D6 and 3A4, 5, 7. Amiodarone is a weak inhibitor at 2D6 [28]. Some more inhibitors include chloramphenicol, isoniazid (INH), atazanavir, valproic acid, miconazole, voriconazole, omeprazole, metronidazole, androgens, cyclosporine, delavirdine, diphenhydramine, disulfiram, enoxacin, mexiletine, propoxyphene, sulfamethizole, zafirlukast, zileuton, dextropropoxyphene, sulfinpyrazone, phenylbutazone and furanocoumarins (substances in grapefruit juice) [8].

Macrolids inhibit theophylline metabolism and increase risk of its toxicity. Phenylbutazone inhibits metabolism of warfarin, which increases risk of bleeding. Valproic acid inhibits metabolism of phenytoin, resulting in phenytoin toxicity. Risk of inhibition of metabolism leading to toxic effects of drugs is common for drugs with narrow therapeutic index. Risk is known with phenytoin, theophylline, warfarin and oral antidiabetics. If the substrate drug follows zero order kinetics at higher doses or if the substrate has a narrow therapeutic index, then the risk of toxicity is predominant. Fatal cardiac arrhythmia due to terfenadine, astemizol or cisapride is precipitated if used concurrently with inhibitors such as fluoxetine or tricyclic antidepressants (TCAs) [24].

Interestingly, benefit may be obtained by inhibition of metabolism as in case of ritonavir, which inhibits metabolism of other antiretrovirals and this is useful to potentiate their effect [24].

Nonmicrosomal enzyme inhibition (other than CYP450): Nonmicrosomal enzymes may be inhibited by certain agents to produce significant drug interactions. Allopurinol is a xanthine oxidase inhibitor, used in gout to decrease the uric acid synthesis. The anticancer drugs, mercaptopurine or azathioprine are also metabolised by the same enzyme. So, if allopurinol is used concurrently with any of the two drugs, their breakdown is inhibited, and their action is potentiated. Failure to recognise this interaction may lead to their toxic effect. On the other hand, this knowledge can benefit in a way that one could decrease the doses of mercaptopurine or azathioprine while giving them concurrently with allopurinol. Carbidopa is a peripheral dopa decarboxylase inhibitor. It inhibits peripheral breakdown of levodopa, which allows more of levodopa to reach the brain, and also reduces the risk of its peripheral adverse effects. MAO inhibitors when given with amphetamine or foods containing tyrosine/tyramine/tryptophan or any other indirectly acting amines, inhibit the breakdown of these amines. These amines escape degradation and enter systemic circulation where they tend to release norepinephrine at nerve endings leading to hypertensive crisis. Cilastatin is combined with imipenem to prevent degradation of imipenem at renal tubular cells as cilastatin inhibits the enzyme renal dehydropeptidase responsible for imipenem degradation. This potentiates the action of imipenem. In addition, because imipenem metabolite is responsible for renal toxicity of imipenem and cilastatin is preventing the breakdown, renal toxicity of imipenem can be minimised [29].

First pass metabolism: Drug interactions sometimes depend on extent of first pass metabolism of drugs. Oral bioavailability of a drug is likely to be increased if its first pass metabolism is inhibited by another drug given concurrently that competes with it for first pass metabolism. Propranolol increases bioavailability of chlorpromazine by decreasing its first pass metabolism. Propranolol decreases breakdown of lidocaine by decreasing hepatic blood flow, because lidocaine metabolism depends on the hepatic blood flow [24].

5.4.1.4 Drug interactions produced by affecting drug elimination

The mechanisms by which a drug can affect the rate of renal excretion of other drugs include alteration in protein binding and filtration, inhibition of tubular secretion, binding to active transporters in proximal tubules or altering the urine flow or urine pH [35].

Transporters involved in tubular secretion of drugs include P-gp, OATP and OCT. Their inhibition decreases the renal elimination, and leads to increased serum drug concentrations. Both probenecid and penicillins are transported through OATP. Probenecid competitively binds to OATP and gets excreted. Thus it inhibits penicillin excretion and increases duration of action of penicillins. Probenecid produces similar effect on cephalosporins. So probenecid is combined with penicillins or cephalosporins to obtain a longer duration of action of these beta lactam antibiotics. Diuretics act from within the tubular lumen, and salicylates inhibit their secretion into tubular fluid, and reduce their effect. Verapamil and quinidine reduce biliary/renal excretion of digoxin by inhibiting P-gp. Quinidine reduces tissue binding of digoxin and also inhibits P-gp. Thus quinidine reduces biliary and renal clearance of digoxin and increases susceptibility to digoxin toxicity. Aspirin decreases tubular secretion of methotrexate [24].

Alteration in urine flow or urine pH can produce interactions at the level of elimination. Diuretics increase the urine flow and tend to increase the urinary excretion of other drugs and their metabolites. When thiazide diuretics and lithium are used concurrently, sodium depletion due to thiazide diuretics tends to reabsorb lithium from proximal tubule, and lithium toxicity precipitates. Changing urine pH is a common method employed in management of drug overdose. Forced alkaline diuresis with the help of systemic alkaliser such as intravenous sodium bicarbonate is useful to manage overdoses with acidic substances such as barbiturates and salicylates. Sodium bicarbonate produces alkalinisation and hence facilitates ionisation of weak acids and inhibits their reabsorption. Hence elimination of weak acids is enhanced. As opposed to this, in conditions of overdose with alkalies like amphetamine and phencyclidine, acidification with ammonium chloride helps elimination by similar principle of ionisation. It has been reported that salicylates, furosemide and penicillin G may bind to active transporters and may interfere with certain drugs [35]. Salicylates compete with OATP and reduce the tubular secretion of methotrexate, causing methotrexate toxicity [8].

5.4.2 Pharmacodynamic drug interactions

In these interactions, there is interference with dynamics of drug action. A drug may interfere with effect or action or may interfere with mechanism of action of other drugs. Thus the primary interference is not with kinetics, but is essentially at the level of action, which may be a receptor or a physiological system. Sometimes it may involve modification of response of a drug as a result of alterations brought about by compensatory homeostatic responses to changes produced by drugs [7]. One of the ways to look at dynamic interactions is to put them into “additive or synergistic drug interactions” or “antagonistic drug interactions”.

5.4.2.1 Additive or synergistic interactions

When action of a drug is facilitated or increased by the other, the phenomenon is termed “synergism” and the combination is termed “synergistic combination”. Synergism between two drugs may take place in different ways [8].

When two drugs with similar effect are concurrently used, there is likelihood of addition of effects. When effect of combination is an arithmetic sum of individual effects of the two drugs, this is termed “additive effect”. Common examples include addition of analgesic effect of two analgesic drugs, additive central nervous system depression on concurrent use of two or more CNS depressants or addition of neuromuscular blocking effect of a competitively blocking skeletal muscle relaxant and an aminoglycoside antibiotic [7].

The term “supraadditive effect” is usually used when effect of combination is greater than just an arithmetic addition of effects of two drugs. A classic example is that of cotrimoxazole, a combination of trimethoprim and sulfamethoxazole. Here the two agents individually act as bacteristatic drugs but the combination produces bactericidal effect by sequential blockade of two steps in folic acid synthesis in microorganisms. Some other examples of synergistic combination include the estrogen-progestin oral contraceptive combination, nitrate-propranolol combination used for prophylaxis of angina or the antihypertensive combination of hydrochlorothiazide-enalapril. In such situations, two drugs in the pair usually have similar effects or varied mechanisms but leading to a common purpose [24].

However, there are examples of interactions in which a drug may not have a direct role in a particular effect, but may enhance or facilitate action or effect of the other drug, which is the main drug used for a specific purpose. What is being referred to, is the combination like levodopa-carbidopa, in which carbidopa is not at all an anti-parkinson agent per se, but facilitates and helps the action of levodopa. Carbidopa is a peripheral dopa decarboxylase inhibitor, and prevents peripheral breakdown of levodopa, so that more of levodopa reaches the brain. So, carbidopa is said to potentiate the effect of levodopa. Epinephrine used along with lidocaine to produce vasoconstriction and prolong the duration of local anaesthesia is a similar example, where epinephrine potentiates or facilitates the action of lidocaine. Using sulbactam or clavulanic acid (beta lactamase inhibitors) to prevent destruction of ampicillin or amoxicillin respectively is another such example wherein the beta lactamase inhibitor does not have antimicrobial action, but facilitates effect of beta lactam antibiotics. Such examples are also looked upon as drug synergism or potentiation [24]. So the terms “synergism” and “potentiation” have to be considered with a general implication of beneficial effect produced when two agents are used in combination irrespective of whether both components of combination have similar effects or not [7,8,24].

5.4.2.2 Antagonistic drug interactions

Antagonism may be pharmacological (receptor antagonism) such as competitive or noncompetitive antagonism, and the other type of antagonism may be non-pharmacologic or non-receptor antagonism, wherein there the interaction between the two drugs is not at the receptor level, but still the two drugs may produce opposite effects by physical, chemical or physiological (functional) antagonism [24].

Receptor antagonism – Competitive: Here the two drugs combine and compete for the same receptor site and one of the drugs is an agonist having intrinsic activity, whereas the other is an antagonist which has poor intrinsic activity. Any one of the two in the pair can compete for the same receptor site and displace the other from the receptor. Competitive antagonism-based interactions are widely applied in management of overdose or poisoning of those substances, which are specific for particular receptors, so that action can be reversed by using a competitive antagonist for same receptor. Common examples include use of naloxone in acute opiate overdose, flumazenil in acute benzodiazepine overdose or atropine in organophosphorous compound poisoning. Organophosphorous compounds are

anticholinesterase agents which cumulate acetylcholine, so atropine is used as a competitive antagonist at muscarinic cholinergic receptors [24].

Receptor antagonism – Noncompetitive: The pairs – diazepam-bicuculline or norepinephrine-phenoxybenzamine are examples of noncompetitive antagonism.

Non-receptor or Non-pharmacologic antagonism: Physiological, physical, and chemical antagonism are various types of non-pharmacologic or non-receptor antagonism. The implication is, the two drugs interact not at the level of same receptor, but by some other mechanisms described below.

Physiological antagonism: When two drugs produce opposite effect on a same physiological system or tissue or function, the term "physiological antagonism" is applied. Hydrochlorothiazide (a thiazide diuretic) and triamterene (a potassium sparing diuretic), although do not interfere with each other at same receptors, but by their own mechanism lead to opposite effects on urinary potassium excretion. Similarly glucagon and insulin have opposite effects on blood sugar level [7,24].

Chemical antagonism: Here the two drugs interact with each other by a chemical reaction. Potassium permanganate is useful for stomach wash in cases of alkaloid poisoning, because it oxidises the unabsorbed alkaloid in the stomach. Similarly, when tannins are used in such cases, they produce a chemical reaction and form an insoluble alkaloidal tannate, and thus prevent further absorption of alkaloid. British anti-Lewisite (BAL or dimercaprol) chelates the heavy metal arsenic and is useful for arsenic poisoning. In acute iron overdose, desferrioxamine is used for chelating iron. Nitrates react chemically with cyanide radical to form methemoglobin, and hence are useful in cyanide poisoning [7,24].

Although occurring outside the body, antagonism between thiopentone-succinylcholine, sodium penicillin G-succinylcholine, heparin-penicillin, heparin-tetracycline, heparin-streptomycin, heparin-hydrocortisone, penicillin-aminoglycoside, penicillin-tetracycline, cephalosporin-aminoglycoside, cephalosporin-tetracycline, erythromycin-aminoglycoside, erythromycin-tetracycline, and similar pairs also can be viewed as chemical antagonism, since there is a chemical reaction between the two drugs [24].

Physical antagonism: In physical antagonism, there is an involvement of a physical phenomenon or physical reaction between two drugs or substances. Physical reactions involve binding or adsorption. Adsorption of alkaloids in the stomach by activated charcoal is an example of physical antagonism. Hence activated charcoal is used for gastric lavage during poisoning with alkaloids [8].

5.4.3 Pharmacokinetic as well as pharmacodynamic interaction

Here two drugs interact with each other by both pharmacokinetic as well as pharmacodynamic mechanisms. Aspirin displaces warfarin from plasma protein binding sites and raises warfarin levels leading to its enhanced effect, which is a pharmacokinetic interaction. In addition, the antiplatelet effect of aspirin and the anticoagulant effect of warfarin potentiate each other at pharmacodynamic level. Interaction can be viewed as occurring at both pharmacokinetic and pharmacodynamic level when an aminoglycoside is used with a beta lactam antibiotic. Beta lactam antibiotic weakens the bacterial cell wall and facilitates entry of the aminoglycoside (which is supposed to act on the nucleus). This is like affecting the aminoglycoside kinetics inside the bacterial cell. At the same time, because

aminoglycoside acts on nucleus and beta lactam antibiotic acts on the cell wall, they are helping each other pharmacodynamically. It is true that using a beta lactamase inhibitor to prevent breakdown of the beta lactam antibiotic is inhibition of its metabolism in the bacterial cell. At the same time, since this interaction makes the beta lactam antibiotic effective against beta lactamase-producing and "supposed-to-be" resistant organisms is a dynamic effect [7,8,24].

5.5 "Clinically Desirable" or "Beneficial" Drug Interactions

A desirable drug interaction is defined as either a beneficial drug effect that is enhanced or a detrimental drug effect that is mitigated by the concomitant use of another drug. These drug interactions are deliberately used or explored to obtain beneficial effects in clinical practice [36].

Combinations such as sulfamethoxazole-trimethoprim or sulfadoxine-pyrimethamine are classical examples of clinically desirable drug interactions. Penicillins or cephalosporins used concurrently with aminoglycosides provide the benefit of two different mechanisms of action. These combinations often have a wider spectrum of activity than that of the individual components. Deliberate use of the beta lactamase inhibitors with beta lactam antibiotics obviously leads to a clinically desirable or beneficial interaction. Ampicillin-sulbactam, amoxicillin-clavulanic acid, piperacillin-tazobactam are such clinically desirable combinations [36]. Use of anticholinergic and dopaminergic drugs in Parkinson disease, adding a potassium sparing diuretic to potassium losing diuretics to prevent potassium loss, and antacid combinations used to prevent adverse effects on gastrointestinal motility are few more examples of desirable drug interactions.

5.6 Serious Drug Interactions

Some adverse (harmful) drug interactions are considered serious and/or fatal. Exaggeration of warfarin effect can lead to bleeding by concurrent use of ciprofloxacin, clarithromycin, metronidazole, cotrimoxazole, lovastatin, acetaminophen and NSAIDs including aspirin. Increased level leading to serious toxicity of antiepileptic medications (carbamazepine, phenytoin, phenobarbitone) is known due to concurrent use of cimetidine, erythromycin, clarithromycin and fluconazole, whereas rifampin is known to significantly decrease the effect of antiepileptics. Concurrent use of NSAIDs or diuretics leads to significant increase in lithium levels and its toxicity. Concurrent use of sildenafil and nitrates leads to dramatic hypotension [8,16].

Some drugs have a potential of precipitating cardiac arrhythmia by prolonging the phase-3 repolarisation, and hence are considered to be proarrhythmics or arrhythmogenic agents. These include terfenadine, astemizole, cisapride, Class IA antiarrhythmics (quinidine, disopyramide, procainamide), class III antiarrhythmics, tricyclic antidepressants and phenothiazines. Concurrent use of inhibitors like azoles, macrolides, fluoxetine, and HIV protease inhibitors with any of the arrhythmogenic agents carries a serious risk of cardiac arrhythmia. Concurrent use of statins with niacin, gemfibrozil, macrolides or azoles precipitates rhabdomyolysis. Concurrent use of SSRIs with tricyclic antidepressants, MAO inhibitors, tramadol, triptans (naratriptan, sumatriptan, rizatriptan or zolmitriptan), and St. John's wort carries a risk of serotonin syndrome and hypertensive crisis [16].

5.7 Clinically Significant / Clinically Manifesting Drug Interactions

Not all drug interactions are clinically significant [14]. The significance of drug interactions can range from theoretical and no effect to life threatening. Interaction is often considered significant when it occurs between two or more co-administered agents and results in the need for dosage adjustments of one of the agents or other medical intervention [14]. Prevalence of drug interactions of potentially major clinical significance has been mentioned to be between 2% and 16% [1]. Inadvertent concurrent administration of synergistic or antagonistic pair of drugs may lead to adverse consequences [24].

Some of the drugs involved in common clinically significant drug interactions include central nervous system depressants, oral anticoagulants, antidiabetics, cardiac glycosides, antihypertensives, nonsedating antihistamines, benzodiazepines, antiepileptics, immunosuppressants and cytotoxic medications. Critically ill, chronically ill and elderly patients are particularly at risk of clinically manifesting drug interactions [7]. A given drug combination known to have potential for drug interaction in humans may not necessarily produce a drug interaction in all patients [7].

5.8 Highly Predictable Drug Interactions

Some of the highly predictable drug interactions help to take due precautions to avoid them. For example, antacids and sucralfate decrease the absorption of fluoroquinolones and tetracyclines, and concurrent administration is avoided. Disulfiram inhibits metabolism of acetaldehyde when ethyl alcohol is consumed. Inhibition of metabolism by cimetidine and azole antifungals carry a risk of increased toxicity of warfarin and statins. Monoamine oxidase inhibitors interact with indirectly acting sympathomimetics (ephedrine, pseudoephedrine, phenylpropanolamine and tyramine) leading to an episode of hypertension due to release of stored norepinephrine. Concurrent use of CNS depressants such as ethyl alcohol, barbiturates, benzodiazepines, classical or sedating antihistamines, opioids, antiepileptics and other CNS depressants leads to additive CNS depression and/or toxicity. Quinidine and oral anticoagulants produce additive hypoprothrombinaemia. Salicylates given in daily dose of more than 1.5 g, decrease the uricosuric effect of sulfinpyrazone. Quinidine by acting at various levels (tissue binding and clearance) increases the digoxin levels. Concurrent use of aspirin and oral anticoagulants carries a risk of bleeding [8].

5.9 Predictable Drug Interactions

Drug interactions which are known to be predictable, also help to modify concurrent drug therapies or avoid adverse events. Iron decreases the absorption of tetracyclines and fluoroquinolones, and vice versa. Iron decreases absorption of also thyroxine, mycophenolate and azoles. Antacids decrease iron absorption. Decreased effect of various drugs due to induction of drug metabolism by rifampin, carbamazepine and phenytoin is predictable and is helpful in modifying treatment strategies. The effect is in terms of failure of treatment to various drugs including oral contraceptive medications, sulfonylurea hypoglycemic agents, theophylline, cyclosporine, sirolimus, tacrolimus, diltiazem, verapamil, colchicine, beta blockers, quinidine and oral anticoagulants, and this knowledge is helpful in decision making. Pyridoxine and phenothiazines decrease the effect of levodopa. Pyridoxine stimulates breakdown of levodopa, because the enzyme dopa decarboxylase is pyridoxine-dependent. Since inhibition of drug metabolism is a comparatively rapid process and also

because the number of drugs capable of producing inhibition is larger, predictable interactions result in toxicity of various drugs. Risk of toxicity exists in case of caffeine, theophylline, carbamazepine, phenytoin, catecholamines, SSRIs, digoxin, colchicine, procainamide, quinidine, TCAs, oral anticoagulants and benzodiazepines (except oxazepam, lorazepam, temazepam which also are metabolised to some extent by extrahepatic conjugation). Inhibitors likely to precipitate these interactions include fluoroquinolones, HIV protease inhibitors, amiodarone, felbamate, cimetidine, macrolides, isoniazid, diltiazem, verapamil and chloramphenicol. MAO inhibitors used concurrently with amine-containing drugs or substances predispose to hypertensive crisis. Disulfiram decreases phenytoin metabolism. SSRIs (fluoxetine, paroxetine) inhibit CYP2D6 and inhibit metabolism of timolol, propranolol, metoprolol, carvedilol and labetolol. Allopurinol enhances effects and toxicity of azathioprine and mercaptopurine. There are some known predictable interactions at the level of clearance. Salicylates decrease renal clearance and precipitate toxicity of methotrexate. Acetazolamide decreases renal excretion of quinidine. Probenecid decreases renal clearance of penicillins, cephalosporins, methotrexate and palatrexate. Diuretics (especially thiazides) decrease lithium excretion. Theophylline increases lithium excretion and decreases its effect [8].

Corticosteroids and salicylates used concurrently lead to more gastric mucosal damage. Potassium sparing diuretics used with potassium supplements lead to hyperkalemia. More than one potassium sparing diuretic used at the same time leads to hyperkalemia. Clofibrate and statins used together are known to increase the risk of myopathy. Beta blockers increase the antihypertensive response to first dose of prazosin. Insulin and beta blockers used together carry a profound risk of hypoglycemia unresponsiveness [8].

Salicylates given in daily dose of more than 1.5 g, decrease the uricosuric effect of probenecid. Salicylates decrease the antihypertensive response to ACE inhibitors, angiotensin II receptor blockers, beta blockers, loop diuretics and thiazide diuretics. Indomethacin decreases antihypertensive response to beta blockers [8].

5.10 Reparative Drug Interactions

The term “Reparative” drug interaction is a specific one. Reparative implies the phenomenon of repair. It is the repair of a disadvantage or an adverse effect. Reparative drug interaction means two drugs in a combination produce clinical benefit in such a way that each one of them takes care of the adverse effect of the other drug [36]. These two drugs work together to target a common beneficial effect. In addition they have certain effects that are opposite to each other, and thus compensate or counter each other’s disadvantage. In a commonly used antacid combination of magnesium hydroxide and aluminium hydroxide, both have a common effect of neutralising the acid, and there is addition of this beneficial effect. At the same time, they have opposite action to each other on gastrointestinal motility. Magnesium hydroxide increases gastrointestinal motility whereas aluminium hydroxide decreases it, thus these two effects get nullified. Nitrate-propranolol combination in prophylaxis of angina is a similar example, where the two drugs by various mechanisms work together to decrease the frequency of anginal attacks. At the same time, they compensate for each other’s effect on heart rate. Nitrates produce reflex tachycardia whereas propranolol (a beta blocker) produces bradycardia. So also, nitrates have an effect of increasing cardiac contractility and beta blockers are known to decrease it, thus nitrates oppose the ventricular dilation produced by beta blockers [36].

5.11 Drug Interactions with Unknown Mechanisms

Some drug interactions occur due to unknown mechanisms. High incidence of skin rashes is known in patients receiving ampicillin and allopurinol. Valproic acid levels can drop 3- to 5-fold in 24 hours after adding meropenem. Extrapyramidal syndrome and severe dementia have been reported if lithium is combined with methyldopa or haloperidol and if methyldopa is combined with haloperidol. Although it is obvious that actions of methyldopa and haloperidol are related to dopamine, the exact mechanism of the interaction is not known. Increased risk of renal failure in patients receiving tetracycline when methoxyflurane is used for anaesthesia is also an interaction with unknown mechanism [7].

6. EXPERIMENTAL METHODS TO STUDY OR DETECT DRUG INTERACTIONS

6.1 *In vitro* Methods to Study/Detect Drug Interactions

Although the pharmacokinetic and pharmacodynamic interactions observed through *In vitro* human or animals studies may not necessarily occur in human beings [7], there is a need of *In vitro* models to decide if and which future drug interaction studies should be performed in man [37].

In vitro study of metabolic drug interactions involves identifying major metabolic pathways involved in biotransformation of the test drug, the specific enzymes responsible (mainly CYP450), enzyme induction or inhibition and the metabolites generated. This allows detection of major pharmacokinetic interactions which can occur in man and identification of specific populations at risk for such interactions. Human *In vitro* models are employed to detect drug interactions in preclinical phases of drug development. These include recombinant enzymes, human liver microsomes and primary human cryopreserved or cryoplateable hepatocyte cell cultures. Results obtained from these models may vary during different phases of drug development [37].

Various models used for studying drug interactions include “Subcellular fractions of human liver tissue”, “Whole cell models”, “Heterologous expressed and purified human drug-metabolising enzymes”, “Pharmacological probes” and “Immunochemical probes” [38]. While using “Subcellular fractions of human liver tissue”, hepatic microsomes are obtained by differential high-speed centrifugation of homogenised liver [39]. In this method, individual or pooled preparations of microsomes from multiple donors need to be used. Enzymes present in these preparations include CYP450 enzymes, flavin mono-oxygenases, epoxide hydrolases and transferases. The advantages of this model include ease of preparation, commercial availability and long-term stability during cryopreservation; however, the method is not appropriate to study sequential metabolic reactions involving coupling of phase I and II reactions. “Whole cell models” employ the harvested livers not used for transplantation as well as the biopsy samples. The characteristics vary with age, health, diet, alcohol/tobacco or medication use, and genotype of the donor. Whole cell models carry the advantages of having the full complement of hepatic drug-metabolising enzymes, endogenous cofactors and preservation of the natural orientation for linked enzymes. In addition, the role of alternative metabolic routes with drugs that inhibit the principal drug-metabolising pathway can be studied. The major limitation is the short-term stability of enzymatic activities. It is less than 3-4 hours for suspensions and less than 24 hours for cultures or slices. “Caco-2 cell monolayers” (derived from human colon cancer cells) serve as a surrogate model for study of drug interactions involving absorption and metabolism at the level of the human

intestine. Caco-2 cell system is useful to investigate drug interactions resulting from inhibition of the P-gp. Underexpression of metabolising enzymes and a time-dependent loss of enzyme activity in culture are the disadvantage of Caco-2 model. Another model includes "Heterologous, expressed and purified human drug-metabolising enzymes". Cloning of the cDNAs (complementary DNAs) for common CYP450 enzymes is done by which recombinant human enzymatic proteins expressed in various cells with low intrinsic CYP450 enzyme activity are obtained. The varieties of cells include bacteria, yeast, insect cells, mammalian cells and human lymphoblastoid or HepG2 human hepatoma cells. Further the lysates of these transgenic cells are subjected to subcellular fractionation. This method has an advantage of allowing the study of the isoform-specific metabolism of a drug or the ability of the drug to inhibit the substrate metabolism related to that particular isoform. Absence of competing pathways may pose a disadvantage, and will prevent assessment of relative contribution of the isoform in question to the overall metabolism of drug *in vivo*. The model of "Pharmacological probes" is helpful to demonstrate the metabolic pathways for the test drug through the use of selective chemical inhibitors of specific CYP enzymes. The inhibitory activity can be expressed either as inhibition constant or the 50% inhibitory concentration. The 50% inhibitory concentration is an estimate of the concentration of the drug inhibiting the maximum rate of metabolism of a fixed concentration of substrate by 50%. These determinations have the advantage of being independent of the biochemical mechanism of inhibition; however, extrapolation to *In vivo* situations may be unreliable if plasma concentrations of the substrate differ markedly from that studied *In vitro*. Knowledge of the *In vitro* inhibition constant of a drug for a particular CYP isoform is therefore considered more useful in assessing the probability of a drug interaction. The inhibition constant is a measure of the affinity of the inhibitor for the enzyme and its determinations require study of inhibition at a range of concentrations. However, because different values of inhibition constant may be obtained using different substrates, it is desirable to perform independent estimations of inhibition constant using multiple substrates. "Immunochemical probes" employ polyclonal or monoclonal antibodies to specific isoform of CYP enzymes in microsomal preparations for selective inhibition. Inhibition of metabolite formation by an antibody specific to a particular isoform will indicate that the test drug is metabolised selectively by that isoform [38,39].

6.2 *In vivo* Methods in Animals

Animal species may provide useful models to determine whether a new chemical species generated *In vitro* by human liver microsomes produces pharmacological or toxicological effects *In vivo*. Comparative drug metabolism in humans and animals can play a useful role in rational selection of animal models for toxicology studies. Development of transgenic animal models represents an *In vivo* approach to the investigation of role of specific enzymes involved in drug metabolism [39].

6.3 Prediction of *In vivo* Drug Interactions from *In vitro* Data

Quantitative predictions of *in vivo* drug-drug interactions resulting from metabolic inhibition are commonly made based upon the inhibitor concentration at the enzyme active site and the *In vitro* inhibition constant. Researchers have used various plasma inhibitor concentrations as surrogates for enzyme active site along with the *In vitro* inhibition constant values obtained from published literature. This approach has led to high proportion of successful predictions, although a number of falsely predicted interactions are also observed by this approach [38,39].

6.4 *In vivo* Methods in Humans

In vivo human methods relate to the drug interaction studies in clinical trials. Pair-wise drug interaction studies to cover as many medications as can be identified for a drug candidate are done. For each medication, drug interaction-induced fold-change in area under curve and maximum concentration on systemic exposure is studied followed by recommending a dose adjustment. The open label cross-over designs are usually acceptable for studying pharmacokinetic interactions. For drugs with long elimination half life, parallel group studies are usually preferred. The appropriate population for drug interaction studies usually includes healthy subjects who meet restrictive eligibility criteria, subjects from general population to permit heterogenicity and subjects selected on the basis of phenotyping or genotyping for metabolic polymorphisms or predisposition to adverse drug reactions. Route of administration should correspond to those recommended in proposed or approved product monographs for the drug in question, and if multiple routes of administration are recommended for a drug, drug interaction findings for a particular route should not necessarily be extrapolated to the other routes. The highest proposed or approved doses of test drugs and the shortest dosing intervals are used in order to maximise the possibility of finding an interaction. For safety reasons, lower doses may be acceptable occasionally. Exploration of differential effects over a range of doses may be useful to characterise the dose-dependency of a drug interaction. The endpoints include various pharmacokinetic parameters, active or toxic metabolites and pharmacodynamic parameters. In general, whether to go for intravenous drug-drug interaction studies is decided on the basis of the extent of first pass effect of a particular drug. Only oral studies are undertaken if the oral first pass effect is less than 20%. If the oral first pass effect is more than 20%, then oral as well as intravenous drug-drug interaction studies are undertaken. Attention is focused to adverse events occurring with greater frequency or severity during combination treatment than during treatment with either agent alone. The clinical trial protocols contain directions for collection of blood samples from patients experiencing serious, severe or unexpected adverse events. Plasma level determinations for concomitant medications are likewise encouraged. The statistical considerations include provision of 90% confidence interval for mean ratios of pharmacokinetic exposure measures, and knowledge of width of equivalence interval beyond which a dosage adjustment is necessary is used in determining sample size. In absence of other information to determine an equivalence interval, a standard interval of 80%-125% can be employed. Sample size has to be larger if inter-subject or intra-subject variability in pharmacokinetic measurements is high [40].

Some of the enzyme inhibitors mentioned as preferred for *In vitro* experiments by FDA (Food and drug administration, USA) are furafylline, montelukast, quercetin, sulfaphenazole, quinidine, itraconazole and ketoconazole. Some inhibitors commonly acceptable for *In vitro* experiments include ticlopidine, gemfibrozil, trimethoprim, fluconazole, fluvoxamine, omeprazole, dithiocarbamate and verapamil [28].

7. DEALING WITH DRUG INTERACTIONS

On the part of the prescriber, awareness and knowledge of possible and clinically manifesting drug interactions is the most important key factor involved in prevention of drug interactions. The roots of this awareness emerge from the clear communication with the patient and meticulous history taking. The physician needs to know all the medications that the patient is receiving in order to understand, prevent or manage the possible drug interactions. This would include the medications prescribed by various prescribers as well as

over-the-counter and herbal medications. To reduce the confusion, it is worthwhile to encourage the patients to prepare and bring the whole list of medications with them to a consultation. It is equally important to know the time and frequency of administration of various medications. It is worthwhile to know if without the knowledge of the doctor the patient stops or starts any of the medications or adjusts their dosages. One needs to inquire in detail regarding the intake of foods, alcohols and beverages. Role of clear communication with patients and with primary care clinician is important [7]. In addition, history taking also needs to include past history of major illnesses and interventions, allergies, illicit drug use and any known genetic factors.

As far as awareness of possible drug interactions, the prescriber should know about serious and clinically manifesting adverse drug interactions, potentially interacting drug pairs, patient-related and drug-specific factors predisposing to drug interactions, and the substrate and precipitant drugs commonly involved in drug interactions. With all the due awareness of possibility of a potential drug interaction, the prescriber should be able to recognise it and then plan the appropriate action. This can minimise the risk of harm due to a drug interaction [8]. Appropriate measures are needed to avoid or minimise the impact of a drug interaction. These measures may include adjusting dose, route, order or sequence of administration or the spacing between the administration of interacting drugs. The measures also include anticipating the onset and peak effect of interaction and monitoring the patient at all times [3]. To minimise the risk of drug interaction, sometimes the physician may be able to simplify the drug regimen, by using one drug that serves two purposes or by reducing the number of times a drug must be taken [10]. At specific times, one of the precipitant drugs may need discontinuation and/or change in modality of an intervention may be required. A classic example is that of changing the method of contraception or delaying the decision to conceive, when a drug is absolutely necessary to serve the primary purpose in a particular illness (such as an anti-tuberculosis drug like rifampin or an antiepileptic agent such as phenytoin or carbamazepine or phenobarbitone), and is known to lead to failure of contraception. Awareness and knowledge of drug interactions is helpful in prevention of adverse events as well as for appropriate management of an illness. Further, pharmacovigilance measures involve anticipation of expected, predictable and highly predictable interactions in order to closely monitor the adverse event in case it happens.

8. CONCLUSION

Preventing adverse drug interactions is of utmost importance for the benefit of the patient. Detailed medication history, watchful prescribing to avoid interacting drug pairs, conscious effort to keep the medication number as less as possible, scrupulous protocols to prevent *In vitro* drug interactions and clear instructions regarding administration of medications are some essential measures to prevent adverse events due to drug interactions.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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