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A Review: Pharmacokinetic Drug Interactions, A Primer For Clinical Pharmacist.

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ABSTRACT
Drug-drug interactions(DDI) are one of the commonest causes of medication error, particularly in the elderly due to poly-therapy, with a prevalence of 20-40%. Drug interactions represent factors of uncertainty in many therapeutic situations. Drug–drug interactions can cause profound clinical effects, either by reducing therapeutic efficacy or enhancing toxicity of drugs. With an increasing frequency in polypharmacy, DDIs are one of the major causes for drug withdrawal from the market. In particular, poly-therapy increases the complexity of therapeutic management and thereby the risk of clinically important DDIs, which can both induce the development of adverse drug reactions or reduce the clinical efficacy. Although DDIs can result in alterations of either drug pharmacokinetics (PK), pharmacodynamics(PD), or both, it is the pharmacokinetic drug interactions that is clinically significant. PK drug interactions, typically characterized by alterations of plasma concentration–time profiles, could be attributed to changes in processes of absorption, distribution, metabolism, and excretion of a drug substance mediated by another drug when they are given concomitantly. In this review we mainly focused on the pharmacokinetic drug interactions with various drug examples and their mechanism of drug interactions that are clinically significant.
KEYWORDS - Drug-drug interaction, Pharmacodynamics, Pharmacokinetics, Polypharmacy**.**

I. INTRODUCTION

As drug use rises worldwide, pharmacists should be increasingly concerned about adverse consequences arising from drug interactions. Pharmacists are often the health professionals who represent the last line of defense between patients and the harmful effects of medications. Interactions between drugs often are predictable and avoidable. Thus, pharmacists who monitor patients and carefully check for rational prescribing can minimize adverse drug interactions. Prescription and nonprescription drugs can interact when given concurrently. Drugs can also interact with environmental chemicals and dietary substances. Some interactions are clinically valuable. However, many are undesirable and have potentially serious consequences for patients.[1] Medicines are often used concomitantly with other drugs, and some degree of drug-drug interaction occurs with concomitant use. drug interactions,especially for the drugs having a very narrow therapeutic index, may have severe adverse reactions. Therefore, within the evaluation and clinical application of medicine, appropriate efforts should be made to predict the character and degree of drug interactions in order that patients won't be adversely affected.[2] The clinical response depends on many factors,including individual patient characteristics such as age, co-morbidities and pharmacogenetics. [3] Most drug interactions are drug-drug interactions that occur when one drug alters the magnitude or duration of the pharmacologic response of another. Drug-drug interactions occur in patients by two mechanisms. Pharmacokinetic interactions occur when one drug changes the disposition of another by affecting the latter's absorption, distribution, biotransformation, or excretion; that is, it alters the concentration of the second drug at the site of action, altering the drug's effect The second type,pharmacodynamic interactions, involves additive, synergistic, or antagonistic effects of drugs acting on the same receptors or physiologic systems, with the result that the drugscombined effect is lesser or greater than either would elicit alone.[1] drug interactions might readily cause clinically significant changes in blood drug levels concentration in whole blood, plasma, or serum in patients having pharmacokinetic parameters markedly deviating from those of the standard population. The former interaction is the phenomenon that is induced by changes in blood levels and tissue distribution of a drug or its active metabolites by the interaction of the drugs, nutritional and environmental by the processes of absorption, distribution, metabolism, and excretion.[2,4]

II. DRUG ABSORPTION INTERACTIONS

The absorption of drugs from the human gastrointestinal tract has received relatively little attention from clinical pharmacologists. Yet the great majority of drugs are given orally, and it has been known for years that there may be enormous intra- and inter-individual variations in the rate and completeness of absorption of drugs. [5] To reach the bloodstream form the alimentary tract,a drug must cross the intestinal epithelium,basement membrane and capillary endothelium. For drugs, the most important process of absorption is passive diffusion, no energy is needed and it is a non-saturable process and the transfer is directly proportional to the concentration gradient and to the lipid – water partition coefficient of the drug. [6]

The extent of absorption is determined by drug solubility, the rate of drug permeation across the intestinal membrane, and the time of exposure (i.e., transit time through the intestine). These variables can be influenced by drug-induced changes in physiological or biochemical activities, and consequently, are potential factors in DDIs. Intestinal absorption is a kinetic process considered to occur under sink conditions wherein soluble drug concentrations in the intestinal lumen unidirectionally diffuse across the intestinal epithelium into a relatively large systemic volume. [7] The complexity of the gastro-intestinal tract, and the effects of several drugs with functional activity on the digestive system, represent favorable conditions for the emergence of DDI that may alter the drug bioavailability. [8] Interactions between drugs that influence absorptionfrom the gastrointestinal tract into thesystemic circulation represent a major problem indrug therapy. While many types of interactionshave been identified, many others probably have not been recognized due to the difficulty of establishing cause-effect relationships for symptomaticchanges in patients receiving multiple drugtherapy. [9] However, there are a number of interrelated factors that can complicate efficient drug absorption like altered gastric pH, complexation and adsorption of compounds, altered gastric motility, modulation of p-glycoprotein and alteration GI microflora.[6,8,9,10,11]

2.1 Interactions altering gastric pH

Several factors may influence the absorption of a drug through the gastrointestinal mucosa. The prerequisite factor is the change in gastric pH. The majority of drugs orally administered requires, to be dissolved and absorbed, gastric pH between 2.5 and 3.[5,8] Because most drugs are administered as solid preparations (such as tablets and capsules), they have to be dissolved in gastric or intestinal fluids to be absorbed. Many factors influence the dissolution. Among them, gastric pH has a crucial influence on the absorption of weakly acidic or basic drugs, because their solubility may be critically dependent on pH. It is well known that the dissolution rate of a formula in the gastric fluid is a rate-limiting step for absorption for some drugs.[12]DDIs can occur as a result of changes in drug solubility and dissolution as a consequence of altered gastric pH, or through changes to GI transit impacting the time of exposure of a drug to the absorptive intestinal epithelium. For the former, the acidic environment of the stomach facilitates dissolution of solid dosage forms and impacts solubility of some drugs. Acid-reducing agents (antacids, H2 antagonists, and proton pump inhibitors) can increase gastric pH from normal values of 1.5–3 to values as high as 5–6.11 Many weak basic drugs show dramatic changes in solubility over this pH range resulting in reduced dissolution and bioavailability at elevated pH. Clinical DDIs associated with increased GI pH resulting from acid-reducing drugs have been observed with many basic drugs, especially those with pH-dependent solubility.[5,8,13]

We consider that changes in the extent of drug absorption (quantified by area under the concentration-time curves [AUC] are more important than changes in the rate of absorption, quantified by maximum drug concentration [Cmax] and time to Cmax [tmax]), because the former is more directly associated with the cumulative systemic exposure to the drug and hence with therapeutic responses.[12]

2.1.1 Antacids,H2 blockers and PPIs associated interactions.

Antacids may interact with drugs or their dosage forms in various ways. By raising the pH in the gastrointestinal tract they may increase the solubility of acids and decrease the solubility of bases. Conversely, they may increase the proportion of solubilized basic molecules that are in the un-ionized state, thus facilitating their absorption, while having the opposite effect on acidic molecules. [9] H2 antagonists (e.g., ranitidine), antacids (e.g., aluminum hydroxide and sodium bicarbonate) and PPI (e.g., omeprazole, esomeprazole, pantoprazole) that increase the gastric pH lead to a decrease in cefpodoxime bioavailability, but on the other hand, facilitate the absorption of beta-blockers and tolbutamide.[8]

Cimetidine increased blood salicylate level when co-administered with aspirin, by inhibiting gastric acid secretion cimetidine increases absorption of aspirin by increasing the dissolution rate of the aspirin tablet.[6] The absorption of most compounds is significantly reduced by coadministration of antacid mixtures. Compounds thus affected include chlorpromazine,chlortetracycline,digoxin,isoniazid,penicillamine,tetracycline and vitamin A. Increased gastric pH due to antacids has been shown to increase the absorption rate of aspirin from an enteric-coated formulation and also of the sulphanomides, sulphadiazine and sulphathiazole. More rapid absorption of the sulphonamides is consistent with faster dissolution of the free acid form of these

compounds with increasing pH. The availability of pseudoephedrine is increased by concurrent aluminum hydroxide, and this is probably because of raised gastrointestinal pH increasing the proportion of pseudoephedrine present in the un ionized, and therefore more readily absorbed, form. [9,14,15]

2.1.2 Antifungal agents association interactions

Antifungal agents (e.g., ketoconazole or itraconazole), requires an acidic environment for being properly dissolved, therefore, their co-administration with drugs able to increase gastric pH, may cause a decrease in both dissolution andabsorption of antifungal drugs. Therefore, antacid or anticholinergics, or PPI might be administered at least 2 h after the administration of antifungal agents.[8]these drugs are weak bases with an acid dissociation constant (pKa) of approximately 3.0, they are nearly insoluble at pH >4.0. If coadministration of an antacid elevates the gastric pH to >4.0 for a period longer than the gastric emptying time (for liquid: 10–20 minutes), the drug may reach the small intestine before dissolution takes place and hence absorption is decreased.[12]

2.1.3 Iron salts and tetracycline associated interactions

The binding of drugs to iron is pH dependent, hence drugs and foodwhich effect gastrointestinal pH will alter iron-drug binding. [16]The decreased absorption of a solid dosage form, but not a solution, of tetracyclinein the presence of bicarbonate indicates that the dissolution step must be involved and can be explained by the importance of a low gastric pH to effect dissolution of solid tetracycline prior to absorption. The aqueous solubility of tetracycline at pH 1 to 3 is 100 times greater than that at 5 to 6. The rate of dissolution is markedly reduced at the higher pH values.Any substance which significantly increase the intragastric pH may result in a decreased fraction of tetracycline in solution available for absorption by a mechanism which is independent of the ability of the substance to chelate with tetracycline. Physiologic or pathologic conditions which increase gastric pH, such as achlorhydria might also result in a decreased absorption of tetracycline.[17,18]

2.2 Complexation and adsorption of compounds

The mechanism of DDIs is explained by chelation rather than elevation of gastric pH It may appear rather simple to alleviate DDIs based on the chelation mechanism. In order to interfere with the absorption of a concomitantly administered drug, a large amount of polyvalent cations must coexist with the susceptible drug in the upper gastrointestinal lumen for long enough to form substantial amounts of chelate complexes before absorption of the susceptible drug is completed.[10,12]

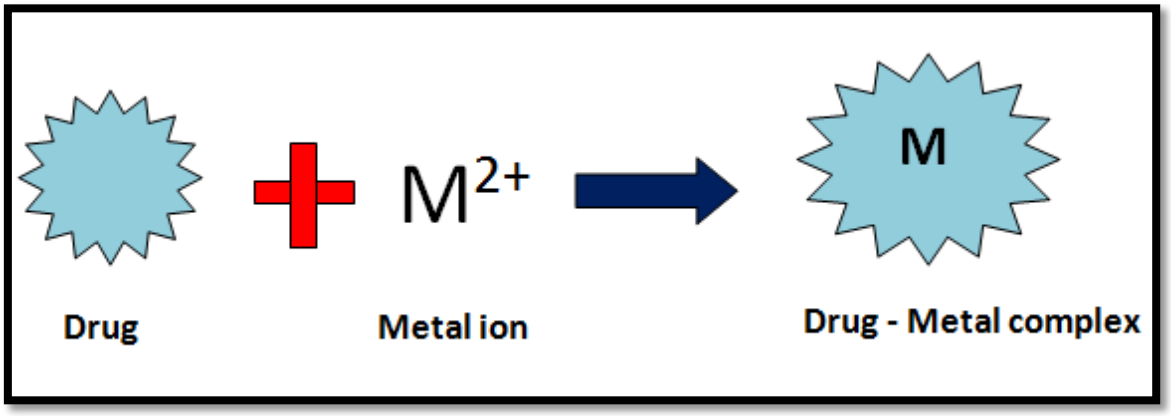

Fig. 1 When a soluble drug reacts with a metal ion it forms a insoluble drug -metal ion complex which interfere with the absorption of drug**.**

2.2.1 Antacids and tetracycline

Subsequent studies have reported that antacids containing aluminum and magnesium hydroxides interfered with the intestinal absorption of tetracycline, doxycycline and demeclocycline by approximately 90% compared with the respective control values Chelation would therefore appear to be the primary mechanism of the antacid-tetracycline interaction. This is the formation of a compound between a metal ion and an organic molecule having two groups spatially arranged so as to form a ring structure with the metal. Although this complex is undoubtedly important in the interaction of tetracyclines with di and trivalent metal ions (e.g., calcium and aluminum in antacid formulations),The rank order of stability of tetracycline-metal complexes is Fe3+ > Al3+ > Cu2+ > Ni2+ > Fe2+ > Co2+ > Zn2+ > Mn2+.Some of these complexes are insoluble and thus cannot be absorbed into the mucosa.[10,12]

2.2.2 cholestyramine associated interactions

Cholestyramine, an anionic exchange resin, binds cholesterol metabolites and bile acids in the intestinal lumen and prevents their reabsorption, thus depleting body cholesterol, Such binding is not limited to bile acids, however, and cholestyramine may markedly reduce the availability of co-administered drugs. especially acidic drugs (e.g., warfarin, acetyl salicylic acid, sulfonamides, phenytoin, and furosemide). Cephalexin ,sulphamethoxazole, thyroxine and also to reduce the absorption rate, but not the overall availability, of trimethoprim.[8,9,15,16]

2.2.3 Adsorption of rifampicin by bentonite

An interaction between two anti-tuberculous drugs, rifampicin and para-amino salicylic acid (PAS), leading to a clinically important decrease in the serum levels of the former, the excipients in the granules, especially the bentonite, which was found in vitro rapidly and strongly to adsorb RMP.[9,20]

2.2.4 Iron salts associated interactions

Iron compounds have been shown to cause marked reduction in the absorption of tetracycline, the tetracycline derivatives doxycycline, methacycline and oxytetracycline as well as penicillamine, methyldopa, levodopa, carbidopa and ciprofloxacin. The mechanism by which iron interacts with these drugs is the formation of iron-drug complexes. The formation of the iron-drug complexes reduces the extent of drug absorption and does not appear to reduce the rate of drug absorption. The ferric form of iron binds strongly to methyldopa with a log Ks of 18 Methyldopa has been shown to increase the rate of oxidation of ferrous iron to its ferric form. Iron-drug complexes may have increased iron-drug interactions hence there will low amount of free drug to be absorbed.[16]

2.2.5 Charcoal and adsorption

Recent reviews have described the effect of activated charcoal on the systemic availability of various drugs including salicylates, paracetamol, phenylpropanolamine, digoxin, dextropropoxyphene, nortriptyline and propantheline. The inhibitory effect of charcoal on the absorption of other drugs is dependent upon the amount of the adsorbent administered. This was demonstrated in two studies in which the availability of oral digoxin, phenytoin, phenobarbitone, carbamazepine and phenylbutazone was reduced by greater than 95% and aspirin by 70%.[9]

2.3 Altered gastric motility

The rate and extent of drug absorption can also be influenced by GI motility. Although GI motility is typically associated with food effects, some drugs (e.g. Metoclopramide, cisapride, and erythromycin) increase gastric emptying and intestinal motility, whereas others (anticholinergic drug, opioids, and anesthetics) can slow these processes. [7,12] On the other hand, the absorption of drugs or formulations with slow dissolution characteristics and compounds actively absorbed from a limited area of the small intestine may actually be enhanced if the gastrointestinal transit time is reduced by propantheline because they remain longer at the sites of maximum absorptionand metoclopramide increases stomach emptying rate. [5,9] For example propantheline delays the gastrointestinal uptake of hydrochlorothiazide.[21] Oral absorption of desmopressin (a poorly permeable nine amino acid peptide) was increased threefold in healthy subjects treated with loperamide relative to untreated controls consistent with enhanced absorption as a consequence of increased intestinal transit time. [7] metoclopramide, may accelerate gastric emptying, hence decreasing the absorption of digoxin and theophylline whereas it can accelerate the absorption of alcohol, acetylsalicylic acid, acetaminophen, tetracycline and levodopa.[8,22,23]Gastric acidity inhibits emptying, whereas slight alkalinity enhances it. [8]the decreased rate of absorption of diazepam following the administration of morphine was a result of delayed gastric emptying. It is well known that morphine slows gastric emptying, and it may delay the passage of gastric contents through the duodenum for as long as 12 h. [11] The administration of glycopyrrolate produced considerable decreases in the plasma paracetamol concentration and the area under the paracetamol concentration curve (total amount of paracetamol absorbed). Since the area under the curve 1 h after administration of paracetamol closely relates to gastric emptying. [24] Oral metoclopramide has also been shownto increase the rate of absorption of other drugs given concurrently by the oral route. Drugs for which this has been demonstrated include tetracycline, levodopa and paracetamol.[25,26]

2.4 Modulation of P-glycoprotein.

P-gp or gp-120 for its molecular weight, is a transmembrane protein. [8]P-glycoprotein (PGP), a member of the superfamily of ATA-binding cassette transporters. Has been increasingly recognized because of the discovery of multidrug resistance (MDR) in chemotherapy. This multidrug transporter prevents the intracellular accumulation and cytotoxic effects of anticancer drugs by actively removing them from the cell membrane before they reach their intracellular targets.[27,28] Among the interactions studied, it is worth mentioning the effects of terfenadine on the transport of doxorubicin as well as the effects chlorpromazine and progesterone on the transport of cyclosporine.[4] The DDIs on P-gp might induce a clinical effect in presence of drugs with a low therapeutic index (e.g., digoxin, theophylline, anticancer drugs) when co-administered with macrolides (e.g., erythromycin, roxithromycin, clarithromycin), PPIs (e.g., omeprazole or esomeprazole) or anti-arrhythmic drugs (e.g., dronedarone, amiodarone, verapamil or diltiazem).[8] cyclosporin A is a substrateof PGP, which is responsible for controlling the rate and extent of cyclosporin absorption.[27]

2.5 Gut microbiome interactions.

The fate and activity of drugs are frequently decided not only by the host *per se* but also by the collection of microorganisms present in the gastrointestinal (GI) tract Drug-induced changes in the gut microbiome may alter the pharmacokinetics of concomitantly taken medication. An increased plasma level of the antiplatelet drug, aspirin, was observed in rats who were treated with a β-lactam antibiotic, ampicillin, 3 days previously. This enhanced bioavailability was attributed to the antibiotic- induced suppression of the metabolic activity of the gut microbiome. Moreover, ampicillin treatment significantly prolonged bleeding time in aspirin treated rats, suggesting antibiotic treatment may potentiate its anti-thrombotic effect.[29] Digoxin, the most widely used cardiac glycoside,it undergoes metabolic conversion in many patients to cardioinactive metabolites during which the lactone ring is reduced. This appears to occur within the gastrointestinal tract Eubacteriumlentum, a common anaerobe of the human colonic flora, converted digoxin to reduced derivatives.[30]

III. DRUG DISTRIBUTION INTERACTIONS

After absorption, drugs are rapidly distributed around the body by the circulation. [31] Distribution is the delivery of drug from the systemic circulation to tissues. [32] Some drugs are totally dissolved in the plasma water, but many others are transported with some proportion of their molecules in solution and the rest bound to plasma proteins. [31,32,33]

Common plasma proteins that bind drugs are human serum albumins, lipoproteins, glycoproteins, and globulins. Albumin is the most abundant contributor in the blood plasma. [31,32,33,34] Many medications extensively bind to the albumins. [33,34] Protein binding plays an important role in the distribution of drugs and can have multiple effects on the pharmacokinetics (PK) of a drug. [32,33] The degree of drug-protein binding might affect a drug's efficiency. [33] The binding of drug to plasma proteins is a major determinant of drug disposition. [33] When a drug is bound to the plasma proteins, it is not actively distributed to the site of action to interact with the target tissues and bound drug may act as a reservoir. There can be delay in therapeutic effect (because no drug is available to react). The free drug distributes from the vasculature into the organs and tissues or may be metabolized and eliminated. [31,32,33,34] Moreover, the bound drug is kept in the blood, while the unbound (free) fraction may be metabolized or excreted. Only the unbound (free) drug interacts with receptors, therefore only the free drug can produce therapeutic effect. [31,32,33,34] The binding has a very important effect also on drug pharmacodynamics (PD). [33]

Despite, the ubiquity and severity of drug-drug interactions, the concept that plasma protein binding displacement is a common cause of clinically significant interaction which is poorly recognized and poorly understood issues within clinical medicine. [35,36] Protein binding interactions are displacement reactions, which has been suspected as the causative appliance in many drug-drug interactions, which are predominant among protein binding reactions. [33]

Competitive displacement interactions are predominant one among protein binding reactions which results in the increased free plasma concentration of the displaced medication. Clinically, displacement reactions acquire importance when the displaced drug is highly bound to plasma proteins. In this case the displacer drug produces a significant rise in the plasma concentration of the displaced medication. [33,37] The result of this interaction can be dramatic, if the second drug (displaced drug) is a drug with narrow therapeutic index, then such type of interaction can lead to enhanced toxicity and pharmacological effects of displaced drug. [33]

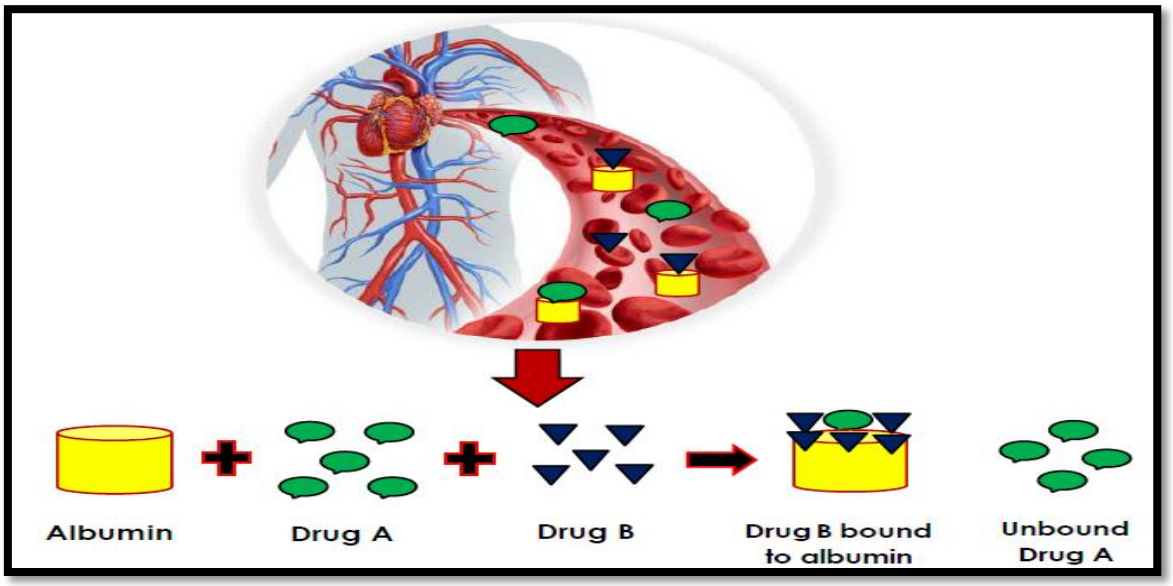

Fig. 2 When Drug A and Drug B is Co-administered, Competitive displacement reaction occurs as result, Drug B (displacing drug) which is highly bound to plasma protein (Albumin) displaces Drug A from Albumin thereby, the plasma concentration of Drug A (unbound or displaced drug) increases resulting in the toxicity of Drug A.

For e.g.a) Warfarin is a widely used anticoagulant which is used for the treatment of venous thromboembolism**,** atrial fibrillation, mechanical and bio-prosthetic heart valves, post-myocardial infarction, and recurrent systemic embolism. Warfarin is a narrow therapeutic range drug and more clinically the important property of warfarin is warfarin's propensity to bind to protein; about 99% is bound to albumin in the plasma.

Many NSAIDs affect warfarin protein binding, but the clinical significance of this interaction has been overstated. The traditional view has been that, NSAIDs are also highly protein-bound, they displace warfarin from albumin thereby enhancing the anti-coagulant effect such as marked increase in the concentration of free coumarin, severe hypothrombinemia by decreasing vitamin-k dependent clotting factors, prolongs bleeding time and it also affects platelet function. [33,36,38]

Free drug plasma concentration must be carefully monitored during warfarin therapy. [33]

b)Phenylbutazone, fibrate antihyperlipidemicand some beta blockers can cause severe hypoglycemia when it is co-administered with oral sulfonylureas due to the displacement of these agents from plasma protein binding sites and inhibition of their metabolic clearance. Tolbutamide is affected the most. [39]

c)Valproic acid displaces diazepam from plasma protein binding sites and inhibits its metabolism. Valproic acid increases the serum levels of diazepam approximately two fold. It also induces a significant increase in apparent volume of distribution and plasma clearance of diazepam. [40]

Table 1 Drug-Drug Interactions Mediated by Plasma Protein Binding displacement

Drug of Interest (Displaced drug)	**Displacing Drug (Highly bound drug)**	**Mechanism of Drug-Drug interaction**
Warfarin	NSAIDs, Tizoxanide	Enhancing the anti-coagulant effect such as marked increase in the concentration of free coumarin , severe hypothrombinaemia by decreasing vitamin-k dependent clotting factors, prolongs bleeding time and it also affects platelet function.
Tolbutamide	Phenylbutazone, Salicylates, Sulphonamides, Fibrates Beta blockers	Can cause severe hypoglycaemia due to inhibition of their metabolic clearance.
Diazepam	Valproic acid	Increases the serum levels of diazepam approximately two folds causing CNS, respiratory depression and cardiac arrest.

IV. DRUG METABOLISM INTERACTIONS

Drug metabolism is a process which is very important for the living organisms and thus provides various metabolic sites at various levels. [41] The major site for the metabolism of drug is liver, whereas the first pass metabolism occurs. [31,37,41,42]

Although a few drugs are cleared from the body simply by being excreted unchanged in the urine, most are chemically altered within the body to less lipid-soluble compounds, which are more easily excreted by the kidneys. If this were not so, many drugs would persist in the body and continue to exert their effects for a long time. This chemical change is called 'metabolism', 'biotransformation', or sometimes 'detoxification'.

Some drug metabolism goes on in the serum, the kidneys, the skin and the intestines, but the greatest proportion is carried out by enzymes that are found in the membranes of the endoplasmic reticulum of the liver cells. [56]

Metabolism is one of the major determinants of the fate of drugs in the body, as it determines their pharmacokinetic properties, their efficacy and toxicity. [43]

Metabolism is a biological process of drugs by the body, normally done with specific catalyst systems. [41] Drug metabolism (biotransformation) involves an outsized sort of chemical reactions, mainly mediated by enzymes, which converts drug into inactive form. [42,43] The metabolism rate of a drug describes the time period and potency of a drug pharmacologic action. [41]

Factors that affect the metabolism of foreign substances (collectively called xenobiotics or drugs) include age, sex, hereditary and genetic factors, disease states, dietary and nutritional status, hormonal changes in the body and the activity of liver enzymes. [42]

Drug-drug interactions are often explained by alterations in the metabolic enzymes that are present within the liver and one of the major pharmacokinetic interactions between drugs are due to hepatic cytochrome P450 (P450 or CYP) enzymes being affected by previous administration of other drugs. [44,45]

Cytochromes P450 (CYP450) are a major source of variability in drug pharmacokinetics and response. [32,46] Cytochrome P450 (CYP450) system is a superfamily of heme-containing mono-oxygenase enzymes embedded primarily in the lipid bilayer of the endoplasmic reticulum of hepatocytes which plays an important role in the metabolism of xenobiotics and endogenous compounds. [31,42,43,44,46,47,48]

Cytochrome P450(CYP450) was firstly named in 1961 to identify the cellular chromophore/pigment (P) that derives the name from the spectrophotometric absorption peak at 450 nm when reduced and bound to carbon monoxide; the P signifies pigment. [41,42,43] The present system of nomenclature for the various CYP isozymes employs a three-tiered classification based on the conventions of molecular biology: numeral and a capital letter designate the amino-acid sequence, with a final number indicating the individual enzyme, e.g. CYP3A4. [42,44]

CYP450 enzymes are ubiquitous in nature and are found in almost all mammalian tissues such as brain, kidney, heart, intestine, lung, nasal and tracheal mucosa, adrenal gland, gonads, skin, and many other tissues. However, the highest abundance and largest number of individual CYP450s is found in the liver. [41,42,43,44]

In humans, 57 putatively functional genes and 58 pseudo-genes divided among 18 families of CYP450 genes and 43 sub-families. [42,43,46]

Specially, the CYP450 isoenzymes primarily responsible for the metabolism of therapeutic drugs in the human liver mostly includes ; CYP1A1, 1A2, 1B1, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4, 3A5, 3A7 and 4A11. [41,42,43,44,45,46, 48]

Of all CYP450 enzymes, the CYP3A4 is the most abundant isoform and is the main metabolizing system of therapeutic drugs, and other xenobiotic, where it may serve as a primary defense mechanism. [37,42,43,44,45,47,48]

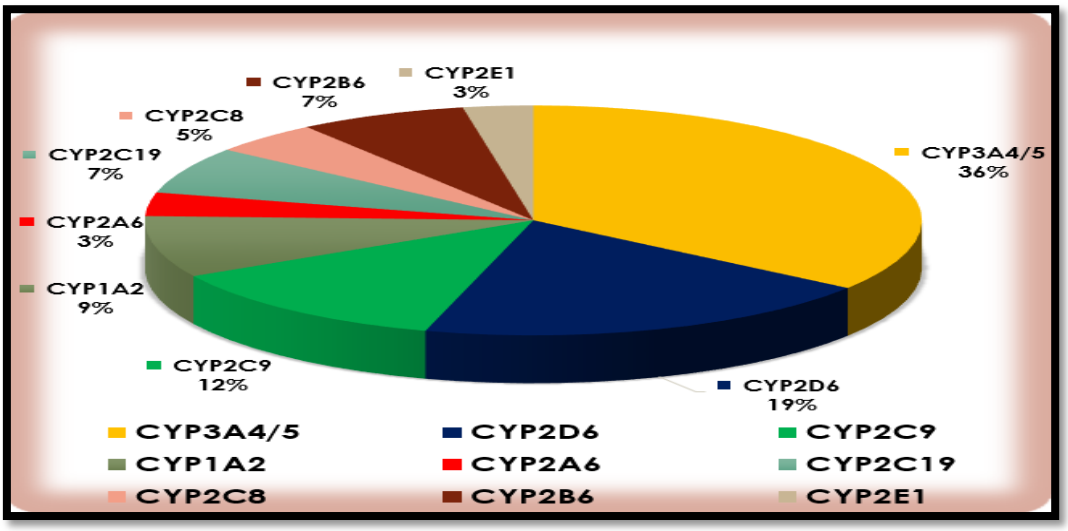

Fig.3 Proportion of drugs metabolized by CPY450 enzymes

Drug interactions involving the CYPP450 isoforms generally are of two types:
Enzyme induction or Enzyme inhibition.[44]

3.1 Enzyme induction:

Hepatic enzyme induction is the result of an increase in the amount of hepatic enzyme. In most cases, enzyme induction leads to an increase in the rate of metabolism of the affected drug (Substrate), with a consequent decrease in the serum concentration of the parent drug and possibly a loss of clinical efficacy. [44,45,49]
Induction of drug-metabolizing activity can be due to,

3.1.1 Increased Enzyme expression

Inducer drug binds a cytoplasmic/nuclear receptor resulting in translocation of inducer-receptor complex to nucleus. Thereby, which give rise to an increased enzyme levels. [42,48]

3.1.2 Enzyme Stabilization or decreased degradation

Inducer binds to active site of enzyme which stabilizes the enzymes or decreases the proteolytic enzyme degradation. [38,45,48] Enzyme induction is most commonly associated with therapeutic failure due to inability to achieve required drug concentrations. [32]
For e.g.

a) In women, co-administration of Oral contraceptives (OCs) with the enzyme-inducing Anti-epileptic drugs (AEDs) such as phenobarbitone, primidone, phenytoin and carbamazepine can cause significant alterations of sex hormones, higher incidence of break through bleeding, can decrease the efficacy of oral contraceptives and pose potential risk of un-intended pregnancy. [49,50,51,52,53]

b) Rifampicin, a very strong inducer of hepatic enzymes, was shown to increase the metabolism and clearance of warfarin, leading to decreased activity of the anticoagulant. [54] Rifampicin can also leads to reduced plasma levels of the anti-diabetic drug pioglitazone. [47]

3.2 Enzyme inhibition:

Hepatic enzyme inhibition usually occurs because of competition at the active site and leads to a decrease in the rate of metabolism of the affected drug (substrate). Clinically, this is associated with an increased plasma concentration of the affected drug and the potential for an increased pharmacologic response. [41,44,45,49]
For e.g.

a) Hepatic enzyme inhibitors such Cyclosporine,macrolide antibiotics, azole antifungal agents, protease inhibitors, and calcium channel blockers can inhibit the metabolism of statins such as atorvastatin, simvastatin, and lovastatin. [55,56]
As a result of this interaction, it is recognized that plasma levels of statins may increase with concomitant administration of CYP3A4 inhibitors. This may in turn increase the risk of significant statin toxicity such as myopathy (muscle pain, weakness and tenderness) which may occur with or without raised concentrations of creatine kinase and rhabdomyolysis, a more severe form of skeletal muscle damage, is the occurrence of muscle related symptoms with creatine kinase greater than 10 times the upper limit of normal. [55,56,57]

b) When single oral dose of metoprolol, a beta-adrenoceptor blocking agent and propafenone (hepatic enzyme inhibitor) were administered, or when the two drugs were given in combination, an approximately two fold reduction in the oral clearance of metoprolol was observed when propafenone was included and increased risk of cardiovascular toxicity has been shown due to increased plasma concentration of metoprolol. [44]

3.2.1 Enzyme inhibitors as therapeutic agents:
In present, many health care professionals use hepatic enzyme inhibitors to the improve the pharmacokinetics of co-administered drug and finally, utilization of inhibitors helps the patient to reduce the economic burden of high cost medications. [41,45,58]

a)Ritonavir boosted HIV regimens

Ritonavir have played an instrumental role in decreasing mortality and morbidity among people with HIV infection. Ritonavir's inhibition of the cytochrome P450 (CYP3A4) enzyme reduces the metabolism of concomitantly administered protease inhibitors and changes their pharmacokinetic parameters.The primary role of ritonavir in boosted Protease inhibitors (PI) regimen is to improve the pharmacokinetics, bioavailability and efficacy of the second Protease inhibitors (PI) such as saquinavir, lopinavir, amprenavir, nelfinavir and indinavir. [45,58,59,60]

b)Prodrugs are not efficacious till they metabolize and regenerated to a active form. Few inhibitors can interact by the in vivo transformation of prodrugs if given at the same time. For example, tamoxifen, the anticancer prodrug, needs cytochrome P450 (CYP2D6) to transform to an active drug. [41]

c) The co-administration of hepatic enzyme inhibitors and proton-pump inhibitor (omeprazole) as part of therapy against Helicobacter pylori infection may have significantly better clinical outcomes. [42,44]

Table 2 Some Common Substrates, Inducers and Inhibitors of CYP450 isoenzymes

Cytochrome P450 Gene Family/subfamily	**Substrate (Drug affected by inhibitors or inducers)**	**Hepatic enzyme Inducers**	**Hepatic enzyme Inhibitors**
CYP1A1	Caffeine, warfarin	Omeprazole	Amiodarone, fluvoxamine
CYP1A2	Acetaminophen, amitriptyline cyclobenzaprine, desipramine, diazepam,	Barbiturates, omeprazole, phenobarbital, phenytoin Rifampin.	Cimetidine, Ciprofloxacin Enoxacin
CYP2A6	Warfarin	Dexamethasone, phenobarbital	pilocarpine, selegiline
CYP2B6	Artemisinin, methadone,	Carbamazepine, phenytoin	Clopidogrel, imidazoles

CYP2C8	Amiodarone	Nelfinavir, rifampin	Gemfibrozil, montelukast
CYP2C9	Celecoxib, diclofenac, losartan, piroxicam, torsemide, warfarin.	Rifampin, secobarbital	Amiodarone, chloramphenicol, cimetidine, fluvoxamine, isoniazid
CYP2C19	Amitriptyline, citalopram, diazepam, omeprazole, phenobarbital, propranolol, warfarin.	Carbamazepine, phenobarbital	Azole antifungals, chloramphenicol, cimetidine fluvoxamine, omeprazole, topiramate.
CYP2D6	Amphetamine, ondansetron	Rifampin	Fluoxetine,methadone
CYP2E1	Acetaminophen, alcohols, dapsone, halogenated alkanes, isoflurane, theophylline	Isoniazid	Acute ethanol ingestion, Disulfiram
CYP3A4/5/7	Acetaminophen, alprazolam, amiodarone, amitriptyline, amlodipine, busiprone, budesonide, calcineurin inhibitors, carbamazepine, celecoxib, codeine, cortisol, dapsone, diazepam, digoxin, diltiazem, donepezil, ethinylestradiol, statins, warfarin.	Carbamazepine, dexamethasone, ethosuximide, phenobarbital, phenytoin rifampin/rifabutin, St. John's wort	Amiodarone, azole antifungals, cimetidine, cyclosporine, fluoxetine, macrolide antibiotics, metronidazole, nicardipine, propofol, protease inhibitors, quinine, sertraline, verapamil.

V. DRUG EXCRETION INTERACTIONS

Excretion is a process whereby drugs are transferred from the internal to the external environment, and the principle organs involved in this activity are the kidneys, lungs, biliary system, and intestine. Despite the reduction in activity that happens as a drug leaves its site of action, it's going to remain within the body for a substantial period, especially if it's strongly bound to tissue components. Thus, reduction in pharmacological activity and drug elimination are to be seen as related but separate phenomena.[32] Most of the drugs are excreted either in the bile or in the urine except inhalational anesthetics.[31] The kidney is principle excretory organ for drugs and their metabolites and has developed high capacity transport systems to rapidly eliminate the large quantities of foreign compounds delivered to it which helps in determining both the duration of drug action and the rate of drug elimination. [32,61,62] Renal elimination is the result of three concurrent processes occurring in the nephron which is glomerular filtration, tubular secretion and tubular reabsorption involving a variety of transporters located on the basolateral, contra-luminal and luminal membranes of the tubular epithelium. [61,63] These selective transporters for organic cations (OC) and organic anions (OA) transporters are predominantly expressed in the proximal tubule and work in diligence to eliminate drugs from the blood circulation to the urine. [61,62,63] Transporter-mediated drug–drug interactions (DDIs) are growingly recognized as an important modifier of the pharmacokinetics and pharmacodynamics of drugs. Drugs inhibiting renal drug transporters may cause marked changes in the pharmacokinetics of the affected drug, resulting in clinically significant DDIs end up in abnormal drug accumulation in renal tubular cells, leading to drug-induced nephrotoxicity.[61]

5.1 Drug interactions biasing active tubular secretion

The clinical importance of the renal transporters resides predominantly in the domain of drug-drug interactions. The pharmacokinetic variable that describes renal excretion is renal clearance of drug in plasma. [62] Various transporters are (as depicted in fig. 4)

5.1.1 Cationic drug transporters

Transporters for organic cations is located predominantly in the **S1** (the early convoluted tubule) segment, whereas in juxtamedullary nephron they are equally located in S1 and S2 segments. [62] In humans, hOCT2 is the major OCT isoform expressed in the kidney, hOCT1 on the other hand, is incredibly expressed in the liver and hOCT3 is broadly expressed in many tissues including the skeletal muscle, heart, placenta, and salivary glands. [61] At the luminal or brush border membrane, the transport of cations given by an electroneutral H+/ organic cation antiport system is present, in which the organic cation is exchanged for a hydrogen ion and facilitated by the inside negative membrane potential existing in the kidney tubular cells. [61,62] Common substrates for hOCT2 includes (cations) endogenous monoamines, [the antidiabetic drug] metformin, [the anti- hypertensive drug] atenolol, [the antiviral drug] lamivudine, and [the cytostatic drug] oxaliplatin. Most hOCT2 inhibitors are larger, more hydrophobic cations that may or may not be transported by the transporter that includes cimetidine, quinidine and dolutegravir. [61,62,63] hOCT2 –mediated active secretion plays important role in metformin renal elimination. However dolutegravir, a newly approved anti-HIV drug is also an inhibitor of hOCT2 that interferes with metformin elimination through an intracellular binding site. Thus, hOCT2-mediated uptake into kidney cells could have an impact on dolutegravir's inhibitory effect towards hOCT2-mediated metformin up take, was thought to be the mechanism underlying the observed interaction with [area under curve] AUC of 2.5 fold increase for metformin. So it's recommended that dose adjustments of metformin be considered when patients are starting or stopping dolutegravir while on metformin therapy. [61]

5.1.2 Anionic drug transporters

These transporters are located equally in the S2 segments (which comprise the latter part of the convolution and the first part of the straight section) of superficial and juxtamedullary nephrons. [62] OATs belongs to SLC22 family that also encodes the OCTs. In human, 10 OAT isoforms have been identified, which includes hOAT1– 8, hOAT10, and the urate transporter1(hURAT1). Most hOATs have been expressed at the renal proximal tubule, except hOAT7,which is limited only to liver. In the kidney, hOAT1–3 are located at the basolateral membrane of renal tubule cells whereas hOAT4, hOAT10 and hURAT1are expressed on the luminal membrane. Basally-expressed hOAT1–3 operates as organic anion/ dicarboxylate exchangers which mediate the first step of OA renal excretion by transporting OAs in to renal tubule cells utilizing the outward dicarboxylate (e.g., α-ketoglutarate for hOAT1/3, succinate for hOAT2)gradient established by the Na^+–dicarboxylate cotransporter. [61,62] Substrate for this transporter have a hydrophobic domain with decreased pKa that increases the affinity for the transporter and may have electron-attracting side groups (chloride/ bromide atoms), which increase the interaction with the transporter. [65] Numerous drugs have been shown to be substrates of hOAT1/3, that includes antibiotics, antivirals, antihypertensive drugs, diuretics, cytostatic, H2-antagonists, non-steroidal anti-inflammatory drugs(NSAIDs), statins and uricosurics. The recorded substrates of hOAT2 includes some endogenous compounds, such as glutamate, nucleobases, nucleosides and nucleotides and some drug molecules, such as salicylate, bumetanide and erythromycin.hURAT1is known to play an important role in urate homeostasis. It reabsorbs urate from lumen of renal tubule by exchanging extracellular urate with intracellular OAs such as lactate and nicotinate. [62] Therapeutically, inhibition of renal anion secretion by inhibitors as such probenecid, a uricosuric and penicillin-sparing agent has also been employed to produce beneficial drug interactions to either enhance activity of antibiotics or reduce renal accumulation and nephrotoxicity of certain antiviral drugs. Probenecid exhibits similar inhibition potencies towards hOAT1 and hOAT3. [61] Probenecid could potentially alter the pharmacokinetics of certain cephalosporins, primarily through a reduction in renal clearance through competition between probenecid and the other acids for secretion by a common tubular mechanism. [64,65,66] Cephalosporins are potentially nephrotoxic besides being broadly used antibiotics. [67] The addition of probenecid to cephalosporin therapy results in sustained systemic concentrations adequate for indication of N. gonorrhoeae. [64,62] Fexofenadine, a non- sedative histamine H1 receptor antagonist which is efficiently transported only by hOAT3 inhibition of basolateral uptake can be one of the sites of interaction between fexofenadine and probenecid. The non-renal clearance of fexofenadine is explained by biliary excretion, showing a minimal inhibitory effect on the hepatic uptake of fexofenadine via hOATP1B3 in liver. Adefovir and cidofovir, a novel antivirals have been suggested to be readmitted by the kidney viaOAT1 leading to luminal accumulation at proximal tubule cells resulting nephrotoxicity. Clinically the combination with probenecid will have a beneficial effect in suppressing the nephrotoxicity on top of prolonging their plasma

retention time, leading to an increase in the concentration in the liver, the target organ for the treatment of hepatitis B. [63,61] Thus rationalizing the antiviral agents.

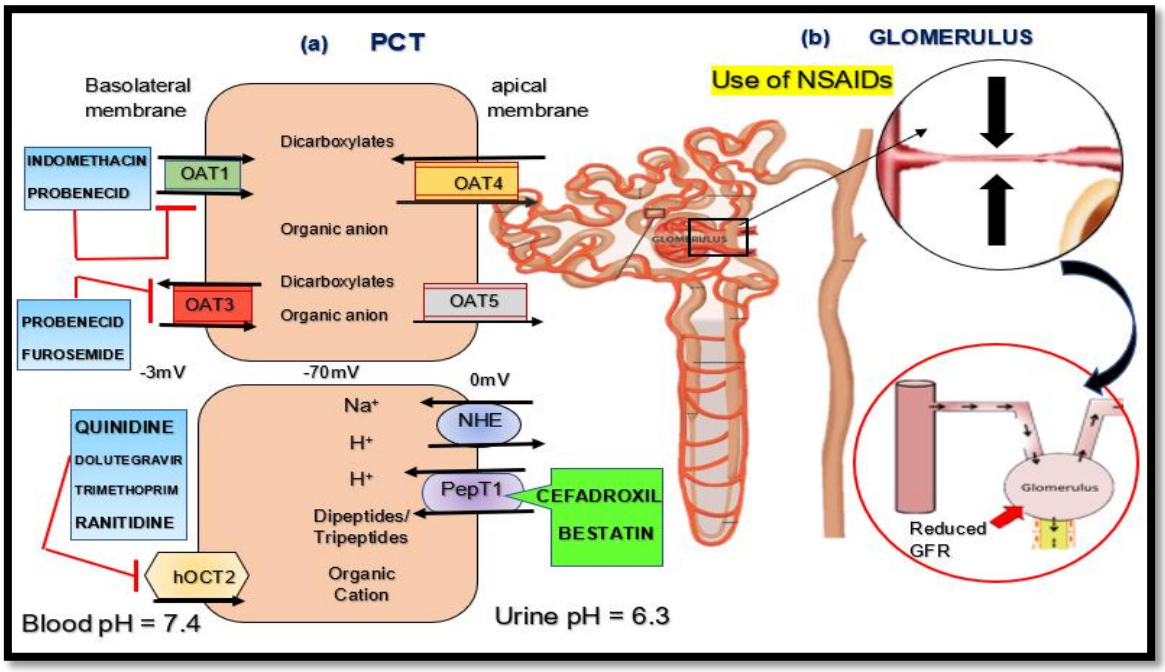

Fig. 4 drug interactions affecting tubular secretion and renal blood flow.

(a) Proximal tubular cell with various basolateral transporters and apical efflux transporters i.e. OAT-Organic Anion Transporter which is inhibited by drugs:- indomethacin and probenecid (OAT1), probenecid and furosemide (OAT3); OCT- Organic Cation Transporters which is inhibited by drugs:- quinidine, dolutegravir, trimethoprim, ranitidine; PepT1-Peptide Transporters, its substrates are cefadroxil, bestatin; NHE – Sodium Hydrogen Exchanger. (b) depicting vasoconstrictor action of NSAIDs on afferent and efferent arterioles of nephron resulting a reduced GFR

5.2 Drug interactions altering renal blood flow

Acute renal failure [ARF] is a frequent complication in postsurgical procedures and in critically ill patients. [62] As during surgery, renal blood flow is reduced by almost 30%. Prostaglandin has vasodilatory effects on renal vascular bed and enhances blood flow from renal cortex to nephrons, that helps to keep up the glomerular filtration rate (GFR). [69] Prostaglandins predominantly doesn't have major role in normal subject but, its inhibition may have profound adverse renal effects. [68] And dopamine too produced an increase in renal blood flow, this increase could be prevented by indomethacin or ibuprofen(cyclo-oxygenase inhibitors). [70] NSAIDs are notable renal toxins that alter renal function by inhibiting protective renal prostaglandins that leads to reversible renal ischemia. [68] Due to the decreased GFR because of NSAIDs administration, there is decreased elimination of ceftriaxone that may lead to the increase of ceftriaxone in plasma and might precipitate toxic effects on kidney resulting in progression of ARF. A way out of this DDI is ceftriaxone can be replaced by other antibiotic which may not depended on renal clearance or can be continued by dose adjustment according to creatinine clearance with other less toxic analgesics. [68] Similar effect was seen with indomethacin that attenuates the vasodilator action of hydralazine causing increase renal blood flow long with the ability to suppress prostaglandins, which is agonized by potassium sparing diuretic triamterene which increases the urinary excretion of prostaglandins. [71,72]

5.3 Drug interactions revamp tubular reabsorption

The renal tubular cells additionally possess active and passive transport systems for the reabsorption of drugs. Intrusion by drugs with these transport systems can alter the excretion of other drugs. [31] Peptide transporter 2[PEPT2]-primarily needed for renal reabsorption of drugs belongs to the class of proton-coupled oligopeptide transporters (POTs) that deliver peptide-bound amino nitrogen to cells. PEPT2 is particularly expressed on the apical (luminal) membrane of epithelial cells of the proximal tubule in the kidney that transports a broad range of peptide-like compounds such as- cefadroxil, enalapril, bestatin [ubenimex] and valacyclovir,`5-amino-levulinic acid. [66] Further there are some other receptors known as g-protein coupled

receptors [gPCR] with adenosine as endogenous ligand. The adenosine receptor subtypes are A1, A2a, A2b, or A3. Adenosine A1 receptors are present in mesangial cells, juxtaglomerular cells and vasa recta and adenosine A2a receptor are present in whole kidney, glomeruli, outer medullary and at descending vasa recta. Whereas A2b receptor are seen at the cortical, in the distal convoluted tubule, the outer medullary descending vasa recta and A3 receptors are present at the brush-border membranes. [73] Methylxanthines- an adenosine receptor antagonist in proximal tubule that reduces collecting duct water reabsorption via inhibition of adenosine receptors. Methylxanthine-induced natriuresis is primarily a consequence of inhibition of salt transport alongside the proximal convoluted tubule which increases in the clearance of lithium. [74,73] Lithium is a drug with many adverse effects and drug interactions. [75] Lithium and sodium have similar properties and both are found in group I A of the Modern Periodic Table. When there is inadequate sodium in the body and lithium is available, reabsorption of lithium is increased end up to lithium toxicity and a negative sodium balance. Lithium is reabsorbed more readily in the proximal tubule where methylxanthine shows its inhibitory effect on adenosine receptors. [74] Adenosine A1 receptor activation stimulates Na^+ dependent phosphate transport that mediate increase inproximal tubular reabsorption include increasing intracellular Ca^{+2}accompanied by reduction of intracellular cAMP levels. The low concentrations of the adenosine stimulate NHE3 and high concentrations inactivated NHE3 which proves it to be pharmacologically significant. [74,73]

5.4 Drug interactions that tackle alteration of urine pH

The effect of urine pH on renal excretion and systemic disposition has been observed for many drugs and metabolites. When urine pH is altered, tubular ionization, passive reabsorption, renal clearance, and systemic exposure of drugs and metabolites may all change dramatically, raising clinically significant concerns. [76] Complex interactions occurs between drugs resulting an altered pH leading to reordering of excretion of other drugs at renal tubules. [77] The mechanism behind this phenomenon is believed to be the altered ionization status of weak acids and bases with changes in renal tubular filtrate pH with consequent alterations in renal passive reabsorption of unionized drugs. For example, when urine pH decreased from alkaline (pH - 7.5–8.5) to acidic (pH _4.5–5.5), the weak bases drug excreted unchanged in urine such as pethidine, methamphetamine and mexiletine is increased, whereas the renal clearance of weak acids, such as chlorpropamide and salicylic acid decreased. Also, after dosing of imipramine, methamphetamine, and amitriptyline, their respective metabolites, desipramine, amphetamine, and nortriptyline, have shown increases in urinary excretion, respectively, in acidic urine condition in comparison with alkaline urine condition. [76]

5.4.1 Acidic urine

Drugs that decrease urine pH are- cholestyramine, an insoluble quaternary ammonium anion exchange resin. When given orally increases fecal excretion of bile acids, blocking their enteral reabsorption. The same may be assumed for MTX as it is a weak organic anion [indicated for hypercholesterolemia]. [78] Cholestyramine was shown to induce metabolic acidosis and therefore can decrease urinary pH to as low as 4.8. Furthermore, urine acidification is observed with diabetes, obesity, and chronic kidney disease. [76]

5.4.2 Basic urine

Drugs that increase urine pH are- acetazolamide, which was indicated for glaucoma and edema, has been shown to increase urinary pH in humans from 5.5 to 7.6. In contrast, and urine alkalinisation is observed with vomiting and urinary tract infection.[76]

Quinidine remains a very useful anti-arrhythmic drug in spite of its well-known toxic potential. With urine alkalinisation there is a decreased excretion of quinidine, an increasing its serum concentration accompanied by decrease in glomerular filtration rate. As the urine pH increases, the net charge on the quinidine molecule decreases to 0.79 at pH 8.0. The decrease in the net charge of the molecule makes passive back diffusion of the non-ionic component more probable, and hence the excretion is decreased with increased resorption. [79]

Aspirin [a salicylate], a potent anti-inflammatory and analgesic produces steady plasma concentrations at normal urinary pH of 5.6 to 6.1, whereas in presence of urine alkalizers such as sodium bicarbonate the urine pH alkalizes to 6.2- 6.9 causing decrease in serum concentration of aspirin. [80] Similar example deals with methotrexate [MTX] is poorly soluble in water at low pH and tends to precipitate in kidney tubules with subsequent nephrotoxicity and decreased elimination. [81] Acetazolamide is a carbonic anhydrase inhibitor that alkalizes urine by the inhibition of tubular-cell carbonic anhydrase, leading to a lack of reabsorption of tubular bicarbonate through the prevention of hydrogen ion synthesis in tubular cells resulting alkaline urine aids in MTX increased renal clearance. [82] A small increase in urine pH increases MTX solubility sharply - from 2.2mM at urine pH 5.7 to 22 mM at pH 6.9. [81] Thus methotrexate – acetazolamide proves to be clinically significant interaction DDIs avoiding crystalluria due to methotrexate renal toxicity.

5.5 Effect of forced diuresis on renal clearance of corresponding drugs

Forced diuresis is induced by administering a fluid overload [usually via furosemide] and a diuretic [usually via mannitol]concurrently. Intoxicants that are most likely to respond to forced diuresis are those with a high level of renal excretion of the primary toxicant (e.g., bromide, lithium, amphetamine, phenobarbital, and salicylate). [83] Mannitol-induced diuresis reduce the duration of tubular necroses, accounting for the protection of renal function. [84] The chemotherapeutic agent cisplatin proposed for a broad spectrum of malignancies. Cisplatin accumulates in proximal tubular epithelial cells occurs via passive diffusion, and then exerts several cytotoxic effects, such as generation of reactive oxygen species bind covalently to macromolecules, activation of apoptosis signaling pathways, and stimulation of inflammation, resulting in nephrotoxicity. [85,84]

However this nephrotoxicity via hydration that decreases the proximal reabsorption rate or proximal tubule transit time of cisplatin. The nephroprotective effect of hydration, in a broad sense, can be regarded as a drug–drug interactions. The forced diuresis treatments increased the cumulative amount of unbound cisplatin excreted in urine. [85]

5.6 Drug interactions biasing protein drug binding

Diuretics concurrently with the antibiotic, an observation that raised the possibility of an interaction between these drugs, leading to the development of acute renal damage. [86] Aminoglycoside antibiotics are widely used in the treatment and prevention of Gram-negative bacterial infections. [87,88] The widespread therapeutic use of the aminoglycoside antibiotic gentamicin (GM) is limited by its nephrotoxic side effect, which can lead to acute renal failure. [87] The glomerular basement membrane [GBM] is composed of two membranes: the lamina rarainterna (LRI; formed from the endothelial cells) and the lamina rara externa (LRE; formed from the pedicels of the epithelial cells), which fuse and generate a common lamina densa (LD) in the central part of membrane. The urine is formed in mature glomeruli by filtration through the GBM, which prevents filtration of the large molecules [proteins]. This selectivity permeability of the GBM is considered to be mainly due to an electrostatic shield made of highly negatively charged heparan sulphate proteoglycans constituting the anionic sites situated in the LRI and LRE. The exposure to gentamycin found that the developing GBM was abnormal morphologically and functionally abnormal. LRI and LRE were thinner while the LD was enlarged. The counting of anionic sites showed an increase of their number per square micrometer of the LRE or LRI and thus an increased density. [87] Furosemide is a potent diuretic which acts by inhibition of active chloride transport in the thick ascending limb of the loop of Henle. Diuresis will reduce reabsorption by reducing the tubular fluid: plasma concentration gradient and by reducing any solvent drag. [89] Furosemide has been reported to increase total renal medullary blood flow by increasing renal prostaglandin production and therefore may cause increased removal of drugs from plasma which are secreted. [90,89] The fall in GFR by furosemide could largely explain the fall in gentamicin clearance. [89,91,92] Accurate correction of fluid deficit during furosemide treatment ensures complete normalization of urinary output of gentamicin by restoration of GFR. Reduced medullary concentration when urine flow is inordinately high seems to demonstrated decreased passive diffusion of the drug in the distal nephron. Since gentamicin is highly hydrophilic, passive movement in the medullary region must be limited using furosemide diuretics. [91] Thus this drug interaction between diuretics and gentamycin approved to be of therapeutically significance in preventing renal toxicity. Similar effect has been seen with nitric oxide that has been proposed to modulate renal response to proteins as well as basal renal hemodynamic.[93]

VI. CONCLUSION

DDIs represent a common clinical problem during the management of patients treated with several drugs. Attention to drug interactions is crucial in order to prevent toxicities and side effects and to avoid decreased efficacy due to subtherapeutic drug levels. Therapeutic drug monitoring of narrow–therapeutic index medications, a long half-life and a higher bound with plasma proteins is crucial when drug interactions cannot be avoided. Often, clinicians must make empiric therapeutic adjustments or perform more intensive clinical monitoring to either prevent or manage drug-drug interactions. Ultimately, due to the clinical variability of drug-drug interactions for various agents, it is important to approach

medication management with a multidisciplinary team, including physicians, nurses, and pharmacists. Pharmacokinetic interactions are the major clinically significant interaction most commonly encountered by a clinical pharmacist and a prescriber,hence it is the responsibility of the prescriber and the clinical pharmacist to closely check for interaction and monitor them and prevent the possible adverse reactions.

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