INDUCERS AND INHIBITORS OF CYTOCHROME P450 3A4 SUBSTRATES AND THE MANAGEMENT OF THEIR DRUG INTERACTIONS

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Submitted by
ROBIN ABRAHAM
REGISTRATION No. 261540107

Under the guidance of
Dr. A.S. MANJULA DEVI, M.Pharm., Ph.D.,
Department of Pharmacy Practice

COLLEGE OF PHARMACY
SRI RAMAKRISHNA INSTITUTE OF PARAMEDICAL SCIENCES
COIMBATORE - 641 044.

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CERTIFICATE

This is to certify that the M.Pharm dissertation entitiled **"Inducers and Inhibitors of Cytochrome P450 3A4 Substrates and the Management of their Drug Interactions**" was carried out by **Robin Abraham (Reg. No. 261540107)** in The Department Of Pharmacy Practice, College Of Pharmacy, Sri Ramakrishna Institute Of Paramedical Sciences, Coimbatore, which is affiliated To The Tamil Nadu Dr. M.G.R Medical University, Chennai, under my direct supervision and guidance to the fullest satisfaction.

Dr. A.S. MANJULA DEVI, M.Pharm., Ph.D.,
Associate Professor
Department of Pharmacy Practice
College of Pharmacy
SRIPMS
Coimbatore - 641044

Place: Coimbatore
Date:

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Dr. S. Sriram, M.Pharm., Ph.D.,
Professor and Head
Department of Pharmacy Practice
College of Pharmacy
SRIPMS
Coimbatore - 641044

Place: Coimbatore

Date:

CERTIFICATE

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Dr. T. K. Ravi, M. Pharm., Ph.D., FAGE.,
Principal ,
College of Pharmacy,
SRIPMS,
Coimbatore - 641044

Place : Coimbatore

Date :

ABSTRACT

A prospective observational study for a period of 8 months was carried out in the general medicine department of a 750 bedded multispecialty tertiary care teaching hospital in order to understand various inducers and inhibitors of CYP3A4 substrates present in prescription and to follow a mechanism based approach in the management of drug-drug interactions. Hundred Prescriptions with at least one CYP3A4 enzyme substrate along with either inducer or inhibitor were selected for the study. All the selected prescriptions had at least one CYP3A4 enzyme substrate along with an inducer or inhibitor. Major diagnosis observed in study population were hypertension (21%) followed by diabetes mellitus (14%), chronic renal failure (12%), and tuberculosis (9%) Nine hundred and twenty five drugs belonging to Eighty eight categories were prescribed in the study subjects. Of these, vitamins and minerals (33.63%), antibiotics (12.5%), antihypertensives (9.09%), antiulcers (6.81%), antiepileptic (6.81%) and anticoagulants (6.81%) were most frequently prescribed. Hundred substrates, 66 inhibitors and 34 inducers of CYP3A4 were identified during the study period. The substrates included clopidogrel (47%), atorvastatin (22%), esomeprazole (13%), omeprazole (5%) domperidone (4%), midazolam (3%), phenytoin (2%) and azithromycin (2%). The various inhibitors of CYP3A4 recorded during the study were atorvastatin (45.45%), amlodipine (19.69%), esomeprazole (12.12%), amiodarone (7.57%), flucanazole (6.06%), cloidogrel (3.03%), oxcarbamazeine(3.03%) and isoniazid (3.03%). Inducers of CYP3A4 enzyme present in the prescritions were phenytoin (55.88%) and rifampicin (44.11%). The study reviewed the strength of inhibition/induction of metabolism of the CY3A4 substrate by the inhibitors/inducers. Mechanism of these interactions as well as the severity and clinical significance of interactions were also reviewed using relevant literatures. A suitable therapeutic alternative was recommended whenever a possibility of major drug-drug interaction between CY3A4 substrate and inhibitor/inducer was observed in the study.

ABBREVIATIONS

ADR	:	Adverse drug reactions
AERS	:	Adverse Event Reporting System
AUC	:	Area under curve
ATP	:	Adenosine triphosphate
ADP	:	Adenosine diphosphate
ACS	:	Acute coronary syndromes
AEDs	:	Anti epileptic drugs
ARBs	:	Angiotensin receptor blockers
ARF	:	Acute Renal Failure
ATN	:	Acute Tubular Necrosis
B.P	:	Blood Pressure
BMI	:	Body Mass Index
CAD	:	Coronary Artery Disease
CHF	:	Congestive heart failure
COPD	:	Chronic Obstructive Pulmonary Disease
CYP	:	Cytochrome
CNS	:	Central nervous system
CL	:	Clearance

CI	:	Confidence interval
CCB	:	Calcium channel blockers
CT	:	Computed tomography
CVD	:	Cardiovascular drugs
CBZ	:	Carbamazepine
DMSO	:	Dimethyl sulphide
DM	:	Diabetes Mellitus
DI	:	Drug interaction
eGFR	:	Estimated glomerular filtration rate
ESRD	:	End Stage Renal Disease
FDA	:	Food and Drug administration
GFR	:	Glomerular Filtration Rate
Hb	:	Haemoglobin
HTN	:	Hypertension
HMG COA	:	3-hydroxy- 3-methylglutaryl coenzyme A
HIV	:	Human immunodeficiency virus
IHD	:	Ischemic Heart Disease
MDRD	:	Modification of diet in renal disease
MRI	:	Magnetic Resonance Imaging
ND	:	Nephrotoxic Drugs

NSAIDs	:	Non-steroidal anti-inflammatory drugs
NAMCS	:	National Ambulatory Medical Care Survey
OATP	:	Organic anion transporting polypeptide
PHT	:	Phenytoin
PPIs	:	Proton Pump Inhibitors
PT	:	Prothrombin Time
PCI	:	Percutaneous coronary intervention
RBC	:	Red blood cells
RBF	:	Renal Blood Flow
RAAS	:	Renin Angiotensin Aldosterone System
Scr	:	Serum Creatinine
V/P	:	Vancomycin/Piperacillin
WBC	:	White Blood Cells
WHO	:	World Health Organization

INTRODUCTION

DRUG INTERACTION

Drug interactions have been recognized for over 100 years. Today, with the increasing availability of complex therapeutic agents and widespread polypharmacy, the potential for drug interactions is enormous and they have become an increasingly important cause of adverse drug reactions (ADR).

An interaction is said to occur when the effects of one drug are altered by the co- administration of another drug, herbal medicine, food, drink or other environmental chemical agents. The net effect of the combination may manifest as an additive or enhanced effect of one or more drugs, antagonism of the effect of one or more drugs, or any other alteration in the effect of one or more drugs.

Clinically significant interactions refer to a combination of therapeutic agents which have direct consequences on the patient's condition. Therapeutic benefit can be obtained from certain drug interactions, for example, a combination of different antihypertensive drugs may be used to improve blood pressure control or an opioid antagonist may be use to reverse the effect of an overdose of morphine.

Most clinically important interactions involve the effect of one drug on the metabolism of another. Metabolism refers to the process by which drugs and other compounds are biochemically modified to facilitate their degradation and subsequent removal from the body. The liver is the principal site of drug metabolism, although other organs such as the gut, kidneys, lung, skin and placenta are involved. Drug metabolism consists of phase I reactions such as oxidation, hydrolysis and reduction, and phase II reactions, which primarily involve conjugation of the drug with substances such as glucuronic acid and sulphuric acid. Phase I metabolism generally involves the cytochrome P450

(CYP450) mixed function oxidase system. The liver is the major site of cytochrome 450-mediated metabolism, but the enterocytes in the small intestinal epithelium are also potentially important[1].

The cytochrome P450 is a well known superfamily of isoenzymes that are responsible for the oxidative and reductive metabolic transformation of medications used in clinical practice. In addition, the CYP enzymes are commonly associated with causing many clinically relevant drug-drug interactions.

Of the CYP enzymes, CYP3A4 is not only the most prevalent CYP enzyme in the liver, but is used by more than 50% of medications for their metabolism and elimination from the body. The CYP3A4 activity can be induced or it can be inhibited, thereby changing the drug concentrations present in the body and its pharmacokinetic profile. The isoforms of CYP3A in humans include 3A3, 3A4, 3A5 and 3A7. Each of these enzymes share at least 85% amino acid sequence homology.

CYP3A4 is the predominant isoform of CYP3A in adult humans. It can catalyse a remarkable number of metabolic processes including aliphatic oxidation, aromatic hydroxylation, *N*-dealkylation, *O*-demethylation, *S*-demethylation, oxidative deamination, sulfoxide formation, *N*-oxidation and *N*-hydroxylation, to mention a few. This usually produces inactivation and elimination of most pharmaceuticals. However, it can also activate carcinogenic substances such as the aflatoxins and polycyclic aromatic hydrocarbons. Although CYP3A4 drug metabolising activity varies widely among individuals, it has a unimodal population distribution and does not appear to be subject to genetic polymorphism as is seen with other CYP isoforms (2D6, 2C9 and 2C19). The wide interindividual variability is likely, in part, to be caused by ethnic or cultural differences, perhaps related to an interaction between race and diet. Other factors known to play a role in activity are age and the presence of small bowel or liver

disease. There may be modest gender differences, perhaps related to the hormonalmilieu in which the enzyme functions, although this is controversial. CYP3A4 content is highest in the liver. Hepatic CYP3A4 content has been shown to vary at least 20-fold among individuals and activity, as measured by the erythromycin breath test, to range 10- fold. Small bowel CYP3A4 is found in the apical enterocytes and its content varies 11-fold among individuals. Hepatic and enteric CYP3A4 content appear to be regulated independently of each other. The location of CYP3A4 in the small bowel and liver makes it well suited to play a significant role in first-pass (or presystemic) drug metabolism. This is illustrated by the dihydropyridine calcium antagonist, felodipine, which is a CYP3A4 substrate that normally undergoes sequential metabolism in the apical enterocytes of the small bowel and then in the hepatocytes of the liver following oral administration, resulting in a mean 15%absolute bioavailability[2].

CYP3A4 Substrate

A number of drugs from a broad range of therapeutic categories are CYP3A4 substrates. With regard to orally administered drugs, knowledge of the extent of, and factors determining, the bioavailability of these substrates allows for prediction of the changes that could occur to their pharmacokinetics with administration of a CYP3A4 inhibitor. Oral bioavailability (i.e. the fraction of the total dose that reaches the systemic circulation unchanged) is determined by 2 major processes: the proportion of the dose that is absorbed from the gut and the fraction that does not undergo presystemic metabolism, mainly in the small bowel and liver. The contributions of enteric and hepatic metabolism can be estimated separately by determining drug clearance following both oral and intravenous administration. If a substrate normally has high presystemic elimination (low oral bioavailability) and is primarily dependent upon CYP3A4 for elimination, then administration of an inhibitor of its metabolism can be expected to produce substantial change in substrate pharmacokinetics under single dose conditions.

The interaction would be characterized by a higher drug peak plasma drug concentration (Cmax) from reduced presystemic metabolism and a greater area under the drug concentration-time curve (AUC) possibly from both lower presystemic and systemic elimination.

Furthermore, there seems to be an inverse relationship between the extent of inherent presystemic elimination and magnitude of the increase in Cmax and AUC among medications. This has been observed with dihydropyridines and grapefruit juice, benzodiazepines and ketoconazole, and 3-hydroxy- 3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors with itraconazole. The interaction appears to be different if the CYP3A4 substrate normally has a high oral bioavailability. In this setting, inhibition of first-pass metabolism in the small bowel and liver would not be expected to have much effect on the Cmax under single dose conditions. The AUC may be somewhat augmented as a result of prolongation of the apparent elimination half-life ($t1/2\beta$) from reduced systemic drug clearance. In this situation, repeat administration of CYP3A4 substrate and inhibitor may produce a cumulative increase in plasma substrate concentrations. Thus, the clinical importance of the inhibitory interaction for CYP3A4 substrates with high inherent oral bioavailability may be realized only during steady-state administration. With regard to intravenous therapy, this route of administration, by definition, results in complete drug bioavailability. Consequently, the pharmaco- kinetic characteristics of the interaction would probably be similar to those observed with a CYP3A4 substrate with high oral bioavailability. It should be noted that certain substrates metabolized by CYP3A4 are also substrates for P-glycoprotein, a transmembrane adenosine triphosphate (ATP)-dependent active transport protein found in a number of organs, including the gut, brain, liver and kidney. P-glycoprotein acts as an efflux transporter to decrease drug absorption into the portal circulation and CNS and to increase drug elimination into the bile and urine. CYP3A4 and P-glycoprotein in the gut and liver appear capable of

acting in concert to decrease plasma drug concentrations. For those drugs that are substrates for both CYP3A4 and P-glycoprotein, inhibition of CYP3A4 or P-glycoprotein might be expected to produce similar changes to the pharmacokinetics of the parent drug. Additionally, certain substances appear capable of inhibiting both CYP3A4 and P-glycoprotein. Consequently, some interactions originally thought to be caused solely by the inhibition of CYP3A4-mediated drug metabolism are likely to be mediated, in part, by the inhibition of P-glycoprotein transport.

List of CYP3A4 substrates

Alfentanil	Ixabepilone
Alfuzosin	Ketoconazole
Almotriptan	Lapatinib
Alprazolam	Levomethadyl
Amiodarone	Loperamide
Amlodipine	Lopinavir
Aprepitant	Loratadine
Atazanavir	Lovastatin
Atorvastatin	Maraviroc
Bepridil	Mefloquine
Bexarotene	Methylprednisolone
Bosentan	Midazolam
Bromocriptine	Mifepristone
Budesonide	Modafinil
Buprenorphine	Nefazodone
Bupropion	Nevirapine
Carbamazepine	Nicardipine

Cevimeline	Nifedipine
Cilostazol	Nimodipine
Cisapride	Nisoldipine
Clarithromycin	Nitrendipine
Clonazepam	Oxybutynin
Clopidogrel	Oxycodone
Colchicine	Paclitaxel
Cyclophosphamide	Paricalcitol
Cyclosporine	Pimozide
Dapsone	Pioglitazone
Darunavir	Praziquantel
Dasatinib	Prednisolone
Delavirdine	Prednisone
Dexamethasone	Propoxyphene
Dihydroergotamine	Quazepam
Diltiazem	Quetiapine
Disopyramide	Quinacrine
Docetaxel	Quinidine
Donepezil	Quinine
Doxorubicin	Ranolazine
Droperidol	Repaglinide
Dutasteride	Rifabutin
Ebastine	Ritonavir
Efavirenz	Saquinavir
Eletriptan	Sibutramine
Eplerenone	Sildenafil
Ergotamine	Simvastatin

Erlotinib	Sirolimus
Erythromycin	Solifenacin
Estazolam	Sufentanil
Eszopiclone	Sunitinib
Ethinyl Estradiol	Tacrolimus
Ethosuximide	Tadalafil
Etoposide	Tamoxifen
Exemestane	Tamsulosin
Felodipine	Teniposide
Fentanyl	Testosterone
Finasteride	Tiagabine
Flurazepam	Tinidazole
Fosamprenavir	Tipranavir
Galantamine	Topiramate
Gefitinib	Triazolam
Granisetron	Vardenafil
Halofantrine	Verapamil
Ifosfamide	Vinblastine
Imatinib	Vincristine
Indinavir	Ziprasidone
Irinotecan	Zolpidem
Isradipine	Zonisamide
Itraconazole	Zopiclone

CYP3A4 Inhibitors

A wide variety of endogenous and exogenous substances has been identified as inhibiting CYP3A4 activity. Although these substances all share the common feature of interfering with CYP3A4 activity, they vary in potency and

mode of action. Many known inhibitors of CYP3A4 are of uncertain clinical relevance. However, specific inhibitors of CYP3A4 that deserve mention because they are potent and have been associated with clinically relevant interactions include azole antifungals, macrolide, antibacterials, nefazodone, the HIV protease inhibitors and grapefruit juice. Several mechanisms of inhibition are possible. Azole antifungals and first generation HIV protease inhibitors appear to act via competitive inhibition by rapid, reversible binding of the inhibitor or its metabolite to CYP3A4.Macrolide antibacterials produce slowly reversible, noncompetitive inhibition. This has been interpreted by some as mechanism based inhibition, but this does not appear to be the case. The furanocoumarins in grapefruit juice, dihydroxybergamottin and bergamottin, cause irreversible, mechanism-based (suicide) inhibition. This presumably involves CYP3A4-mediated formation of a reactive metabolite that covalently binds to the enzyme, leading to its inactivation. Most potent orally administered inhibitors act at the level of the small bowel and liver. However, grapefruit juice is an example of an inhibitor that appears to be clinically active against only enteric CYP3A4 and may be useful as a probe of enteric CYP3A4 activity. Conversely, intravenous administration of a CYP3A4 inhibitor probably produces more selective action in the liver.

List of CYP3A4 inhibitors

• Amiodarone • Anastrozole • Azithromzcin • Cannabinoids • Cimetidine • Clarithromycin • Clotrimazole • Cyclosporine • Danazol • Delavirdine • Dexamethasone • Diethyldithiocarbamate • Diltiazem • Dirithyromycin • Disulfiram • Entacapone (high dose) • Erythromycin • Ethinyl estradiol • Fluconazole • Fluoxetine • Fluvoxamine • Gestodene • Grapefruit juice • Indinavir • Isoniazid • Ketoconazole • Metronidazole • Mibefradil	Miconazole • Nefazodone • Nelfinavir • Nevirapine • Norfloxacin • Norfluoxetine • Omeprazole • Oxiconazole • Paroxetine (weak) • Propoxyphene • Quinidine • Quinine • Quinupristine and dalfopristin • Ranitidine • Ritonavir • Saquinavir • Sertindole • Sertraline • Troglitazone • Troleandomycin • Valproic acid

Drugs metabolised by cytochrome P450 (CYP) 3A4 and extent of

presystemic metabolism

Presystemic metabolism	Oral bioavailability (%)	Drugs
Very high	<10	Astemizole, buspirone, ergotamine, lovastatin, nimodipine, nisoldipine, saquinavir, simvastatin and terfenadine
High	10-30	Estradiola, atorvastatin, felodipine, indinavir, isradipine, nicardipine, nitrendipine, propafenonea and tacrolimus
Intermediate	30-70	Amiodaronea, amprenavir, carbamazepine, carvedilola, cisapride, cyclosporin, diltiazema, ethinylestradiol, etoposide, losartana, midazolam, nifedipine, nelfinavir, ondansetron, pimozide, sildenafila, triazolam and verapamila
Low	>70	Alprazolam, amlodipine, dapsone, dexamethasone, disopyramide, donepezil, quinidinea, ritonavir and temazepam

CYP3A4 Inducers

CYP3A4 inducers are drugs that increase the activity of CYP3A4. Note that the CYP3A4 enzyme is particularly susceptible to enzyme inducers, and marked reductions in the plasma concentrations of CYP3A4 substrates may occur. For example, a patient taking the potent CYP3A4 inducer rifampin may have a roughly 90% reduction in serum concentrations of CYP3A4 substrates, such as buspirone, triazolam, and verapamil[3].

List of CYP3A4 inducers

• Carbamazepine	• Oxcarbazepine
• Dexamethasone	• Phenobarbital
• Ethosuximide	• Phenylbutazone
• Glucocorticoids	• Rofecoxib (mild)
• Griseofulvin	• St John's wort
• Phenytoin	• Sulfadimidine
• Primidone	• Sulfinpyrazone
• Progesterone	• Troglitazone
• Rifabutin	
• Rifampin	
• Nafcillin	
• Nelfinavir	
• Nevirapine	

Many drugs commonly used in clinical practice are known substrates, inducers or inhibitors of CYP3A4 isoenymes but the severity of interaction depends upon the substrate sensitivity and the strength of induction or inhibition[4].

LITERATURE REVIEW

Gandhi *et al*[5] (2013) conducted a study on calcium-channel blocker–clarithromycin drug interactions and acute kidney injury. This interaction resulted in acute kidney injury, hypotension when compared with azithromycin. The author concluded that among older adults taking a calcium-channel blocker, concurrent use of clarithromycin compared with azithromycin was associated with a small but statistically significant greater 30-day risk of hospitalization with acute kidney injury. These findings support current safety warnings regarding concurrent use of CYP3A4 inhibitors and calcium-channel blockers.

Sprave *et al*[6] (2013) conducted a study on clinical studies of CYP3A4 and p-glycoprotein. The inductive property of rifampicin on four other CYP450 enzymes, a probe drug and an endogenous biomarker were compared regarding their properties for measuring CYP3A4 activity. Induction was achieved by administration of rifampicin in three different doses (20-500 mg once daily) to healthy volunteers. The endogenous biomarker 4β-hydroxycholesterol had a linear relationship with the metabolic ratio of the CYP3A4 probe drug quinine. In this study four other probe drugs were also used simultaneously, each specific for a different CYP450 enzyme. All enzymes except CYP2D6 were induced by rifampicin. This cocktail had been designed not to cause any drug-drug interactions among the probes, which are also specific for each enzyme. The author concluded that the endogenous biomarker has some limitations compared to phenotyping with the probe drug. The half-life of 4β- hydroxycholesterol is 17 days, which makes the method less suited for measuring rapid changes in enzyme activity.

Knibbe *et al* [7](2013) conducted a study on Drug Metabolism - The Importance of Cytochrome P4503A4. CYP3A4 is responsible for the metabolism of around 50% of the drugs. The latter involves the inactivation of the enzyme via

the formation of metabolic intermediates that bind irreversibly to the enzyme and then inactivate it. Medicines that are potent CYP3A4 inhibitors include clarithromycin, diltiazem, erythromycin, itraconazole, ketoconazole, ritonavir, and verapamil. Medicines that are potent inducers include phenobarbital, phenytoin and rifampicin. Many glucocorticoids in clinical use also induce CYP3A4.

Henneman *et al*[8] (2012) performed a study on risk of hypotension with concomitant use of calcium-channel blockers and macrolide antibiotics. Both dihydropyridine and nondihydropyridine CCBs are CYP3A4 substrates. Potentially significant hypotension and shock may occour when macrolide antibiotics especially erythromycin and clarithromycin interact with calcium channel blocker. The author investigated that the frequency of hypotension as a result of concomitant CCB and macrolide administration appears to be small, but the risk of adverse effects and the severity of the effects appear to be greater for those patients who are older and in those with multiple Comorbidities.

Patel *et al*[9] (2011) conducted a study on estimation of clinical pharmacokinetic interaction between atorvastatin and clopidogrel in atherosclerotic heart disease patients. This study was conducted by estimating the carboxylic acid clopidogrel metabolite level in blood serum and estimating the effect of atorvastatin on blood serum level of clopidogrel metabolite level. In this non randomized, prospective, crossover, single centric and open labeled study was carried out on patients (n=11) of atherosclerotic heart disease with or without PCI. The author investigated that Atorvastatin enhances the systemic bioavailability of clopidogrel. This might be due to the inhibition of intestinal P-gp function by atorvastatin and so clopidogrel efflux was reduced. This might have led to increased concentration of clopidogrel in systemic circulation. Therefore, concomitant use of clopidogrel with atorvastatin may require close monitoring for potential drug interactions.

Eric *et al*[10] (2011) conducted a study on Clopidogrel–Drug Interactions. Dual antiplatelet therapy with aspirin and clopidogrel is recommended treatment for percutaneous coronary intervention (PCI) and acute coronary syndromes (ACS). Whereas multidrug therapy with antiplatelet drugs, lipid-lowering and glucose-lowering agents, antihypertensive drugs, and even antidepressants has been suggested as a therapeutic strategy to reduce cardiovascular risk, multiple drug prescriptions increase the risk for drug– drug interactions. The author investigated that of prescribing a different platelet P2Y12 receptor inhibitor without known drug interactions. Another option is to prescribe a hydrophilic statin in place of atorvastatin; or pantoprazole or ranitidine, an H2RA not metabolized by CYP isoenzymes, in place of omeprazole.

Rowans *et al*[11] (2009) reviewed a comparative case series of rhabdomyolysis reports associated with simvastatin and pravastatin. Domestic spontaneous reports were obtained from the FDA's Adverse Event Reporting System (AERS). Drug utilization data were obtained from IMS HEALTH and the National Ambulatory Medical Care Survey (NAMCS). Adverse event reporting rates (AER) and ratios of rhabdomyolysis associated with simvastatin and pravastatin with and without stratification by CYP3A4 inhibitor concomitancy were determined. The author concluded that there is an increased risk of rhabdomyolysis during concomitant use of SV, a CYP3A4 substrate statin, and a CYP3A4 inhibitor. Additionally, the results support observations regarding muscle toxicity in simvastatin clinical trials with concomitant CYP3A4 inhibitors.

Jing *et al*[12] (2009) reported that rifampicin alters atorvastatin plasma concentration on the basis of SLCO1B1 521TNC polymorphism. Both atorvastatin and rifampicin are substrates of OATP1B1 (organic anion transporting polypeptide 1B1) encoded by SLCO1B1 gene. Rifampicin is a potent inhibitor of SLCO1B and SLCO1B1 521TNC functional genetic polymorphism alters the kinetics of atorvastatin. Rifampicin might influence atorvastatin kinetics

in a SLCO1B1 polymorphism dependent manner. The author investigated that co-administration of rifampicin and atorvastatin may significantly change atorvastatin pharmacokinetics in vivo, while this effect could vary according to SLCO1B1 521TNC genotypes. Single oral dose of rifampicin significantly led to 5-fold increase of peripheral exposure of atorvastatin and the increase percentage of AUC (0–48) values were nearly triplesd in SLCO1B1 c.521TT participants compared with c.521CC carriers.

Molden *et al*[13] (2008) performed a study on risk management of simvastatin or atorvastatin interactions with CYP3A4 inhibitors. Co-prescription of the selected CYP3A4 inhibitors diltiazem, verapamil, clarithromycin, erythromycin, fluconazole, itraconazole and ketoconazole with either simvastatin or atorvastatin was detected with the aid of a simple computer programme. The author concluded that co-administration of cytochrome P450 (CYP) 3A4 inhibitors with simvastatin or atorvastatin was associated with increased risk of developing myopathy or rhabdomyolysis.

Bhindi *et al*[14] (2008) conducted a study on interaction between statins and clopidogrel. They have been shown to be safe as well as efficacious in a number of different clinical trials; however, studies have suggested that they can interact with other co-administered therapies. The author finally concluded that there is presently no compelling clinical evidence to stop co-administration of CYP3A4 statins and clopidogrel, it is plausible that an important pharmacokinetic interaction exists, and further more robustly designed studies are needed to address this issue.

Foisy *et al*[15] (2008) performed a study on adrenal suppression and Cushing's syndrome secondary to an interaction between ritonavir and fluticasone. Ritonavir is a potent inhibitor of CYP3A4. Ritonavir co-administration will lead to greater propensity to induce adrenal suppression. The author recommended to replace ritonavir with other antiretroviral drug while

maintaining fluticasone or substituting fluticasone with another inhaled or intranasal steroid or oral monteleukast.

Neuvonen *et al*[16] (2006) performed a study on drug interactions with lipid-lowering drugs. Simvastatin, lovastatin, and atorvastatin are metabolized by cytochrome P450 (CYP) 3A4. The interaction of statins with immunosuppersant drugs can lead to increase in plasma statin concentration which ultimately leads to muscle toxicity.

Saad *et al*[17] (2006) performed a study on factors influencing the magnitude and clinical significance of drug interactions between Azole antifungals and selected immunosuppressants. Drug interactions between azoles and immunosuppressants are agent specific and depend on the potency of the azole inhibition of CYP3A4 and the plasma concentrations of each agent.

Castberg *et al*[18] (2005) performed a study on prolonged pharmacokinetic drug interaction between terbinafine and amitriptyline. *In vitro* and *in vivo* studies have shown that terbinafine is a highly potent competitive inhibitor of CYP3A4. Concomitant use of terbinafine leads to an increase in serum concentration of amitriptyline.

Niwa *et al*[19] 2005 performed a study on effect of antifungal drugs on cytochrome P450 (CYP) 1A2, CYP2D6, and CYP2E1 Activities in Human Liver Microsomes. The study compared the effects of five antifungal drugs on specific activities by CYP1A2, CYP2D6, and CYP2E1 in human liver microsomes under the same experimental conditions. In addition, the effect of preincubation was estimated in order to investigate whether these antifungal drugs are the mechanism-based inhibitors. The author concluded that CYP1A2, CYP2D6, and CYP2E1 are inhibited only by miconazole, whereas the inhibition by other antifungal drugs was not observed. In addition, the antifungal drugs investigated are not suggested to be the mechanism-based inhibitors.

Strandell *et al*[20] 2005 performed a study on interaction between statins and azithromycin interaction. The individual case reports in VigiBase and the

original files were reviewed. In order to investigate the reporting over time for rhabdomyolysis with azithromycin and statins to VigiBase, Omega values were generated retrospectively. Rhabdomyolysis under concomitant use of azithromycin and statins was reported more often than expected from 2000 and onwards in Vigibase. The author concluded that interactions between azithromycin and statins resulting in rhabdomyolysis may occur.

Serebruany *et al*[21] (2004) conducted a study on absence of interaction between atorvastatin or other statins and clopidogrel. Some, but not all, post hoc analyses have suggested that the antiplatelet effects of clopidogrel are inhibited by atorvastatin. We sought to address this issue prospectively by performing serial measurements of 19 platelet characteristics using conventional aggregometry, rapid analyzers, and flow cytometry. The author investigated that statins in general, and atorvastatin in particular, do not affect the ability of clopidogrel to inhibit platelet function in patients undergoing coronary stenting. The prospective data also suggest that statins may inhibit platelets directly via yet unknown mechanism possibly related to the regulation of the PAR-1 thrombin receptors.

Gennere *et al*[22] 2004 conducted a study on Regulation of CYP3A4 by the bile acid receptor FXR: evidence for functional binding sites in the CYP3A4 gene. Experiments performed *in vitro* in different cell culture systems, gel-mobility shift assays and experiments performed *in vivo* in transgenic mice lacking FXR or PXR and treated with the synthetic FXR agonist GW4064 were undertaken to study the implication of FXR in the regulation of CYP3A4. The author concluded that although elevated concentrations of precursors of bile acids and secondary bile acids elicit CYP3A activation via PXR, primary bile acids, at only a slightly increased or even at physiological concentration, may modulate the expression of CYP3A via FXR.

Hesse *et al*[23] (2003) carried out a study on clinically important drug interactions with Zopiclone, Zolpidem and Zaleplon. Potent CYP3A4 inhibitors such as ketokonazole, itraconazole and erythromycin increases the area under the

curve of zolpidem ,zapiclone by 1.5 to 2 fold. The authors concluded that a reduction of 50% of the hypnotic dose may lead to decrease in the adverse reactions.

Cheung *et al*[24] (2001) carried out a study on inhibition of CYP3A4 activity by grape fruit flavanoids, furanocoumarins and other related cpompounds. The effect of various flavanoids and furanocoumarin derivatives on CYP3A4 activity in two human liver microsomal samples was determined using quinine as a substrate. All flavanoids and furanocoumarins derivatives were dissolved in DMSO. In all cases inhibition activities were compared with activities in control incubation containing 0.2 % (v/v) DMSO. The author concluded that more than one component present in grape fruit juice may contribute to the inhibitory effect on CYP3A4. Bergapten appears to be a potent inhibitor of CYP3A4 and may therefore be primarily responsible for the effect of grapefruit juice.

Andrew *et al*[25] (2001) performed a study on Effect of amlodipine on platelet inhibition by clopidogrel in patients with ischaemic heart disease: a randomised, controlled trial. Amlodipine inhibits cytochrome P450 (CYP) enzyme and has the potential to reduce clopidogrel bioactivation *in vivo.* Reports in previous retrospective studies described greater platelet reactivity in patients on amlodipine. The author concluded that amlodipine does not significantly attenuate the antiplatelet effect of clopidogrel in patients with ischaemic heart disease with respect to pharmacological end-points. The common practice of concomitant use of these two drugs may be continued.

Ogu *et al*[26] (2000) conducted a study on drug interactions due to cytochrome P450. Cyclosporine, tacrolimus, and carbamazepine are all substrates of CYP3A4. Another drug class of note in this category is the 3-hydroxy- 3-methylglutaryl-coenzyme A (HMG CoA) reductase inhibitors. High serum concentrations of some of these agents are strongly linked to the development of rhabdomyolysis. Adding a CYP3A4 inhibitor to a drug regimen that includes

certain HMG CoA reductase inhibitors greatly increases the patient's risk of developing rhabdomyolysis. One advantage of recognizing this drug interaction has been the subsequent studies conducted to identify which agents can be used safely in multidrug combinations. Research focusing on CYP3A4 inhibitors and HMG CoA reductase inhibitors has found that pravastatin and fluvastatin can be coadministered with itraconazole, a potent CYP3A4 inhibitor, without significant changes in maximum serum concentrations.

Kenworthy *et al*[27] (1999) performed a study on CYP3A4 drug interactions: correlation of 10 *in vitro* probe substrates. The effects of 34 compounds on CYP3A4-mediated metabolism were investigated in a recombinant CYP3A4 expression system. Inhibition of erythromycin, dextromethorphan and diazepam *N*-demethylation, testosterone 6b-hydroxylation, midazolam 1-hydroxylation, triazolam 4-hydroxylation, nifedipine oxidation, cyclosporin oxidation, terfenadine C-hydroxylation and *N*-dealkylation and benzyloxyresorufin *O*-dealkylation was evaluated at the apparent *K*m or S50 (for substrates showing sigmoidicity) value for each substrate and at an inhibitor concentration of 30 mm. The author finally investigated that multiple CYP3A4 probes, representing each substrate group, are used for the *in vitro* assessment of CYP3A4-mediated drug interactions.

Meyer *et al*[28] (1996) performed a study on metabolic interaction of proton pump inhibitors with other drugs. Proton pump inhibitors are strongly metabolized by CYP3A4 enzyme. Interaction with anti-psychotic drugs has been carried out in this study. The authors investigated that proton pump inhibitors increases the hypnotic drug concentration in the plasma.

Guengerich *et al*[29] (1990) conducted a study on clinically significant drug interaction with the cytochrome P450 enzyme system. The CYP450 enzyme system is a key pathway for drug metabolism. When either drug is co-administered with an inhibitor of CYP3A4, such as an azole antifungal medication

or macrolide antibiotic, a build-up of the parent compound takes place, resulting in toxicity. Cetirizine has not been found to have clinically significant drug interactions with the CYP3A4 inhibitors erythromycin, azithromycin, ketoconazole or low-dose theophylline. Erythromycin and clarithromycin, both potent inhibitors of CYP3A4, can inhibit the metabolism of drugs which are metabolized by CYP3A (e.g., astemizole, cisapride and theophylline). Statins that are substrates of CYP3A4 have the greatest potential for interacting with drugs known to inhibit the CYP450 system, increasing the concentrations of substrate and the potential for adverse drug interactions.

Backman *et al*[30] (1989) performed a study on concentrations and effects of oral midazolam are greatly reduced in patients treated with carbamazepine or phenytoin. First studied the pharmacokinetic and pharmacodynamic aspects of an oral 15-mg dose of midazolam in 6 patients with epilepsy who are also taking carbamazepine (CBZ) or phenytoin (PHT). Then compared results with those obtained in 7 no induceds control subjects. Plasma concentrations and effects of midazolam were measured for 10 h. the author investigated that Midazolam is extensively metabolized by CYP3A enzymes during first-pass and elimination phases, and its oral bioavailability is normally <50%. When midazolam is administered intravenously or intramuscularly to treat such conditions as status epilepticus, it bypasses the altered presystemic metabolism and its pharmacokinetics is not affected to the same extent as after oral administration. However, during continuous administration of intravenous or intramuscular midazolam, larger than normal doses are probably needed in patients taking AEDs because the hepatic clearance of midazolam is increased. Larger than usual oral doses of midazolam would be needed to produce any hypnotic effects in patients receiving chronic AED therapy. Because of variability in the extent of this interaction, other hypnotic drugs may be preferable in patients taking AEDs.

SCOPE OF THE STUDY

The cytochrome P450 is a well known super family of isoenzymes that are responsible for the oxidative and reductive metabolic transformation of medications used in clinical practice. In addition, the CYP enzymes are commonly associated with causing many clinically relevant drug-drug interactions. Of the CYP enzymes, CYP3A4 is not only the most prevalent CYP enzyme in the liver, but is used by more than 50% of medications for their metabolism and elimination from the body. The CYP3A4 activity can be induced or it can be inhibited, thereby changing the drug concentrations present in the body and its pharmacokinetic profile[2].

It is also important to note that all medications within a particular drug class do not have the same effect on CYP3A4 substrates. For example, within the macrolide antibiotics, all of them are known inhibitors of CYP3A4 with the exception of azithromycin. For the calcium channel blockers, it is only the non-dihydropyridine calcium channel blockers that are known inhibitors of CYP3A4, but not amlodipine or nifedipine. Lastly, within the fluoroquinolone antibiotics, ciprofloxacin is a strong inhibitor of CYP3A4 while levofloxacin is a weak inhibitor. This is important as it reveals that the pharmacokinetic profiles do not always completely follow a class effect[3].

Many drugs commonly used in clinical practice are known substrates, inducers or inhibitors of CYP3A4 isoenymes but the severity of interaction depends upon the substrate sensitivity and the strength of induction or inhibition.

A strong inhibitor is one that causes a > 5-fold increase in the plasma AUC values or more than 80% decrease in clearance of CYP substrates in clinical evaluations. A moderate inhibitor is one that caused a > 2- but < 5-fold increase in the AUC values or 50- 80% decrease in clearance of sensitive CYP substrates

when the inhibitor is given at the highest approved dose and the shortest dosing interval in clinical evaluations. A weak inhibitor is one that causes a > 1.25 – but < 2-fold increase in the AUC values or 20-50% decrease in clearance of sensitive CYP substrates when the inhibitor is given at the highest approved dose and the shortest dosing interval in clinical practice.

Sensitive substrates are drugs that demonstrate an increase in AUC of ≥5-fold with strong index inhibitors of a given metabolic pathway in clinical drug-drug studies. Moderate sensitive substrates are drugs that demonstrate an increase in AUC of ≥2 to <5-fold with strong index inhibitors of a given metabolic pathway in clinical drug-drug interaction studies[31].

OBJECTIVE

To study various inducers and inhibitors of CYP3A4 substrates in clinical practice and to follow a mechanism based approach in their management of drug-drug interactions

PLAN OF THE STUDY

The proposed study entitled "Inducers and inhibitors of Cytochrome P450 3A4 substrates and the management of their drug interactions" was planned and carried out as given below.

Phase I:

- Identification of research problems and scope of the study.
- Preparation of study protocol.
- Obtaining consent from the hospital authorities.
- Literature survey.

Phase II:

- Design of structured performance.
- Patient selection, inclusion/exclusion criteria.
- Data retrieval from general medicine department.
- Evaluation of prescription for possible drug-drug interaction based on CYP3A4 metabolism and pharmacist recommendation.

Phase III:

- Data analysis
- Report submission

METHODOLOGY

Study Site

General medicine department of a 750 bedded multispecialty tertiary care teaching hospital.

Study Design

Prospective observational study

Study Duration

10 months from November 2016 to August 2017.

Inclusion criteria

Prescriptions from the General Medicine Department during the study period and having at least one CYP3A4 enzyme substrate along with an inducer or inhibitor are included in the study

Exclusion criteria

Prescriptions with no CYP3A4 substrates are excluded from the study.

Consent from the hospital authorities

It is mandatory that every project work carried out in the hospital has to be approved by the Institutional Ethical Committee of hospital. A protocol of the proposed study which includes the objectives, methodology and probable outcomes was prepared and submitted to the Institutional Ethical Committee of the study hospital. The approval from the committee was obtained as a letter **[SRH/EC.9-**

8/2017-18 dated 25TH February 2017] and the same was given in **Annexure No.1** for reference. The author was permitted to utilize the hospital facilities to make a follow up of the cases, in the selected departments. All the health care professionals of the study site were well informed through Dean's official circular.

Design of Patient Information Form

A patient information form has been prepared to inform the patients and care givers of patients about the purpose, necessity of the study assuring them that the confidentiality will be strictly maintained and this is for only the betterment of patient's health. The format includes the details like Department address, name and signature of the investigator and supervisor, date, place and details of the study. The model of the patient information form was given in the **Annexure No.: 2** for reference.

Design of Patient Consent Form

A patient consent form has also been prepared to obtain written consent from all the patient or bystander and will be included in the study. The format contains details like address, date, place, provision for signature of the patient or bystander, investigator and supervisor. The same was given in the **Annexure No.: 3** for reference.

Design of Data Entry Form

A separate data entry form was also designed for collecting the data related to patients including name, age, gender, height, weight, IP. No., date of admission, date of discharge, vital signs, reason for admission, past medical history and past medication history. Provision was also given in the format for entry of clinical lab data like blood counts, liver function test, renal function test, pulmonary function test, electrolytes, urine examination, diagnosis, drug chart, and drug interaction chart and

any interventions. The data entry form also had details of CYP3A4 substrates, inhibitors, inducers and relating drug interactions with respect to each prescription. The model of a patient data entry form is given in the **Annexure No.: 4** for reference.

Sample Size

A sample size of 100 patients.

Method

Demographic characteristics of the patients such as age, gender, date of admission, date of discharge were recorded in customized data entry forms. Their major diagnosis, co-morbid conditions, prescribed medications, their strength and dosing schedule were also noted down during daily ward rounds. Cytochrome P450 3A4 substrates, their inducers or inhibitors present in the prescription were identified using Micromedex database. The sensitivity of the substrate to the inhibitor or inducer as well as the strength of enzyme induction or inhibition is studied using the above mentioned database, Medline and Pubmed search.

A strong inhibitor is one that causes a > 5-fold increase in the plasma AUC values or more than 80% decrease in clearance of CYP substrates in clinical evaluations. A moderate inhibitor is one that caused a > 2- but < 5-fold increase in the AUC values or 50- 80% decrease in clearance of sensitive CYP substrates when the inhibitor is given at the highest approved dose and the shortest dosing interval in clinical evaluations. A weak inhibitor is one that causes a > 1.25 - but < 2-fold increase in the AUC values or 20-50% decrease in clearance of sensitive CYP substrates when the inhibitor is given at the highest approved dose and the shortest dosing interval in clinical practice.

Sensitive substrates are drugs that demonstrate an increase in AUC of ≥5-fold with strong index inhibitors of a given metabolic pathway in clinical drug-drug studies. Moderate sensitive substrates are drugs that demonstrate an increase in AUC of ≥2 to <5-fold with strong index inhibitors of a given metabolic pathway in clinical drug-drug interaction studies[31].

RESULTS

Prescriptions of 100 patients from the General Medicine department were evaluated for CYP3A4 based drug-drug interactions. All the selected prescriptions had at least one CYP3A4 enzyme substrate along with an inducer or inhibitor. The mean age group of study subjects was 53.12±15.13 years. Fifty five of them were male patients. Duration of hospital stay of different age groups varied between 5.38±1.19 days to 6.80±1.30 days. Number of drugs prescribed in patients of different age groups ranged from 9.33±4.04 to 15.11±3.32. Demographic details of patients are shown in table 1.

Major diagnosis observed in study population were hypertension (21%) followed by diabetes mellitus (14%), chronic renal failure (12%), tuberculosis (9%), viral fever (7%), ischemic heart disease (7%) and others. Major diagnosis and various co morbid conditions of study populations are shown in table 2 and 3 respectively.

Nine hundred and twenty five drugs belonging to Eighty eight categories were prescribed in the study subjects. Of these, vitamins and minerals (33.63%), antibiotics (12.5%), antihypertensives (9.09%), antiulcer drugs (6.81%), antiepileptics (6.81%) and anticoagulants (6.81%) were most frequently prescribed. Table 4 and 5 summarizes the details of drugs prescribed.

Hundred substrates, 66 inhibitors and 34 inducers of CYP3A4 were identified during the study period. The substrates included clopidogrel (47%), atorvastatin (22%), esomeprazole (13%), omeprazole (5%) domperidone (4%), midazolam (3%), phenytoin (2%) and azithromycin (2%). The various inhibitors of CYP3A4 isoenzymes recorded during the current study were atorvastatin (45.45%), amlodipine (19.69%), esomeprazole (12.12%), amiodarone (7.57%), flucaanazole (6.06%), cloidogrel (3.03%), oxcarbamazeine (3.03%) and isoniazid

(3.03%). Inducers of CYP3A4 enzyme present in the prescritions were phenytoin (55.88%) and rifampicin (44.11%). Table 6 shows the list of CYP3A4 substrates, and inhibitors as well as inducers of CYP3A4 based metabolism. The study identified sixty six inhibitors and 34 inducers of CYP3A4 enzyme. Interacting drug combinations of various substrates and inhibitors of CYP3A4 are summarized in table 7. Table 8 summerizes the details of substrates and inducers of CYP3A4 mediated metabolism. Table 7 and 8 also presents the strength of inhibition/induction, mechanism of interaction, severity of interaction, possible effect of interaction based on available reports and pharmacist's recommendations.

TABLE 1: DEMOGRAPHIC DETAILS (n = 100)

SL. NO	AGE GROUP	NO OF PATIENTS (%)	MEAN AGE (YRS) ±SD	GENDER	DURATION OF HOSPITALIZATION	NO OF DRUGS PRESCRIBED
1	CHILDHOOD (1-12)	0	53.12 ±15.13	Male 55 Female 45	0	0
2	ADOLESCENT (13-18)	5			6.80 ±1.30	9.33 ±4.04
3	EARLY ADULTHOOD (19-35)	16			6.44 ±1.51	13.42 ±1.88
4	ADULTHOOD (36-50)	21			6.19 ±1.50	14.61 ±1.41
5	LATE ADULTHOOD (51-65)	39			5.87 ±1.36	15.11 ±3.32
6	YOUNG ADULTHOOD (66-74)	13			5.38 ±1.19	10.14 ±4.22
7	OLD ADULTHOOD (75-84)	6			6.17 ±1.96	12.01 ±4.69
8	OLD AGE (85-95)	0			0	0

TABLE 2 : MAJOR DIAGNOSIS OBSERVED IN THE STUDY

POPULATION (n=100)

SL NO	MAJOR DIAGNOSIS	NO OF PATIENTS	PERCENTAGE
1	HYPERTENSION	21	21
2	DIABETES MELITUS	14	14
3	CHRONIC RENAL FAILURE	12	12
4	TUBERCULOSIS	9	9
5	VIRAL FEVER	7	7
6	ISCHEMIC HEART DISEASE	7	7
7	HYPERLIPIDEMIA	6	6
8	UTI	4	4
9	MIOCARDIAL INFARCTION	4	4
10	CHRONIC KIDNEY DISEASE	3	3
11	SEIZURE	2	2
12	COPD	2	2
13	DENGUE FEVER	2	2
14	ULCER	1	1
15	VIRAL PYREXIA	1	1
16	RHEUMATIC HEART DISEASE	1	1
17	STROKE	1	1
18	CORONARY HEART DISEASE	1	1
19	PNEUMONIA	1	1

TABLE 3: VARIOUS CO-MORBID CONDITIONS OBSERVED IN THE

STUDY POPULATION (n=92)

SL NO.	CO-MORBIDITY	NO OF PATIENTS	PERCENTAGE
1	DIABETES MELITUS	24	26.08
2	HYPERTENSION	17	18.47
3	HYPOTHYROIDISM	6	6.52
4	GASTRITIS	6	6.52
5	ISCHEMIC HEART DISEASE	5	5.43
6	HYPERLIPIDEMIA	4	4.34
7	CHRONIC RENAL FAILURE	4	4.34
8	PEPTIC ULCER	4	4.34
9	ACUTE INFARCT	3	3.26
10	PNEUMONIA	2	2.17
11	ANXIETY	2	2.17
12	SEIZURE	2	2.17
13	CHRONIC KIDNEY DISEASE	2	2.17
14	HEPATITIS	1	1.08
15	OTHERS	19	20.65

TABLE 4: DRUG CATEGORIES (n=88)

SL NO	DRUG CATEGORIES	NO OF PATIENTS	NO OF DRUGS	PERCENTAGE
1	VITAMINS AND MINERALS	63	12	13.63
2	ANTIBIOTICS	41	11	12.5
34	ANTIHYPERTENSIVES	57	8	9.09
5	ANTIULCER DRUGS	64	6	6.81
6	ANTIEPILEPTICS	14	6	6.81
7	ANTICOAGULANTS	51	6	6.81
8	ANTIHYPERLIPIDEMIC DRUGS	34	4	4.54
9	HYPOGLYCEMIC AGENTS	58	4	4.54
10	DIURETICS	12	3	3.40
11	ANALGESICS	12	3	3.40
12	HORMONES	18	3	3.40
13	ANTIASTHMATICS	10	3	3.40
14	ANTITUBERCULAR AGENTS	9	2	2.27
15	ANTIEMETICS	34	2	2.27
16	ANTIINFLAMATORY AGENTS	11	2	2.27
17	ANXIOLYTICS	12	2	2.27
18	ANTIDIARRHOEALS	4	2	2.27
19	ANTI ANGINAL DRUGS	5	2	2.27
20	LAXATIVES	4	2	2.27
21	ANTACIDS	10	1	1.13
22	ANTI VERTIGO AGENTS	5	1	1.13
23	ANTIGOUT AGENTS	2	1	1.13
24	SEDATIVES	2	1	1.13
25	ANTIFUNGAL DRUGS	8	1	1.13

TABLE 5: DETAILS OF DRUGS PRESCRIBED (N = 925)

SL NO	DRUG CATEGORY	NAME OF THE DRUG	NO OF DRUGS	PERCENTAGE
1	**VITAMINS AND MINERALS**	Calcitrol	57	6.16
2		Vitamin supplements	43	4.64
3		Methylcobalamin	38	4.10
4		Alphaketoanalogue	25	2.70
5		Calcium acetate	24	2.59
6		Alfacalcidol	13	1.40
7		Calcium	13	1.40
8		Calcium carbonate	12	1.29
9		Folic acid	9	0.97
10		Calcium Gluconate	4	0.43
11		Iron	3	0.32
12		Pregabalin	2	0.21
1	**ANTIBIOTICS**	Piperacillin sodium+tazobactum	32	3.45
2		Pre –probiotics	20	2.16
3		Ceftriazone + sulbactam	11	1.18
4		Cefixime	6	0.64
5		Amoxicillin+clavulanic acid	4	0.43
6		Azithromycin	4	0.43
7		Ceftriazone	3	0.32
8		Linezolid	3	0.32
9		Tetracyclines	1	0.10
10		Trimethoprim + Sulfamethoxazole	1	0.10

SL NO	DRUG CATEGORY	NAME OF THE DRUG	NO OF DRUGS	PERCENTAGE
11		Carbapenem	1	0.10
1	**ANTIHYPERTEN-SIVES**	Telmisartan	43	4.64
2		Amlodipine	13	1.40
3		Nebivolol	5	0.54
4		Cardevilol	3	0.32
5		Verapamil	2	0.21
6		Clinidipine	2	0.21
7		Nifedipine	2	0.21
8		Propanolol	1	0.10
1	**ANTIULCER DRUGS**	Pantoprazole	87	9.40
2		Sucralfate	14	1.51
3		Rabeprazole	10	1.08
4		Esomeprazole	10	1.08
5		Omeprazole	12	1.29
6		Ranitidine	9	0.97
1	**ANTIHYPERLIPID EMIC DRUGS**	Atorvastatin	38	4.10
2		Trimetazidine	2	0.21
3		rosuvastatin	3	0.32
4		Rosuvastatin + Fenofibrate	1	0.10
1	**HYPOGLYCEMIC AGENTS**	Insulin	29	3.13
2		Metformin	25	2.70
3		Glimepiride + Metformin	2	0.21
4		Glimipride	8	0.86

SL NO	DRUG CATEGORY	NAME OF THE DRUG	NO OF DRUGS	PERCENTAGE

1	**ANTICOAGULANTS**	Clopidogrel	58	6.27
2		Aspirin	7	0.75
3		Asprin+clopidogrel	14	1.51
4		Enoxaparin Sodium	4	0.43
5		Warfarin	2	0.21
6		Heparin	2	0.21
1	**ANTACIDS**	Sodium bicarbonate	2	0.21
1	**ANTIGOUT AGENTS**	febuxostat	2	0.21
1	**ANTIEMETIC S**	Ondansetron	25	2.70
2		Ramosetron	4	0.43
1		Torsemide	4	0.43
2	**DIURETICS**	Furosemide	15	1.62
3		Spiranolactone	3	0.32
1	**ANTIINFLAMATORY AGENTS**	Paracetamol	5	0.54
2		Tramadol	5	0.54
3		Paracetamol + Tramadol	2	0.21
1	**HORMONES**	Levothyroxine	4	0.43
2		Prednisolone	7	0.75
3		Methyl prednisolone	5	0.54
1	**ANTIEPILEPTICS**	Phenytoin	16	1.72
2		Clobazam	2	0.21
3		Flunarazine	2	0.21
4		Oxcabazepine	4	0.43
5		Fosphenytoin	2	0.21
6		Clonazepam	1	0.10
SL NO	**DRUG CATEGORY**	**NAME OF THE DRUG**	**NO OF DRUGS**	**PERCENTAGE**
1	**ANTIASTHMATIC**	Etophylline+theoph	8	0.86

	DRUGS	ylline		
2		Acebrophylline	2	0.21
3		Salbutamol	16	1.72
1	**ANTI**	Chymotrypsin	4	0.43
2	**INFLAMMATORY AGENTS**	Tramadol	4	0.43S
1	**ANXIOLYTICS**	Midazolam	1	0.10
2		Alprazolam	5	0.54
1	**ANTIVERTIGO AGENTS**	Betahistine	2	0.21
1	**ANTIDIARRHOELS**	Vibact	4	0.43
2		Racecadotril	5	0.54
1	**ANTITUBERCULAR AGENTS**	Rifampicin	9	0.97
2		Isoniazid + Rifampicin	7	0.75
1	**ANTI ANGINALS**	Nitroglycerine	6	0.64
2		Isosorbide dinitrite	4	0.43
ss1	**LAXATIVES**	Lactulose	2	0.21
2		Liquid paraffin	1	0.10
1	**ANTIFUNGAL DRUGS**	Fluconazole	9	0.97
1	**SEDATIVES**	Zolpidem	2	0.21

Table 6: Substrates, Inhibitors and Inducers of CYP3A4 Isoenzymes Present In the Prescriptions

SL NO.	SUBSTRATES	NO	%	INHIBITORS	NO	%	INDUCERS	NO	%
1	Clopidogrel	47	47	Atorvastatin	30	45.45	Rifampicin	19	55.88
2	Atorvastatin	22	22	Amlodipine	13	19.69			
3	Esomeprazole	13	13	Esomeprazole	8	12.12			
4	Omeprazole	5	5	Amiodarone	5	7.57			
5	Domperidone	4	4	Flucanazole	4	6.06	Phenytoin	15	44.11
6	Midazolam	3	3	Clopidogrel	2	3.03			
7	Phenytoin	2	2	Oxcarbamazepine	2	3.03			
8	Azithromycin	2	2	Isoniazid	2	3.03			

Table 7: Substrates and Inhibitors of CYP3A4 mediated metabolism (n=66)

Substrate	Precipitant	No.	%	Strength of Inhibition	Strength of Substrate	Mechanism of Interaction	Severity of Interaction	Effect of Interaction	Pharmacist Recommendation
Clopidogrel	Atorvastatin	26	39.39	Strong inhibitor	Sensitive substrate	Competition with CYP3A4 mediated metabolism and inhibition of p-glycoprotein efflux transport of clopidogrel by CYP3A4 metabolized statins.	Major	Results in decreased formation of clopidogrel active metabolite in plasma finally resulting in high on treatment platelet activity	Discontinue the current statin and substitute with the statin that is not metabolized by CYP3A4(pravastatin, rosuvastatin)
Clopidogrel	Amlodipine	11	16.66	-	-	Inhibition of CYP3A4 mediated clopidogrel activation by amlodipine	Major	Results in increased plasma concentration of clopidogrel and decreased antiplatelet effect	The addition of cilostazol may reduce the potentially harmful interaction.
Clopidogrel	Esomeprazole	7	10.60	-	-	Inhibition of CYP2C19 and CYP3A4 mediated clopidogrel metabolism to active metabolite by esomeprazole	Moderate	Concurrent use may result in reduced plasma concentration of clopidogrel active metabolite	Instead of esomeprazole use pantaprazole as it has less effect on antiplatelet activity.
Atorvastatin	Amiodarone	5	7.57	-	-	Inhibition of CYP3A4 mediated atorvastatin metabolism	Moderate	Concurrent use may result in an increased risk of myopathy or rhabdomylosis	Monitor creatinine kinase levels. Consider substuting other HMGCoA reductase inhibitors such as pravastatin or rosuvastatin.
Esomeprazole	Flucanazole	4	6.06	Moderate inhibitor	Moderately sensitive substrate	Inhibition of CYP3A4 mediated esomeprazole metabolism by flucanazole.	Moderate	Results in increased esomeprazole plasma concentration	Avoid concomitant use of both these drugs. Patients should be monitored for potentially increased adverse effects of PPIs during co-administration.
Phenytoin	Clopidogrel	2	3.03	-	-	Inhibition of CYP2C19 and CYP3A4 mediated phenytoin metabolism by clopidogrel	Moderate	Results in increase plasma concentration of phenytoin and phenytoin toxicity.	Avoid concomitant use of both these drugs.

Substrate	Precipitant	No.	%	Strength of Inhibition	Strength of Substrate	Mechanism of Interaction	Severity of Interaction	Effect of Interaction	Pharmacist Recommendation
Phenytoin	Oxcarbama-Zepine	2	3.03	Moderate inhibitor	Moderately sensitive substrate	Inhibition of CYP3A4 mediated phenytoin metabolism	Moderate	Results in increase plasma concentration of phenytoin and phenytoin toxicity.	Phenytoin dose should be reduced.
Domperidone	Amlodipine	2	3.03	-	-	Inhibition of CYP3A4 mediated domperidone metabolism	Major	Results in increased domperidone concentration in plasma	Domperidone should be given at lowest possible dose.
Domperidone	Atorvastatin	2	3.03	-	-	Inhibition of CYP3A4 mediated domperidone metabolism	Major	Results in increased domperidone concentration in plasma	Domperidone should be given at lowest possible dose.
Clopidogrel	Isoniazid	2	3.03	-	-	Inhibition of CYP2C19 and CYP3A4 mediated clopidogrel metabolism to active metabolite by isoniazid	Moderate	Results in reduced antiplatelet activity of clopidogrel	Avoid concomitant use of both these drugs.
Azithromycin	Atorvastatin	2	3.03	Strong inhibitor	Sensitive substrate	Inhibition of CYP3A4 mediated azithromycin metabolism	Moderate	Concurrent use may lead to rhabdomylosis	Avoid concomitant use and check for rhabdomylosis. Rosuvastatin can be preferred choice of statins for a concomitant therapy with azithromycin.
Clopidogrel	Omeprazole	1	1.51	Moderate inhibitor	Moderately sensitive substrate	Inhibition of CYP2C19 and CYP3A4mediated clopidogrel metabolism by omeprazole	Major	Results in reduction in clinical efficacy of clopidogrel and increase in risk for thrombosis	Use dexlanzoprazole instead of omeprazole for concomitant therapy with clopidogrel.

Table 8: Substrates and Inducers of CYP3A4 mediated metabolism (n=34)

Substrate	Precipitant	No.	%	Strength of Inhibition	Strength of Substrate	Mechanism of Interaction	Severity of Interaction	Effect of Interaction	Pharmacist Recommendation
Atorvastatin	Phenytoin	12	35.29	Moderate inhibitor	Moderately sensitive substrate	Induction of CYP3A4 mediated atorvastatin metabolism by phenytoin	Moderate	Results in decreased atorvastatin plasma concentration and decreased atorvastatin efficacy	Adjust the dose of atorvastatin. Rosuvastatin can be replaced instead of atorvastatin.
Esomeprazole	Rifampicin	9	26.47	Moderate inhibitor	Moderately sensitive substrate	Induction of CYP3A4 and CYP2C19 mediated esomeprazole metabolism by rifampicin	Moderate	Concurrent use may result in decreased esomeprazole plasma concentration	Avoid concurrent use of these drugs.
Atorvastatin	Rifampicin	5	14.70	Strong inhibitor	Sensitive substrate	Induction of CYP3A4	Severe	Concurrent use may	Atorvastatin administration

Substrate	Precipitant	No.	%	Strength of Inhibition	Strength of Substrate	Mechanism of Interaction	Severity of Interaction	Effect of Interaction	Pharmacist Recommendation
						metabolism of atorvastatin by rifampicin		result in decreased plasma concentration of atorvastatin	should be delayed after rifampicin administration
Omeprazole	Rifampicin	5	14.70	Moderate inhibitor	Moderately sensitive substrate	Induction of CYP3A4 and CYP2C19 mediated omeprazole metabolism by rifampicin	Moderate	Concurrent use may result in decreased omeprazole plasma concentration	Avoid concurrent use of these drugs.

Substrate	Precipitant	No.	%	Strength of Inhibition	Strength of Substrate	Mechanism of Interaction	Severity of Interaction	Effect of Interaction	Pharmacist Recommendation
Midazolam	Phenytoin	3	8.82	-	-	Induction of CYP3A4 mediated midazolam metabolism by phenytoin	Moderate	Results in decreased midazolam plasma concentration and reduction in midazolam efficacy.	A hypnotic other than midazolam would be preferable. Benzodiazepines (Diazepam)

DISCUSSION

Hundred drug-drug interaction based on CYP3A4 metabolism of drugs were obtained from the current study. Of these 66 were between CYP3A4 substrates and inhibitors while 34 were between CYP3A4 substrates and inducers.

Most prevalent interacting combination of CYP3A4 substrate and inhibitor was clopidogrel + atorvastatin (39.39%) followed by clopidogrel + amlodipine (16.66%). Most frequently observed interacting combination of CYP3A4 substrate with an inducer was atorvastatin + phenytoin (35.29%) followed by esomeprazole + rifampicin (26.47%).

The clinical significane of each interacting drug combination along with pharmacist's recommendation for a suitable therapeutic alternative are discussed below.

1. CLOPIDOGREL + ATORVASTATIN

CYP3A4 based interaction between clopidogrel and atorvastsatin leads to decreased formation of clopidogrel active metabolite in plasma resulting in high platelet activity leading to thrombosis. This is due to the competition with CYP3A4 mediated metabolism of clopidogrel by atorvastatin and inhibition of P-glycoprotien efflux transport of clopidogrel. In presence of pravastatin and rosuvastatin the clearance of clopidogrel reduces to 24% and 46% respectively. Hence instead of atorvastatin either pravastatin or rosuvastatin may be prescribed in combination with clopidogrel[14].

2. ESOMEPRAZOLE + FLUCANAZOLE

Due the inhibition of CYP2C19 and CYP3A4 mediated esomeprazole metabolism, esomeprazole exposure may increase by more than two fold when administered concurrently with flucanazole. However, flucanazole is a moderately

sensitive substrate of CYP3A4 based metabolism of esomeprazole. Patients should be monitored for potentially increased adverse effects of PPIs during co-administration[32].

3. PHENYTOIN + OXCARBAZEPINE

When phenytoin was combined with oxcarbazepine in dose greater than 1200 to 2400 mg daily, there was upto a 40% increase in phenytoin plasma concentrations. But oxcarbazepine in a moderate inhibitor of CYP3A4 mediated metabolism of phenytoin. Therefore dose reduction of phenytoin may be considered[33].

4. AZITHROMYCIN + ATORVASTATIN

Bellosta *et al* 2012 have reported 73% decrease in the clearance of azithromycin when coadministered with atorvastatin due to inhibition of CYP3A4 metabolism of azithromycin by atorvastatin. Cytochrome P450 metabolism of rosuvastatin appears to be minimal (10%) and is principally mediated by CYP2C9 enzyme with little involvement of 3A4. Literature also supports the absence of clinically significant pharmacokinetic drug-drug interaction between rosuvastatin and other CYP substrates. Therefore, rosuvastatin can be a preferred choice of statin for concomitant therapy with azithromycin[16].

5. CLOPIDOGREL + OMEPRAZOLE

In dedicated drug-drug interaction studies, proton pump inhibitors (dexlansoprazole, lansoprazole, pantoprazole, rabeprazole and omeprazole) use significantly reduced the AUC of the clopidogrel active metabolite versus clopidogrel alone. Omeprazole use resulted in the greatest reduction in clopidogrel metabolite AUC, while dexlansoprazole was associated with the least reduction. Therefore when such a combition therapy is necessary omeprazole may be replaced with dexlansoprazole[34].

6. ATORVASTATIN + PHENYTOIN

Phenytoin induces CYP3A4 mediated metabolism of atorvastatin, resulting in decreased atorvastatin plasma concentration and decreased atorvastatin efficacy. When such a combination therapy is necessary, the dose of atorvastatin may be adjusted. However, rosuvastatin, which is minimally metabolized (10%) by CYP enzyme system, can be recommended instead of atorvastatin. Also, there is no documented evidence of interaction between rosuvastatin and phenytoin[35].

7. ATORVASTATIN + RIFAMPICIN

Eighty percentage decrease in AUC and 40% decrease in Cmax of atorvastatin when given along with rifampcin was reported by Backman et al 2005. Mechanism of this interaction is induction of CYP3A4 metabolism of atorvastatin by rifampicin. Hence atorvastatin administration should be delayed after rifampicin administration[30].

8. ESOMEPRAZOLE + RIFAMICIN

Esomeprazole Cmax and AUC decreased by 37.5% and 37.9%, respectively in poor metabolizers, and by 49.6% and 43.9%, respectively in extensive metabolizers (Willington *et al* 2011) Rifampcin induces CYP3A4 and CYP2C19 mediated metabolism of omeprazole. Hence concurrent therapy may be avoided[32].

9. OMEPRAZOLE + RIFAMPICIN

Omeprazole rifampicin coadministratin also yielded results similar to previous studies[32].

SUMMARY

A prospective observational study for a period of 8 months was carried out in the general medicine department of a 750 bedded multispecialty tertiary care teaching hospital in order to understand various inducers and inhibitors of CYP3A4 substrates present in prescription and to follow a mechanism based approach in the management of drug-drug interactions. Hundred Prescriptions with at least one CYP3A4 enzyme substrate along with either inducer or inhibitor were selected for the study. All the selected prescriptions had at least one CYP3A4 enzyme substrate along with an inducer or inhibitor. Major diagnosis observed in study population were hypertension (21%) followed by diabetes mellitus (14%), chronic renal failure (12%), and tuberculosis (9%) Nine hundred and twenty five drugs belonging to Eighty eight categories were prescribed in the study subjects. Of these, vitamins and minerals (33.63%), antibiotics (12.5%), antihypertensives (9.09%), antiulcers (6.81%), antiepileptic (6.81%) and anticoagulants (6.81%) were most frequently prescribed. Hundred substrates, 66 inhibitors and 34 inducers of CYP3A4 were identified during the study period. The substrates included clopidogrel (47%), atorvastatin (22%), esomeprazole (13%),omeprazole (5%) domperidone (4%), midazolam (3%), phenytoin (2%) and azithromycin (2%). The various inhibitors of CYP3A4 recorded were atorvastatin (45.45%), amlodipine (19.69%), esomeprazole (12.12%), amiodarone (7.57%), flucanazole (6.06%), cloidogrel (3.03%), oxcarbamazeine(3.03%) and isoniazid (3.03%). Inducers of CYP3A4 enzyme present in the prescritions were phenytoin (55.88%) and rifampicin (44.11%). The study reviewed the strength of inhibition/induction of metabolism of the CY3A4 substrate by the inhibitors/inducers. Mechanism of these interactions as well as the severity and clinical significance of interactions were also reviewed using relevant literatures. A suitable therapeutic alternative was recommended whenever possibility of a major drug-drug interaction between CY3A4 substrate and inhibitor/inducer was observed in the study.

CONCLUSION

Evaluation of 100 prescriptions in the current study resulted 66 drug-drug interactions between CYP3A4 substrates with inhibitors and 34 between CYP3A4 substrates and inducers. The most commonly identified combination was clopidogrel+atorvastatin (39.39%) and clopidogrel+amlodipine (16.66%). Both atorvastatin and amlodipine act as an inhibitor of CYP3A4 based metabolism of clopidogrel, possibly resulting in decreased formation of copidogrel active metabolite in plasma. Rosuvastatin which is minimally metabolized by CYP enzyme system may be substituted instead of atorvastatin. The study also identified phenytoin (35.92%) and rifampicin (26.47%) as the inducers of CYP3A4 based metabolism of atorvastatin and esomeprazole leading to a decreased plasma concentration of atorvastatin and esomeprazole.

FUTURE OUTLOOK

Further studies are needed to assess the impact of pharmacist recommendation on reducing major drug-drug interaction of CYP3A4 substrates with inhibitors or inducers. The present study may also be extended to other departments of the hospital.

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Sri Ramakrishna Hospital

Medical Service : M/s. S.N.R. SONS CHARITABLE TRUST

SRI RAMAKRISHNA HOSPITAL ETHICAL COMMITTEE

395, SAROJINI NAIDU ROAD, SIDHAPUDUR, COIMBATORE - 641 044.
Phone : 0422 - 4500000, 4500201, Grams :"RAMHOSP" Fax : 0422-2240521
E-mail : dean@snrsonstrust.org, website : sriramakrishnahospital.com
Ethics Committee Registration No. ECR/690/Inst/TN/2014

Ethics Committee Chairman

Dr. P. M. Murali, M.Sc.,Ph.D.,D.Sc.,

Ethics Committee Member Secretary

Dr. P. Sukumaran, MS.,M.Ch.,FIACS.,

Ethics Committee Members

Dr. MohanKumar T. MD.,AB.,D.Sc., DPPR.,FCCP., Clinician

Dr. R. Lalitha, DGO., Clinician

Dr. S. Rajagopal, M.Ch., Clinician

Dr. M. Rangasamy, B.E.,M.Sc.(Engg.)Ph.D., Lay Person

Dr. T.K. Ravi, M.Pharm.,Ph.D., Scientific Member

Dr. N. Paramasivan, MBBS., MD.,(Pharmacology) Basic Medical Scientist

Mr. P. R. Ramakrishnan, B.Com.,B.L., Legal Expert

Mrs. Mythili Padmanabhan, M.Sc., Social Scientist

SRH/EC.9 – 8/2017-18 25th February 2017

ETHICAL CLEARANCE CERTIFICATE

Project title: Inducers and Inhibitors of Cytochrome P450 3A4 substrate and the management of their drug interactions".

Researcher: Mr.ROBIN ABRAHAM
M.Pharmacy II year,
Department of Pharmacy Practice,
College of Pharmacy,
Sri Ramakrishna Institute of Paramedical Sciences,
Coimbatore – 641 044

The following members of the ethics committee were present at the meeting held on 18.02.2017 at 11am at New Auditorium, Sri Ramakrishna Hospital Campus, Coimbatore.

Sl NO	Members Name	Qualification	Designation	Address	Affiliation To the Institution Yes/NO
1.	Dr.P.Murali	M.Sc.,Ph.D., D.Sc	Scientist Mg. Director & CEO	Mg.Director & CEO Evolve Biotech Pvt.Ltd., 401 – 405, 4th floor Ticel Bio park Ltd, Taramani, Chennai - 13	No
2.	Dr.P.Sukumaran	MS., M.Ch., FIACS	Scientific / EC Member Secretary Dean	Dean Sri Ramakrishna Hospital, 395, Sarojini Naidu Road, Sidhapudur, Coimbatore	Yes
3.	Dr.T.Mohan Kumar	MD.,D.Sc., AB.,DPPR., FCCP.,	Clinician	Sr.Consultant Pulmonologist Sri Ramakrishna Hospital, 395, Sarojini naidu Road, Sidhapudur, Coimbatore.	Yes
4.	Dr.R.Lalitha	DGO.,(OG)	Clinician	Sr.Consultant Gynecologist & HOD Sri Ramakrishna Hospital, 395, Sarojini naidu Road, Sidhapudur, Coimbatore.	Yes