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Original Article

Impact of Cytochrome P450 and P-gp-Mediated Drug Interactions in Patient Prescriptions at a Tertiary Care Hospital: A Cross-Sectional Follow-Up Study

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ABSTRACT

Background: Drug interactions, especially those mediated by CYP450 enzymes and P-glycoprotein (P-GP), contribute significantly to medication errors and are often overlooked in clinical practice. Identifying and managing these interactions is vital for patient safety. This study aims to assess the prevalence of CYP450- and P-gp-mediated drug interactions in hospitalized prescriptions, including narrow therapeutic index drugs and patients with alcohol or smoking history, and to explore strategies to reduce clinically significant interactions. **Materials and Methods:** It is a cross-sectional observational study; the collected data are analysed for potential drug interactions using Micromedex, Drug Bank, and SuperCYP to identify which of the CYP450 enzymes and P-GP could be involved in the drug interactions, considering patients' personal habits and medical and medication-related information. **Results:** A total of 196 patients had the potential for a drug interaction, but about 29 had clinically significant drug interactions. Logistic regression was performed, and all the predictor variables for PDIs were statistically significant. The most frequent drug-drug, drug-alcohol, drug-smoking, drug-food, and clinically significant interactions mediated by CYP450 and P-GP interactions were tabulated. **Conclusion:** Our study discusses the importance of proactively identifying preventable drug interactions. Clinical pharmacists can significantly reduce adverse outcomes and enhance patient safety by designing tailored drug regimens based on biological and pharmaceutical factors and evidence-based prescribing.

Keywords: Cytochrome P 450 enzymes, P-glycoprotein, Clinical pharmacy, Narrow therapeutic index drugs, Potential drug interactions.

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INTRODUCTION

Drug interactions are common hindrances in implementing an effective therapy plan, which may often produce unintended reactions because of the co-administered drugs, sometimes due to patient-related factors. CYP-mediated drug interactions account for 80-90% of overall prevalence and pose a significant risk to patients' safety and therapeutic outcomes, especially in hospitalised patients receiving multiple medications (Doan *et al*., 2013). Metabolism has a major impact on the bioavailability of drugs, specifically cytochrome P450 enzymes, which metabolise more than 90% of the currently available drugs. There are more than 50 CYP450 enzymes (Lynch and Price, 2007). P-Glycoprotein (P-GP), a membrane efflux protein present in various organs such as the liver, brain, kidney, and adrenal glands, additionally plays a crucial role in blood-tissue barriers, including the blood-brain barrier, blood-testis barrier, and placenta (Fromm, 2004). Similar to CYP450 enzymes involved in drug metabolism, Co-administered drugs can influence the activity of P-GP, as its induction may reduce the bioavailability, leading to subtherapeutic effects, and its inhibition can result in excessive drug accumulation, potentially causing toxicity (Ledwitch and Roberts, 2017). Notably, alcohol consumption increases the expression of CYP2E1, CYP2B6, and CYP2J2 while reducing the levels of CYP1A2, CYP2C8, CYP2C9, CYP2D6, and CYP4A11 in heavy drinkers. These disrupt the balance of the CYP450 enzyme pool, ultimately affecting the metabolism and clearance of various drug substrates (Gaither *et al*., 2025; Gomes *et al*., 2017). Tobacco smoking influences drug metabolism primarily through

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the activation of CYP and UGT enzymes. Smokers who take medications metabolised by CYP1A1, CYP1A2, and CYP2E1 enzymes may require higher doses, as polycyclic aromatic hydrocarbons in tobacco smoke induce these enzymes, leading to increased metabolism and lower plasma drug concentrations (Taghavi *et al*., 2012). Despite vast research in NTI drugs, we lack a definite list of NTI drugs; hence, understanding about them was made possible by utilizing drug experts (Blix *et al*., 2010). Our study aims to identify the prevalence of CYP-450 enzyme and P-glycoprotein drug interactions in hospitalized patients and develop strategies to prevent or overcome clinically significant Drug-Drug Interactions (DDIs).

MATERIALS AND METHODS

Study design

It is a Cross-sectional observational study that aims to assess the prevalence of CYP-450 and P-glycoprotein-mediated drug interactions in hospitalized prescriptions. This study was carried out for six months, and a systematic methodology was followed for precise data collection, data assessment, and interpretation.

Study population

The study included male and female patients above 18 years who provided informed and written consent. Hospitalized patients prescribed two or more medications from departments like General Medicine and allied specialties were eligible. Prescriptions exhibiting CYP450 enzyme- or P-glycoprotein-mediated drug interactions, and those involving narrow therapeutic index drugs, were included in the study. Patients who did not provide informed and written consent, individuals below 18 years, pregnant or lactating women, and pediatric patients were excluded from the study. Prescriptions from outpatient departments and non-medicine or non-allied specialities were not considered. A total of 260 prescriptions were eligible, but only 196 of them had Potential Drug Interactions (PDIs) and were included in the study

Data collection and assessment

Each case file was thoroughly reviewed, and relevant data were extracted using a standardized form designed for the study. Collected information included patient demographics, comorbid conditions, therapy regimen, personal habits, and clinical findings such as laboratory investigations, imaging results, and sonological evidence. Patients were monitored throughout their hospital stay, with daily updates recorded on drug regimens, vital signs, and clinical examinations. This continuous follow-up provided a comprehensive assessment of each patient's prognosis and facilitated the early detection of Clinically significant Drug Interactions. (CDIs) We assessed drug-drug interactions by classifying their severity using Micromedex and relevant literature. CYP450-mediated interactions were analyzed through the SuperCYP database and SuperCYPsPred models, while P-glycoprotein interactions were screened using Drug Bank classifications. The metabolic pathways, mechanisms, and clinical consequences of interactions were interpreted through patient monitoring and interviews.

Statistical analysis

Statistical analysis will be conducted to interpret study results, logistic regression and ROC were performed to estimate the possible predictors for drug interactions, using JAMOVI version 2.6.26. The level of significance was set at $^{*}p<0.05$.

Ethical considerations

This Observational Cross-sectional study was conducted at a tertiary care center, following approval from the Institutional Ethics Committee (IEC/SRMC/SRCP/RESEARCH/026/2024). We ensured that written informed consent was obtained from all participants, and patient anonymity was strictly maintained throughout the study.

RESULTS

Prevalence of CYP450 enzyme and p-glycoprotein drug interactions

A total of 196 in-patient prescriptions were screened for drug interactions, and 156 (79.59%) prescriptions had only CYP-mediated drug interactions, 10 (5.10%) prescriptions had only P-GP-mediated drug interactions, and 30 (15.31%) prescriptions had both types of drug interactions, as in Table 1.

Narrow therapeutic index drugs that are highly susceptible to CYP450 enzyme and p-glycoprotein drug interactions

The following are the NTI drugs that are identified in our study, they are Phenytoin (13); Amitriptyline (9); Amiodarone (6); Valproic acid (6); Carbamazepine (4); Levo thyroxine (3); Digoxin (2); Nortriptyline (2); Vancomycin, Amikacin, Methotrexate, Mycophenolate mofetil. A total of 46 potential drug interactions are noted, comprising these NTI drugs and are listed in Table 2.

CYP450-mediated drug interactions in patients with alcohol consumption and smoking

Among 196 patients, 91 patients have a habit of alcohol consumption, and a total of 68 patients have shown potential to develop alcohol influenced CYP mediated drug interactions. A total of 99 drug interactions were noted. Refer to Table 3.

Detection and Management of Unintended Interactions

In 196 patients, 29 (14.79%) have shown clinically significant interactions traced by regular follow-up, laboratory investigations, and signs and symptoms. We documented the effect seen in

the patient along with the advisable management based on recommended guidelines in Table 4.

Statistical results

Logistic regression (Table 5) is performed by considering PDDIs as a dependent variable and Age, Gender, Comorbid status, Polypharmacy, and personal habits as independent variables. The results of this regression are represented in Table 5, which denotes the predictors for PDDIs; Logistic regression for CDIs is not statistically significant.

ROC curves for four predictors showed the AUC for Hypertension was 0.631, for Diabetes 0.596, for Alcohol 0.649, and Number of drugs 0.628. These values indicate poor to fair discriminative ability, with Alcohol showing the highest predictive value. All AUCs were above 0.5, suggesting the models performed better than random chance but lacked strong predictive accuracy.

DISCUSSION

Potential drug-drug interactions mainly cause Adverse Drug Reactions (ADR), and these occur at a higher rate in patients who are on multiple drug therapy and have comorbid conditions. These consequences can sometimes range from causing minor unintended effects to drug-related mortality and morbidity.

Our study revealed that most potential interactions were noted in middle-aged (40 to 60 years) patients. A study conducted by John E Hughes revealed that these DDIs are more prevalent among middle-aged individuals, and approximately two-thirds of all studies involve clinically significant interactions, and most commonly prescribed drugs include ACE inhibitors, diuretics, and other hypertensives (Hughes *et al.*, 2023). This indirectly implies that middle-aged people are at risk of developing DDIs due to various factors like polypharmacy, comorbidities, and multiple drug therapies that they are concomitantly taking for a very long time.

Among different types of CYP enzymes, CYP3A4 was most profoundly involved in drug interactions, and it is involved in the metabolism of most of the drugs, like statins, antibiotics, anti-arrythmias, and anti-psychotics (Gallo *et al.*, 2019). Studies also described a significant reduction of these enzymes with aging and chronic kidney disorders; hence, our study observed unexpected clinical effects, mainly due to the CYP3A4 enzyme in the elderly. Drug interaction between Aspirin and Clopidogrel

Table 1: CYP-450 enzyme and P-gp-mediated drug-drug interactions.

Interacting drugs	Enzyme/ P-gp	Mechanism	Risk	Frequency (%)
Aspirin and Clopidogrel	CYP2C19	Inhibition	internal bleeding	41 (17.37%)
Atorvastatin and Clopidogrel	CYP3A4	Inhibition	ischemic events	36 (15.25%)
Aspirin and Spironolactone	CYP2C8	Inhibition	hyperkalaemia and nephrotoxicity	18 (7.63%)
Aspirin and Metoprolol	CYP2C19	Induction	cardiac arrhythmias	8 (3.39%)
Azithromycin and Ivabradine	CYP3A4	Inhibition	Secondary and tertiary heart block	7 (2.97%)
Clarithromycin and Piperacillin	P-gp	Inhibition	Neurotoxicity	3 (8.33%)
Azithromycin and Ivabradine	P-gp	Inhibition	Anaphylactic Reaction	2 (5.56%)
Atorvastatin and Dabigatran	P-gp	Inhibition	Bleeding	2 (5.56%)
Amiodarone and Digoxin	P-gp	Inhibition	Digoxin toxicity	1 (2.78%)

Table 2: CYP450 and P-gp Mediated NTI Interactions.

Interacting Drugs	Enzyme/P-gp	Mechanism	Risk
Alcohol and Phenytoin	CYP2B6	Inhibition	Seizure Recurrence
Clonazepam and Valproic Acid	CYP3A4	Inhibition	Somnolence
Levothyroxine and Pantoprazole	CYP3A4	Induction	Hypothyroidism
Phenytoin and Propranolol	CYP3A4	Inhibition	Tachycardia, Hypotension
Dexamethasone and Phenytoin	P-gp	Induction	Subtherapeutic effect
Hydroxychloroquine and Methotrexate.	P-gp	Inhibition	Bone marrow, liver toxicity
Carbamazepine and Clonazepam.	P-gp	Induction	Inefficacy leading to seizures or anxiety

Table 3: Alcohol and Smoking-Influenced CYP-Mediated Drug Interactions.

Interacting drug	Enzymes	Mechanism	Risk	Frequency
Alcohol (Ethanol)				
Aspirin	CYP2C9	Inhibition	GI Bleeding	25(25.2%)
Acetaminophen	CYP1A1	Inhibition	Hepatotoxicity	23(23.2%)
Metoprolol	CYP2C19	Inhibition	Hypotension and Tachycardia	9(9.09%)
Chlordiazepoxide	CYP3A4	Inhibition	CNS Depression	8(8.08%)
Propranolol	CYP2C19	Inhibition	Bradycardia, Hypotension	6(6.06%)
Promethazine	CYP2B6	Inhibition	Serotonin Syndrome	4(4.04%)
Phenytoin	CYP2B6	Induction	Relapse of Seizures	4(4.04%)
Smoking (Nicotine)				
Clopidogrel	CYP1A2	Induction	Bleeding	21(34.4%)
Acetaminophen	CYP1A2	Inhibition	Hepatotoxicity	17(27.8%)
Ondansetron	CYP1A2	Induction	Hypovolemic shock	9(14.7%)
Propranolol	CYP1A2	Induction	Hypertension	5(8.1%)

Table 4: Clinically Significant Interactions and Their Management.

Interacting drugs	Effects seen in the patient	Management
Aripiprazole and Fluoxetine	Weight gains due to long-term use of both drugs	Dose reduction of Aripiprazole from 10 mg to 5 mg.
Acetaminophen and Alcohol	Increased alkaline phosphatase	Dose reduction from 650 mg to 500 mg.
Fluoxetine and Propranolol	Hypotension and bradycardia noted	Avoid co-administration
Aspirin and Clopidogrel	Elevated prothrombin time	Opt for Ticagrelor as per dosing guidelines.
Hydrocortisone and Levofloxacin	Hypokalaemia noted	Slow IV infusion (<10 mmol/hr) of diluted KCl.
Alcohol and Propranolol	Fainting was observed	Opt for Metoprolol 25 mg
Aspirin and Clopidogrel	Increased PT, INR	Adjust the dose of Clopidogrel and monitor.
Mycophenolate mofetil and Pantoprazole	flare-up of SLE, nephritis was observed	Administer Mycophenolate mofetil after 1 hr.
Phenytoin and Valproic acid	Vertigo noted	Add beta-histine 8 mg for vertigo and monitor.
Acetaminophen and Isoniazid	Tingling, numbness, and weakness on prolonged use	Dose reduction of Acetaminophen from 650 mg to 500 mg.
Lacosamide and Nicardipine	Cardiac arrest noted	Dose reduction of Lacosamide from 100 mg to 50 mg IV.
Aspirin and Clopidogrel	Anaemia noted	Dietary management along with Folate therapy.
Amiodarone and Levofloxacin	Ataxia noted	Opt for Amoxicillin and Clavulanate as streptococci species are isolated.
Alcohol and Zolpidem	Somnolence	Monitor
Amikacin and Vancomycin	Persistent elevated serum creatinine levels	Administration of vancomycin on alternate days.
Aripiprazole and Fluoxetine	Disorientation	Dose reduction of Aripiprazole from 10 mg to 5 mg.
Aspirin and Spironolactone	Respiratory alkalosis was observed	Avoid co-administration
Alcohol and Propranolol	Hypotension was observed	opt for sotalol 40 mg
Atorvastatin and Dabigatran	Decreased platelet count	Avoid co-administration

NOTE: IV = Intravenous; KCl = Potassium chloride; PT = prothrombin time; INR = International normalized ratio; SLE = systemic lupus erythematosus.

Table 5: Predictors of PDIs using Logistic regression.

Variables	Group	Patients with PDI	Patients without PDI	Odds ratio (CI)	*p* value
Age	18 ≤ 40	43	18	1.03 (1.01-1.05)	0.007
	41 ≤ 60	84	36		
	61 ≤ 80	65	10		
	> 80	4	0		
Gender	Male	148	36	2.4 (2.31-4.06)	0.004
	Female	48	28		
Diseased Conditions	< 3	114	59	2.7 (1.82-4.02)	0.002
	≥ 3	82	5		
Comorbidities	Hypertension	82	10	3.88 (1.87-8,08)	0.001
	Diabetes	59	7	3.51 (1.51-8.14)	0.004
Medications	≥ 8	96	15	3.14 (1.65 - 5.96)	0.002
Personal Habits	Smoking	76	15	2.07 (1.08-3.95)	0.027
	Alcohol	91	11	4.18 (2.06-8.47)	0.003

Note: Values of $p<0.05$ are considered statistically significant. All the variables (independent) have shown significance, as shown above. PDI: cytochrome and p-glycoprotein mediated Potential Drug Interactions. CI: confidence interval (95%).

mediated by CYP2C19 is the most frequent DDI noted, and research shows combined therapy involving both drugs carries a significant risk of bleeding, and this combination is prescribed clinically to patients undergoing percutaneous transluminal angioplasty and other heart-related disorders. The result of this interaction showed an increased rate of bleeding and was generally less with conventional drugs like heparin, hence, this combination shows thrombotic risk and should be considered for monitoring (Payne *et al*., 2002).

Drug interaction between dabigatran and atorvastatin is P-GP mediated, and preexisting research shows a decline in dabigatran concentration by 18% due to concomitant administration with atorvastatin; hence, patients with such interactions are at a risk of developing thromboembolism and stroke (Stangier *et al*., 2009).

Majority of patients with NTI mediated drug interactions fall in the age group 0f 40-60 years and pose a significant risk to patients affecting their overall quality of life, for example interaction between Amiodarone and Digoxin usually results in digoxin intoxication through P-GP mediated drug interaction and this is an important aspect as both the drugs are identified as narrow therapeutic and have a high chance of developing serious adverse effects in patient due to their narrow therapeutic range (Vivean *et al*., n.d.).

Our study focussed on Alcohol and smoking influenced CYP mediated drug interactions and almost half of the patients have habit of alcohol consumption and abuse of nicotine in various forms and research shows that patients with history of smoking and alcohol consumption (acute and chronic) have upregulated CYP2B6, CYP2E1 and downregulated CYP1A1, CYP1A2 and CYP2C19 making it clear that carry-on effects due to these chemical metabolites contribute to drug interactions which is generally most ignored while designing a drug regimen to patient (Gaither *et al*., 2024).

Clinically significant interactions seen in patients make our study wholesome, In our study, a total of 29 patients experienced clinical effects because of drug interactions, and there were several studies on the prevalence, risk factors, and adverse outcomes of potential DDIs, and most of these interactions were seen in the Emergency and ICU departments. For example, CYP-mediated interaction between lacosamide and nicardipine had shown a serious adverse event of cardiac arrest in a 20-year-old patient, and throughout our entire study, we have seen such unpredictable adverse events during our follow-up and were listed in Table 4 along with their management strategies.

CONCLUSION

Our study underscores the need for proactive identification of drug interactions that are usually preventable. The findings of our study strengthen the fact that middle-aged and older people are at higher risk due to personal habits, polypharmacy, altered enzyme expression, and prolonged hospitalization. Our study highlighted the importance of individualised medication monitoring to prevent adverse outcomes, and this can be made possible by effective health care collaboration. The involvement of clinical pharmacists in identifying, preventing, and managing drug interactions and thereby providing evidence-based medicine helps in safer prescribing practices and enhances patient outcomes.

Our study provides a comprehensive analysis of clinically significant CYP and P-gp-mediated drug interactions, including alcohol, smoking, and NTI drugs, in hospitalized patients. However, limitations include reliance on databases, exclusion of genetic and pharmacokinetic variations, and restricted generalizability. Future work should focus on pharmacogenetic testing, real-time interaction management via clinical decision support systems, and interdisciplinary collaboration to enhance patient safety.

ABBREVIATIONS

CYP 450: Cytochrome: P450; **P-GP:** P: glycoprotein; **PDIs:** Potential drug interactions, **CDIs:** Clinically significant drug interactions; **MDR:** Multi drug resistance; **WHO:** World health organisation; **PHAs:** Polyhydroxyalkanoates; **UGT enzymes:** Uridine diphosphate: glucuronosyltransferase; **NTIs:** Narrow therapeutic index drugs, **DRPs:** Drug related problems; **PK:** Pharmacokinetic, **PD:** Pharmacodynamic; **DDIs:** Drug-drug interactions, **AKI:** Acute kidney injury; **CKD:** Chronic kidney disease; **HTN:** Hypertension, **ESRD:** End: stage renal disease; **T2DM:** Type2 diabetes mellitus; **SD:** Standard deviation, **DIs:** Drug interactions; **CAD:** Coronary artery disease; **GI:** Gastro intestinal, **CNS:** Central nervous system; **KCl:** Potassium chloride; **CDDI:** Clinically significant drug-drug interactions; **CI:** Confidence interval; **ADR:** Adverse drug reactions; **ACE:** Angiotensin Converting enzyme; **DMETs:** Drug metabolising enzymes and transporters; **ICU:** Intensive critical care unit.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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