IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
December 2019 Vol.:17, Issue:1

Pharmacokinetic Drug-Drug Interactions and Role of Pharmacists in Drug Therapy Management

IJPPR
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An official Publication of Human Journals
ISSN 2349-7203
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Manjula Devi. A.S*, Mohammed Fawas, Ebin Siby, Jambulingam. P

College of Pharmacy, Sri Ramakrishna Institute of Paramedical Science, 395, Sarojini Naidu Road, Sidhapudur, Coimbatore - 641 044.

Submission: 23 November 2019
Accepted: 29 November 2019
Published: 30 December 2019

Keywords: Drug interaction, CYP450, pharmacokinetic, metabolism, inducer, inhibitor

ABSTRACT

Background: Pharmacokinetic profiles of drugs do not always follow a class effect. Therefore, all medications within a particular drug class do not have the same effect on drug substrates. This concept may be related to the management of drug-drug interactions by understanding the mechanism of interactions. **Objective and Methodology:** The study aims at identifying the best possible choice of drug management in drug-drug interactions. **Methodology:** The sensitivity of substrates as well as the strength of inhibition and induction of CYP450 coenzymes was investigated by reviewing the changes in drug clearances and area under the plasma concentration-time curve values reported in selected studies of interactions. **Results:** A total of 86 potential drug-drug interactions were identified in 120 prescriptions, of which 38 (45.78%) were pharmacokinetic interactions with 79% of known interactions altering the metabolism of substrate drugs. There were 30 substrates, 22 inhibitors, and 7 inducers of the Cytochrome P450 enzyme family. Sensitive substrates, strong inhibitors as well as strong inducers present in the prescriptions were identified. **Conclusion:** The above approach can reduce a significant number of drug-drug interactions, and it is helpful to recommend safe treatment alternatives with the right evidence.

INTRODUCTION

A drug interaction can be defined as the alteration of the pharmacological activity of a drug with the concomitant use of another drug or the presence of another substance. The drug whose activity is affected by such an interaction is called the object drug and the agent which precipitates such an interaction is referred to as the precipitant [1]. Drug-drug interactions represent an important and widely under-recognized source of medication errors and 23% of hospital admissions. [2].

The clinical pharmacists play an important role in health care settings, where they work in a team and use professional skills, knowledge and expertise to provide excellent patient care. Monitoring drug-related problems like potential drug-drug interactions (DDIs) is the most important one in patient care in hospital settings. Because DDIs are the leading cause of morbidity and mortality in hospitalized patients, it is important to evaluate potential DDIs in hospitalized patients. Moreover, the issue of drug interaction is a global concern. A US study found that 30.3% of patients had DDI in the ambulatory care unit [3]. In India, 66 percent of DDIs were found in the General Medicine section of a tertiary care hospital in Karnataka [4]. Another study in Chandigarh found that 8.3% of prescriptions had multiple DDIs [5]. Pharmacokinetic profiles of drugs do not always follow the class effect. Therefore, not all drugs of a particular drug class have the same effect on drug substrates [6]. This idea may be related to the management of pharmacokinetics drug-drug interactions. The study aims to analyze the prevalence and nature of pharmacokinetic DDIs seen in hospitalized patients in the Department of General Medicine and to recommend safe therapeutic alternatives for the management of drug-drug interactions by understanding the underlying mechanism.

MATERIALS AND METHODS

A prospective observational study was conducted in the Department of General Medicine for 10 months at 1000 bed multispecialty hospital, Coimbatore. This study protocol was approved by the Hospital Ethics Committee. Data were obtained from all inpatients in the General Medicine department with more than one prescribed medicine. Written informed consent was obtained from patients before data collection. The confidentiality of patient data was maintained throughout the study. Relevant data were obtained from patient records using customized data entry form. Prescriptions with cytochrome P450 substrates, inducers and inhibitors were recognized using the Micromedex database. We investigated the sensitivity of

the substrate to the inhibitor or inducer and the potential for enzyme inhibition or induction by reviewing selected research studies of drug interactions reported in peer-reviewed journals and the Micromedex Database.

RESULTS

Prescriptions of 120 patients from the General Medicine Department were evaluated for pharmacokinetic drug-drug interactions. The mean age of study subjects was 44.6±29.49 (range 14 to 84) years and sixty-seven were female patients. The number of medications prescribed in different age groups varied from 7.01 ± 1.09 to 8.95 ± 2.35 (range 3 to 12). Patient demographics are shown in Table 1. Various clinical conditions observed in the study population were diabetes mellitus (15.65%) followed by hypertension (13.04%), viral fever (7.82%), bronchitis (6.08%) and renal failure (5.65%). Eight hundred and ninety-eight medications in thirty-nine categories were prescribed for the subjects. Of these, anti-ulcer drugs (14.8%), antibiotics (14.25%), analgesics (9.68%), anti-emetics (7.01%), vitamins and minerals (5.79%), and antihypertensives (5.34%) were more frequently prescribed. About 79% of the interactions were known to alter the CYP450 based metabolism of the substrate drugs. Six of them alter the extent of drug absorption in the gastrointestinal tract while two were reported to affect the elimination of the substrate drugs. Thirty substrates, twenty-two inhibitors, and seven inducers of CYP450 were identified during the study as presented in Table 2. Table 3 and 4 summarizes the available reports on the sensitivity of substrates towards the inhibitors or inducers of CYP450 metabolism, the strength of inhibition/induction, mechanism of interactions, severity of interactions, and possible effects of interactions.

The substrates included ondansetron (16.66%), clopidogrel (16.66), amiodarone (10%) and theophylline (6.66%). The inhibitors of CYP450 isoenzymes recorded during the study were clarithromycin (22.72%), clopidogrel (13.63%), amlodipine (9.09%), rabeprazole (9.09%) and omeprazole (4.54%). Rifampin (57.14%) and phenytoin (42.85%) were the inducers of CYP450 enzymes present in the prescriptions.

Table No. 1: Patient demographic details (n=120)

Sl. No	Age group	No. of patients	Mean age (yrs) ± SD	Gender	No. of drugs prescribed
1	Infants (0-2)	0	44.6±29.49	Male 53	0
2	Children (3-12)	0			0
3	Adolescents (13-18)	4			8.5±1.5
4	Early Adulthood (19-35)	13			7.9±1.5
5	Adulthood (36-50)	29			8.4±2.95
6	Late Adulthood (51-65)	52		Female 67	7.1±2.45
7	Young Old (66-74)	15			7.01±1.09
8	Old (75-84)	7			8.95±2.35
9	Old (Greater than 85)	0			0

Table No. 2: Substrates, inhibitors, and inducers of CYP450 mediated metabolism (N=59)

Sl No.	Substrates	No	%	Inhibitors	No	%	Inducers	No	%
1	Ondansetron	5	16.66	Clarithromycin	5	22.72	Rifampin	4	57.14
2	Clopidogrel	5	16.66	Clopidogrel	3	13.63	Phenytoin	3	42.85
3	Amiodarone	3	10	Amlodipine	2	9.09			
4	Tramadol	3	10	Isoniazid	2	9.09			
5	Atorvastatin	3	10	Rabeprazole	2	9.09			
6	Paracetamol	2	6.66	Itraconazole	2	9.09			
7	Theophylline	2	6.66	Omeprazole	1	4.54	Total no. of		
8	Simvastatin	1	3.33	Amiodarone	1	4.54	Substrates – 30		
9	Moxifloxacin	1	3.33	Erythromycin	1	4.54	Inhibitors – 22		
10	Mefloquine	1	3.33	Ofloxacin	1	4.54	Inducers - 7		
11	Warfarin	1	3.33	Promethazine	1	4.54			
12	Gliclazide	1	3.33	Ofloxacin	1	4.54			
13	Clarithromycin	1	3.33						
14	Glibenclamide	1	3.33						

Table No. 3: Substrates and inhibitors of CYP450 mediated metabolism (N=23)

Substrate	Precipitant	No.	Frequency (%)	Strength of inhibition	Strength of substrate
Ondansetron	Clarithromycin	4	17.39	NA	NA
Amiodarone	Clopidogrel	3	13.04	NA	NA
Clopidogrel	Amlodipine	2	8.69	Moderate Inhibitor	Moderately Sensitive substrate
Paracetamol	Isoniazid	2	8.69	Weak Inhibitor	Weak Sensitive substrate
Theophylline	Clarithromycin	2	8.69	Moderate Inhibitor	Moderately Sensitive substrate
Clopidogrel	Rabeprazole	2	8.69	NA	NA
Simvastatin	Itraconazole	1	4.34	Moderate Inhibitor	Moderately Sensitive substrate
Clopidogrel	Omeprazole	1	4.34	Moderate Inhibitor	Moderately Sensitive substrate
Warfarin	Amiodarone	1	4.34	Strong Inhibitor	Strong Sensitive substrate
Atorvastatin	Erythromycin	1	4.34	Moderate Inhibitor	Moderately Sensitive substrate
Tramadol	Promethazine	1	4.34	Strong Inhibitor	Strong Sensitive substrate
Atorvastatin	Clarithromycin	1	4.34	Moderate Inhibitor	Moderately Sensitive substrate
Atorvastatin	Itraconazole	1	4.34	Moderate Inhibitor	Moderately Sensitive substrate
Gliclazide	Ofloxacin	1	4.34	Moderate Inhibitor	Moderately Sensitive substrate

NA – Reports Not Available

Table No. 4: Substrates and Inducers of CYP450 Mediated Metabolism (N=7)

Substrate	Precipitant	No.	Frequency (%)	Strength of induction	Strength of substrate
Tramadol	Phenytoin	2	28.57	NA	NA
Moxifloxacin	Rifampin	1	14.28	Moderate inducer	Moderate Sensitive substrate
Mefloquine	Rifampin	1	14.28	Strong Inducer	Strong Sensitive substrate
Clarithromycin	Phenytoin	1	14.28	Weak Inducer	Weak Sensitive substrate
Ondansetron	Rifampin	1	14.28	Moderate Inducer	Moderate Sensitive substrate
Glibenclamide	Rifampin	1	14.28	Strong Inducer	Strong Sensitive substrate

DISCUSSION

Cytochrome P450 is a family of isoenzymes responsible for the biotransformation of many drugs and is a key determinant of many drug-drug interactions. In our study, twenty three major interactions were due to the inhibition of CYP450 mediated metabolism of drugs. The substrates and inhibitors were ondansetron + clarithromycin, amiodarone + clopidogrel, clopidogrel + amlodipine, paracetamol + isoniazid, theophylline + clarithromycin, clopidogrel + rabeprazole, simvastatin + itraconazole, clopidogrel + omeprazole, warfarin + amiodarone, atorvastatin + erythromycin, tramadol + promethazine, atorvastatin + clarithromycin, atorvastatin + itraconazole, and gliclazide + ofloxacin respectively. Seven major interactions were based on the induction of CYP450 based metabolism of drugs. The CYP450 enzyme substrates and inducers recognised were tramadol + phenytoin, moxifloxacin + rifampin, mefloquine + rifampin, clarithromycin + phenytoin, and ondansetron + rifampin. A similar study reported by Ogu *et al* also mentioned about these substrates, inhibitors, and inducers [7].

The mechanism of pharmacokinetic interaction between ondansetron and clarithromycin is based on the inhibition of CYP3A4-mediated ondansetron metabolism by clarithromycin.

This may increase the risk of QT interval prolongation due to prolonged ondansetron exposure. If concurrent use is indicated, ECG monitoring is recommended. However, palonosetron is not metabolized by CYP3A4 but has almost similar pharmacokinetic and pharmacodynamic profile as that ondansetron [8]. Hence, ondansetron may be replaced with palonosetron whenever possible [9].

The simultaneous use of amiodarone and CYP2C8 inhibitors such as clopidogrel may increase plasma concentrations of amiodarone due to inhibition of CYP2C8-mediated amiodarone metabolism. Due to the long half-life of amiodarone, effects of drug interactions may persist for weeks to months after discontinuation. Thus, the coadministration of amiodarone and clopidogrel must be avoided or proper spacing between the two drugs is required [10].

Siller-Matula *et al (*2008) and Lee *et al (*2011) mentioned that calcium channel blocking agents significantly decreases the effect of clopidogrel on platelet activity by CYP3A inhibition of the activation of clopidogrel to its active metabolite, and increasing thrombotic events. Addition of cilostazol may reduce these potentially harmful interactions. Cilostazol acts as an anti-platelet agent partially by inhibiting cAMP metabolism in platelets and also by potentiating the effect of prostaglandin E1, which is different from clopidogrel's action mechanism [11]. Although the metabolism of cilostazol is mainly by CYP3A4 and 5, cilostazol is not a prodrug unlike clopidogrel; so the effect of cilostazol may be less influenced by CYP3A pathway-dependent drugs. Caution is advised if clopidogrel and calcium channel blockers such as amlodipine are used simultaneously [12].

Epstein *et al* has conducted a study to investigate the effect of isoniazid on acetaminophen kinetics and metabolism. The result of the study shows that isoniazid is a potent inhibitor of the oxidative metabolism of paracetamol, thus decreasing the exposure to the formed oxidative metabolite, NAPQI, which is a major hepatotoxin. This significant inhibition of paracetamol by isoniazid has resulted in decreasing the total clearance of paracetamol by 15%. If concurrent therapy is needed, administration of a different analgesic such as aceclofenac may be considered [13].

Pharmacokinetic interactions between older macrolides and theophylline may be caused by inactivation of CYP3A and inhibition of theophylline acquisition into hepatocytes.

Azithromycin may be substituted as it does not appear to affect the disposition of theophylline derivatives [14].

Rabeprazole may reduce the risk of GI bleeding in patients treated with clopidogrel. However, studies indicate that PPIs reduce the antiplatelet effect of clopidogrel. The reason for this reaction is the inhibition of the CYP450 isoenzyme 2C19 by rabeprazole. This can significantly reduce the serum concentrations of clopidogrel's active metabolites. Studies have shown that pantoprazole is a low-risk alternative to rabeprazole [15].

Fichtenbaum *et al* explains the interaction of simvastatin, whose concentration has been reported to increase 20-30 folds with the addition of itraconazole, a moderate inhibitor of CYP3A4. Itraconazole reduces the formation of active and inactive metabolites during first pass metabolism resulting in increased bioavailability of the simvastatin. The author recommends avoiding simvastatin and initiating atorvastatin at doses of 10 mg/day and should not exceed 40 mg/day. Dose escalation should be based on clinical indication [16].

In a study on drug interactions between clopidogrel and proton pump inhibitors, Norgard *et al* highlighted that individual PPIs differ in their metabolism profiles and that clopidogrel is rapidly and widely metabolized by CYP3A4 and CYP2C19. Omeprazole has 10 times greater affinity to CYP2C19, and its binding is stronger with a greater potential for competitive inhibition. Pharmacodynamic studies suggest that omeprazole reduces the antiplatelet effects of clopidogrel. Pantoprazole is the drug of choice when a PPI is required with clopidogrel because it has little effect on the metabolism of clopidogrel and has been identified as a PPI that is not associated with the risk of MI in patients taking clopidogrel [17].

Being a potent inhibitor of a number of cytochrome p450 enzymes, amiodarone has shown to interfere with the metabolism of warfarin and may result in increased INR and an increased risk of bleeding. Hence it is necessary to reduce the maintenance dose of warfarin by about 30% when initiating amiodarone and closely follow the INR for a period of at least 4–8 weeks, and adjust the warfarin dose accordingly, until a new steady-state is achieved[18].

Studies have shown that steady-state erythromycin increased the Cmax and AUC values of a single 10 mg dose of atorvastatin by 37.7% and 32.5%, respectively [19]. This may result in increased atorvastatin exposure and an increased risk of myopathy or rhabdomyolysis. When possible, substitute atorvastatin (a CYP3A substrate) with a statin independent of CYP3A metabolism, such as fluvastatin or pravastatin[20].

Ping *et al* observed several pharmacokinetic interactions between tramadol and promethazine. The AUC of tramadol was found to decrease more than 30% by concomitant administration of promethazine [21]. Therefore, promethazine may be replaced with palonosetron, 5-HT_3 antagonist.

The coadministration of clarithromycin with atorvastatin significantly increased atorvastatin exposure. Subjects receiving atorvastatin 80 mg daily for 8 days who were coadministered clarithromycin 500 mg twice daily had a 4.4-fold increase in atorvastatin AUC. Clinically significant rhabdomyolysis was reported by patients treated with atorvastatin and clarithromycin concomitantly. If myopathy or rhabdomyolysis is diagnosed or suspected, or if creatine kinase (CK) levels show a marked increase, temporarily withhold atorvastatin. If treatment with clarithromycin is required, atorvastatin, a CYP3A substrate may be substituted with a statin such as fluvastatin or pravastatin which are independent of CYP3A metabolism [22].

Kantola *et al* conducted a study on 10 healthy volunteers, identifying the pharmacokinetic effect of itraconazole on atorvastatin. The study reports that itraconazole increased the mean AUC of total HMG-CoA reductase inhibitors by 1.7-fold. This effect may be associated with increased risk of myopathy or rhabdomyolysis. Alternative HMG-CoA reductase inhibitors that are less likely to interact with itraconazole include fluvastatin, rosuvastatin, pitavastatin, and pravastatin [23].

Increase in serum concentrations of gliclazide and the potentiation of hypoglycemic effect of oral antidiabetic agents due to the inhibition of CYP2C9 isoenzyme system by ofloxacin was reported by Thumugant*iet al.* Ofloxacin enhanced the hypoglycaemic activity of gliclazide on multidose treatment and significant alterations in pharmacokinetic parameters were observed. There was about 49.4%, 52.9%, 26.8% increase in Cmax, AUC total and MRT respectively. Clearance and volume of distribution have decreased by 54.5% and 52.5%. Therefore, monitoring and dose adjustment of gliclazide may be necessary [24].

Coadministration of tramadol and phenytoin necessitate close monitoring of patients for decreased efficacy or signs of opioid withdrawal syndrome due to the induction of CYP3A4-mediated tramadol metabolism, resulting in reduced tramadol exposure. Therefore, increased dose of tramadol may be necessary [25].

In a study by Nijin *et al* in Indonesian patients with tuberculosis, co-administration of moxifloxacin with intermittent rifampicin resulted in a 31% decrease in the exposure to moxifloxacin plasma concentrations, most likely due to rifampicin induced glucuronidation or sulfation. Avoid concurrent administration of moxifloxacin and rifampicin and space between the two drugs may be considered [26].

Sousa *et al* reported that rifampin induces mefloquine metabolism, decreasing its AUC by 68% and half-life by 63%. Importantly, the AUC and clearance of mefloquine metabolite has substantially increased by 30% and 25%, respectively. Rifabutin may be considered as an alternative option when concomitant use is necessary [27].

Concurrent use of phenytoin and clarithromycin may result in reduced clarithromycin exposure and efficacy due to the induction of CYP3A4 mediated metabolism of clarithromycin. Erythromycin tends to be a safer option when co-administering a macrolide with phenytoin [28].

A randomized crossover study in 10 healthy volunteers suggested that rifampin may cause a clinically significant interaction with ondansetron, a potent antiemetic agent. After the administration of rifampin, the AUC of oral and IV ondansetron decreased by 65% and 48%, respectively. Rifampin decreased the Cmax of oral ondansetron by 50% and increased iv ondansetron clearance by 83%. Thus, concomitant use of rifampin with ondansetron may result in a reduced antiemetic affect. Ondansetron may be replaced with palonosetron, which has an almost identical pharmacokinetic and dynamic behavior but is not metabolized by CYP3A4 [29]**.**

Induction of CYP2C9 may result in decreased glibenclamide efficacy. For better blood glucose control, we need to monitor the combination therapy and increase the dose of sulfonylurea [30].

A preclinical study indicated that verapamil increases the accumulation of digoxin in the rat heart and potentiates the positive inotropic effects of digoxin[31]. Moreover, verapamil was reported to reduce the renal and extrarenal clearance of digoxin. A potentially toxic interaction has been reported by Hamann *et al*, in which renal excretion of the glycoside was impaired [32].

The study has identified warfarin, tramadol, mefloquine and glibenclamide as sensitive substrates, while amiodarone and promethazine as strong inhibitors and rifampin as the strong inducer of CYP450 enzyme substrates. In a study by Joseph *et al* [32], Warfarin was found as the major substrate of CYP2C9 isozyme, amiodarone as strong inhibitors of CYP2C9, CYP2D6, and CYP3A and Rifampin as a CYP2C9 isozyme inducer.

CONCLUSION

Majority of the pharmacokinetic drug-drug interactions were based on the mechanism of inhibition of the cytochrome P450 enzymes. The isoenzymes more commonly involved in such interactions were the CYP3A4 followed by CYP2C9 and CYP2C19. However, other isoenzymes such as CYP2C8, CYP2E1, CYP1A2, and CYP2D6 were also involved. Interactions of warfarin, tramadol, mefloquine and glibenclamide, amiodarone, promethazine and rifampin often involve the CYP450 enzymes. Drug combinations should be judiciously chosen in order to avoid drug-drug interactions. Knowledge of the CYP450 isoenzymes involving the metabolism of interacting drugs can help minimize the possibility of drug-drug interactions and adverse drug reactions.

FUNDING: *No funding sources.*

CONFLICT OF INTEREST: *No conflicts of interest*

ETHICAL APPROVAL: *The study was approved by the Institutional Ethics Committee (EC/2019/0503/CR/08).*

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