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A Study of Potential Drug-Drug Interactions in Indoor Patients of Medicine Department at a Tertiary Care Hospital

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ABSTRACT

Drug interactions are an important cause of medication errors. The present study was conducted to evaluate the nature and clinical significance of potential drug-drug interactions (DDIs) in inpatients of Medicine Department at a tertiary care hospital in India. The second day prescription of every alternate indoor patient from five randomly selected medical units of a tertiary care hospital were collected. Prescriptions were analyzed for potential DDIs using the web based interaction checkers of Medscape and Current Index of Medical Specialties. The average numbers of drugs per prescription and potential DDIs per prescription and the types, age wise distribution and clinical significance of the potential DDIs were evaluated. A total of 3405 potential DDIs were detected in 257 prescriptions. An average 8.28 drugs were prescribed per prescription. The most common drug groups involved in potential DDIs were diuretics (n=255), NSAIDs (n=225), β blockers (n=143), cardiac glycosides (n=129) and statins (n=122). Potential DDIs were most frequent in patients between 61-75 years of age. The clinical significance was graded as serious (n=123), significant (n=949), minor (n=2328) and contraindicated (n=5). An increased risk of rhabdomyolysis (n=41) and an increase in QTc interval (n=38) were the most common potentially serious DDIs detected. Of the 1077 DDIs (excluding minor DDIs), 615 were pharmacodynamic and 462 were pharmacokinetic interactions. Potential DDIs increased with an increase in the number of prescribed drugs. Improved awareness among prescribers is required to reduce the risks associated with DDIs. Use of drug groups, commonly involved in potential DDIs, should be minimized and optimized while prescribing.

INTRODUCTION

Drug interactions are one of the important factors that modify the response to a drug (Tripathi, 2010). A drug interaction is said to occur when the effects of a drug is altered by another drug(s), food, drink or an environmental chemical (Bista et al., 2006). Drug-drug interactions (DDIs) are defined as the modifications of the effect(s) of one drug by the prior or concomitant use of another drug. These are important, yet under-recognized contributors to medication errors. The risk of DDIs increases with an increase in number of drugs prescribed (Tripathi, 2010) and is estimated at approximately 6% when two to four drugs are used, 50% with five drugs and nearly 100% when eight drugs are prescribed (Raich et al., 1997). It is difficult to estimate the incidence of DDIs as the data regarding drug-related hospital admissions are focused mainly on ADRs (Gillespie, 2012). Drug interactions can occur both in vivo and in vitro. Drug interactions outside the body can occur when different drugs are mixed in an intravenous infusion. Drug interactions inside the body can be pharmacodynamic or pharmacokinetic in nature (Satoskar et al., 2011). Pharmacodynamic interactions affect the pharmacological effect of drug involved. These interactions result in synergism, antagonism, alteration of effect or an immune mediated idiosyncracy. Pharmacokinetic interactions affect absorption, distribution, metabolism or elimination (Mallet et al., 2007). Irrespective of the mechanism and type, if combination therapy leads to an unexpected change in condition of the patient, it is labeled as an interaction of potential clinical significance (Bista et al., 2006). The type and number of medicines prescribed in India differs from the West and other countries. Currently, data regarding the incidence of potential DDIs in Indian settings is limited. The present study was therefore carried out to evaluate the potential DDIs and their clinical significance in inpatients of the medicine department of a tertiary care hospital. We hope to identify

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potentially serious and significant DDIs along with the common drug groups involved. The information could prove useful to suggest modifications in the prescribing patterns and to optimize drug therapy in these patients.

AIMS AND OBJECTIVES

The present study was designed to evaluate the potential DDIs in inpatients of medicine department at a tertiary care hospital with particular reference to potentially serious and significant DDIs, evaluation of the nature and mechanism of these interactions and identification of common causal drug groups for these interactions.

MATERIALS AND METHODS

This was a single point observational, prospective study carried out in the medicine department of a tertiary care hospital in India. Of the ten medical units of Medicine department, five were randomly selected for evaluation of prescriptions. Permission of Heads of the respective medical units was taken to collect the data for the study. The prescriptions were selected by simple randomization. The second day prescription of every alternate patient admitted to the selected units was collected over a period of six months between November 2011 to April 2012. Illegible prescriptions which could not be deciphered were excluded. The collected prescriptions were evaluated for potential DDIs using web based drug interaction checkers of Medscape (Medscape, 2013) and CIMS (Current Index of Medical Specialities) (CIMS, 2012). Medscape is a freely available web resource for physicians and other health professionals, featuring articles, CME, drug database, drug interaction checker, etc. CIMS is another freely available web based source of drug information, which provides information about the available drug products with reference to brand and generic names, composition, data regarding clinical use and drug interactions. The clinical significance of interactions was classified into four categories: (i) Contraindicated (drugs which should not be co administered), (ii) Serious (interactions which require alternate drugs to be administered) (iii) Significant (close monitoring for interaction is required) and (iv) Minor (interactions which are not significant and do not require any change in treatment) (Medscape, 2013). The prescriptions were analyzed for the total number of potential DDIs, number of drugs per prescription, the number of potentially serious and significant DDIs and age wise incidence of potential DDIs. The prescriptions were further evaluated for the nature and possible mechanism of DDIs and the common drug groups involved. IBM SPSS Statistics (version 20) and GraphPad InStat (version 3.10) softwares were used for analysis.

RESULTS

A total of 257 prescriptions were analyzed. In majority of these (n=114, 44.35%), 1 to 10 potential DDIs were detected. A total of 3405 drug-drug Interactions (DDIs) were detected, which were classified as serious (n=123), significant (n=949), minor (n=2328) and contraindicated (n=5) (Medscape, 2013). An average of 8.28 ± 2.77 drugs were prescribed per prescription with an average of 13.30 ± 11.07 potential DDIs per prescription. These included 19 prescriptions with less than 5 drugs (average 3.57 ± 0.50 drugs with 1.94 ± 1.95 average potential DDIs), 98 prescriptions with 5-7 drugs (average 6.40 ± 0.64 drugs with 7.06 ± 5.75 average potential DDIs) and 140 prescriptions with 8 or more drugs (average 10.23 ± 2.12 drugs with 19.22 ± 11.04 average potential DDIs). Most number of potential DDIs in a single prescription was 59, which included 13 drugs. No potential DDIs were detected in eleven prescriptions (Figure 1). The average number of potentially serious and significant interactions per prescription was 0.478 and 3.76 respectively. The average number of drugs prescribed (9.26 ± 2.97) and the number of potential DDIs (15.91 ± 13.88) per prescription were highest in the prescriptions of patients of age group of 61-75 years. The average number of the drugs prescribed and number of potential DDIs increased with an increased age of patients (Table 1). A positive correlation was detected between age of the patients and the number of drug prescribed (Correlation coefficient (r) = 0.1782, p = 0.0051). Similarly the number of potential DDIs increased with the number of drugs prescribed (Correlation coefficient (r) = 0.7909, p value < 0.0001) [Figures 2 and 3]. No significant correlation was detected between age of the patient and the number of potential DDIs (Correlation coefficient (r) = 0.08740, p = 0.1727). The serious (n=123), significant (n=949) and contraindicated (n=5) DDIs were analyzed for their mechanism of interaction. These included a total of 615 pharmacodynamic and 462 pharmacokinetic DDIs.

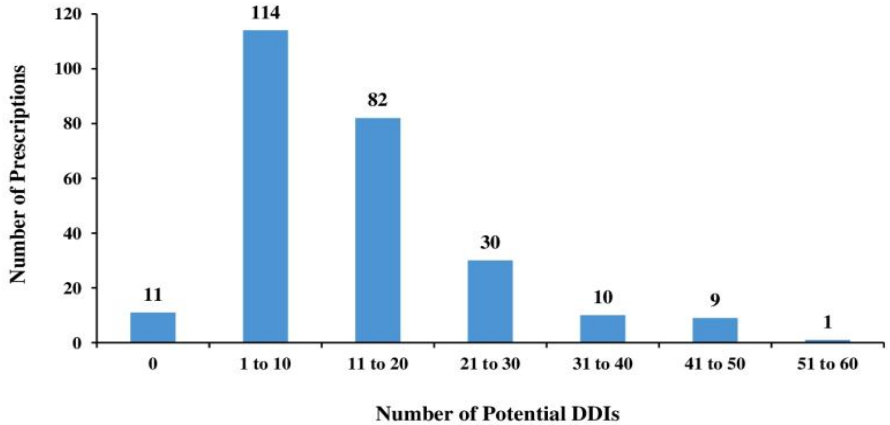

Fig. 1: Number of Potential DDIs detected from prescriptions for inpatients (n=257) of Medicine Department at a Tertiary Care Hospital.

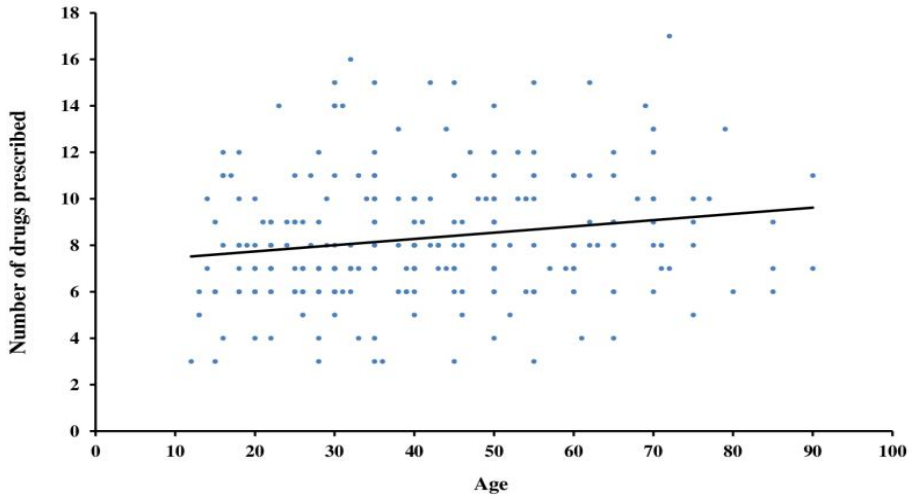

Fig. 2: Age wise distribution of number of drugs prescribed in Medicine Department of a Tertiary Care Hospital.

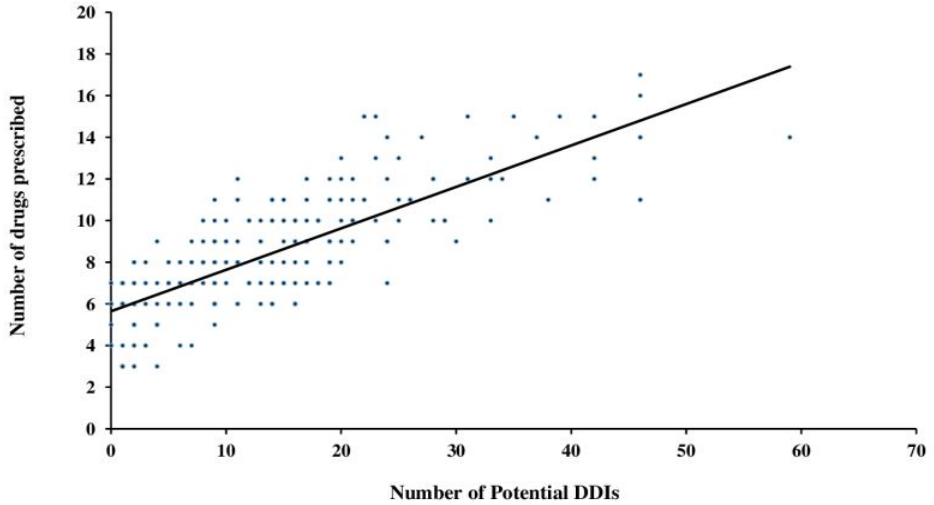

Fig. 3: Potential DDIs with reference to the number of drugs prescribed in Medicine Department of a Tertiary Care Hospital.

Table. 1: Age wise distribution of the number of drugs prescribed and potential DDIs in Medicine Department of a Tertiary Care Hospital.

Age (in years)	Total number of prescriptions (n=245)*	Average number of drugs prescribed	Average number of potential DDIs
0-15	9	6.11 ± 2.37	10.77 ± 9.28
16-30	77	7.85 ± 2.49	11.88 ± 10.62
31-45	65	8.49 ± 2.90	13.73 ± 10.77
46-60	52	8.50 ± 2.57	14.25 ± 9.96
61-75	34	9.26 ± 2.97	15.88 ± 13.82
76-90	8	8.62 ± 2.56	12.00 ± 12.98

* Age of patient was not recorded in 12 patients.

Table. 2(A): Serious Potential Pharmacodynamic DDIs detected from prescription in a Tertiary Care Hospital.

Mechanism	Potential Effect	Effect of DDI	Drug Groups	Number of DDIs
Synergism	Increased risk of toxicity	Increased risk of Rhabdomyolysis	Vitamin + Statin	41
		Increased Hepatotoxicity	Rifampin + Pyrazinamide	7
		Prolongation of QTc Interval	Macrolide + Antiemetic	18
			Quinolones + Antiemetic	16
			Antidepressant + Antiemetic	2
			Others	2
	Increase in therapeutic effect of one drug	Increased antihypertensive effect	(α + β) blocker + β blocker	1
		Increased anticoagulant effect	Cephalosporin + anticoagulant	1
		increased anticoagulant effect	anticoagulant + anticoagulant	1
Antagonism	Decreased therapeutic effect of one drug	Decreased antiplatelet effect of aspirin	Ibuprofen + aspirin	2
		Decreased Antihypertensive effect of Methyldopa	Antiemetic + Methyldopa	1

Table 2(B): Significant Potential Pharmacodynamic DDIs detected from prescription in a Tertiary Care Hospital.

Mechanism	Potential Effect	Effect of DDI	Drug Groups	Number of DDIs
Synergism	Decrease in serum potassium	Hypokalemia	β_2 agonist + Diuretic	15
			Others	2
	Increase in serum potassium	Hyperkalemia	β blocker + Aspirin	23
			β blocker + K^+ sparing diuretic	15
			K^+ sparing diuretic + Aspirin	12
			Aspirin + Cardiac glycoside	10
			ACE inhibitor + K^+ sparing diuretic	10
			K^+ sparing diuretic + Cardiac glycoside	9
			Others	22
	Increased effect of one or both drugs	Increased antihypertensive effect	ACE Inhibitors + Diuretic	22
			β blocker + CCB	13
			Diuretic + Cardiac glycoside	11
		Increased anticoagulant effect	Aspirin + Antiplatelet	18
			Anticoagulant + Antiplatelet	18
		Others	Others	54
	Increase in toxic effect of one or both drug	Prolongation of QTc Interval	Macrolide + Antiemetic	2
		Increased renal toxicity	ACE Inhibitor + Aspirin	29
		Others	Others	13
Antagonism	Altered serum potassium	fluctuation in serum potassium level	Aspirin +Diuretic	28
			K+ sparing diuretic + diuretic	28
			β blocker + diuretic	21
			Aspirin + β_2 agonist	13
			Cardiac glycoside + diuretic	11
			Others	16
	Decrease in therapeutic effect of drug	decreased antihypertensive effect	Aspirin + ACE inhibitor	29
			Aspirin + β blocker	22
		Others	Others	41

*ACE inhibitor: Angiotensin Converting Enzyme inhibitor, CCB: Calcium Channel Blocker, K+ sparing diuretic: Potassium Sparing Diuretic.

Table. 3: Potential Pharmacokinetic DDIs detected from prescription in a Tertiary Care Hospital.

Severity	Mechanism affecting	Potential effect of DDI	Drug groups	Number of DDIs
Serious	Absorption	Increased absorption	Antacids + Cardiac glycoside	6
			Others	3
		Decreased absorption	Antiemetic + α agonist	1
			$NaHCO_3$ + levofloxacin	1
			RL + levofloxacin	1
	Metabolism	Increased metabolism	Rifampin + Isoniazid	7
		Decreased metabolism	AKT + steroid	3
			AKT + BZDs	2
			Macrolide + anticoagulant	2
			Others	3
	Excretion	Decreased elimination	CCB + cardiac glycoside	2
Significant	Absorption	Increased absorption	Statin + steroid	10
			K^+ sparing diuretic + statin	9
			K^+ sparing diuretic +cardiac glycoside	9
			Others	39
		Decreased absorption	Macrolide + vitamin	35
			PPI + Iron preparation	14
			Antiemetic + Statin	11
			Others	27
	Distribution	Altered plasma protein binding	β lactam antibiotic + Aspirin	13
			Aspirin + antiepileptic	4
			Others	4
	Metabolism	Increased metabolism	Antiepileptic + antiemetic	26
			Antiepileptic + BZDs	16
			Antiepileptic + statin	11
			Steroid + statin	10

*****AKT: Anti Koch's Therapy, BZDs: Benzodiazepines, RL: Ringer's Lactate, K^+ sparing diuretic: Potassium Sparing Diuretic, PPI: Proton Pump Inhibitor, NSAIDs: Non Steroidal Anti-inflammatory Drugs, CCB: Calcium Channel Blocker.

Table 4: CYP450 enzyme subtypes detected in common significant potential drug-drug interations.

Potential DDIs	Number of DDI
CYP3A4	
Antiepileptic + Antiemetic	26
Antiepileptic + BZDs	15
AKT + Antiemetic	14
Antiepileptic + Statin	11
Steroid + Statin	10
Nitroimidazole + Statin	7
Others	44
CYP2C9/10	
Nitroimidazole + Antiepileptic	8
Antiepileptic + Antiepileptic	5
Others	5
CYP1A2	
AKT + Antiemetic	7
CCB + Anticoagulant	3
Antiepileptic + Antiemetic	2
CYP2E1	
Nitroimidazole + AKT	3
AKT + NSAIDs	2
CYP2C19	
AKT + PPI	7
AKT + BZDs	1

*AKT: Anti Koch's Therapy, BZDs: Benzodiazepines, CCB: Calcium Chanel Blocker, PPI: Proton Pump Inhibitor.

Potential Pharmacodynamic DDIs

Of the 615 potential pharmacodynamic interactions, 92 were serious and 523 were significant. Two types of pharmacodynamic interactions i.e. synergism and antagonism were detected. Of the 92 serious potential DDIs, 89 showed synergism and 3 showed potential antagonism between drugs. Of the 89 interactions showing potential synergism, majority (n=86) showed an increased risk of toxicity of drugs involved, while a possible increase in therapeutic effect was observed in three DDIs. The most common synergistic reactions were increased risk of rhabdomyolysis (n=41) and a potential increase in QTc interval (n=38). Among the reactions showing potential antagonism (n=3), a potential decrease in the therapeutic effect was detected [Table 2(A)]. A total of 523 significant potential pharmacodynamic DDIs were detected, of which 298 were synergistic and 209 had a potential for antagonism. Mechanism of 16 significant potential DDIs were unspecified. Among the synergistic reactions, the different interactions included a potential increase in serum potassium levels by both drugs (n=101), a potential increase in therapeutic effect of one drug (n=136), an increased risk of toxicity of one drug (n= 44) and a potential decrease in serum potassium levels by both drugs (n=17). Potential DDIs showing antagonism included an alteration of serum potassium level by the drugs (n=117) or decreased therapeutic effect of one drug (n=92) [Table 2(B)].

Potential Pharmacokinetic DDIs

A total of 462 potential pharmacokinetic DDIs (31 serious and 431 significant) were observed. Of the 31 serious potential pharmacokinetic DDIs, 17 had the potential to affect metabolism, 12 could affect absorption and two could affect excretion of the drugs (Table 3). A total of 431 significant potential pharmacokinetic DDIs were detected: 186 that could affect the metabolism, 154 affecting absorption, 57 affecting excretion and 21 with a potential to affect distribution of the drugs. Mechanism of 8 significant DDIs was not specified in the drug interaction checkers used (Table 3). Of the 186 significant potential DDIs, 170 were shown to affect CYP450 enzymes (Table 4). Common enzymes involved in these interactions were CYP3A4 (n=127), CYP2C9/10 (n=18), CYP1A2 (n=12), CYP2C19 (n=8) and CYP2E1 (n=5).

Five potential contraindicated DDIs were detected which could affect the distribution of drugs. The drug groups involved were cephalosporin and Ringer's Lactate, leading to a risk of precipitation of cephalosporin-calcium complex in vivo.

DISCUSSION

Drug interaction is recognized as an important cause of medication errors. Different types of drug interactions includes drug-drug interactions, drug food interactions, drug disease interactions and drug herb interactions. Of these, drug-drug interactions (DDI) are most important in terms of frequency and severity (Bista et al., 2006). A review of nine studies suggested the reported incidence of hospitalization due to DDIs of 0-2.8% (Jankel and Fitterman, 1993). Also, it has been shown that nearly 1% of all hospitalized patients suffer an adverse drug event due to DDI during hospitalization and DDIs account for nearly 17% of adverse drug events in hospitalized patients (Zwart-van Rijkom et al., 2009). Potential DDIs are more frequent in elderly women more than 55 years of age (Cruciol-Souza and Thomson, 2006). The cost of treating drug related problems in US has increased from $76.6 billion in 1994 (Johnson and Bootman, 1995) to $177.4 billion by the year 2000 (Ernst and Grizzle, 2001). Currently, data regarding types and frequency of potential DDIs in Indian settings is limited. Also, the prescribing pattern for most diseases differ in India vis a vis the western and other countries. Hence, the present study was conducted to evaluate the potential DDIs in inpatients of medicine department with reference to their nature, mechanisms, clinical significance and common drug groups involved.

This single point observational study was conducted in inpatients of five randomly selected medical units of a tertiary care teaching hospital in India for a period of six months. The prescriptions of every alternate patient was evaluated for potential DDIs using freely accessible web based drug interaction checkers of Medscape (Medscape, 2013) and Current Index of Medical Specialities (CIMS) (CIMS, 2012), the average number of drugs prescribed, average number of potential DDIs per prescription and age wise distribution of potential DDIs.

A total of 257 prescriptions were analyzed. A total of 3405 potential DDIs were detected, which were graded according to severity as serious, significant, minor and contraindicated (Medscape, 2013). Nearly one third of potential DDIs were either serious or clinically significant. Polypharmacy was frequent in the

present study with more than 50% prescriptions consisting of more than eight drugs and only 7.39% with less than five drugs. The average number of drugs prescribed per prescription was 8.28. Polypharmacy was also observed in a study conducted in geriatric hospitalized patients at Nepal (Joshi et al., 1997). Polypharmacy increases the risk of DDIs (Lin et al., 2011) and ADRs (Satoskar et al., 2011) and hence should be avoided. An average of 13.30 potential DDIs were detected per prescription in the present study. The risk of DDIs increases with an increase in number of drugs prescribed (Tripathi KD, 2010). Accordingly, the average number of potential DDIs per prescription increased from 1.94 in prescriptions with less than five drugs to 19.22 in prescriptions with more than eight drugs.

Literature suggests that DDIs are more common in patients aged more than 55 years (Cruciol-Souza and Thomson, 2006). A study from Sweden had reported an incidence of DDIs of 31% in elderly patients with an average age of 78.2 years (Bergendal et al., 1995). Similarly, at least one potential DDI was detected in 46% of 1601 elderly outpatients in a study conducted in six European countries (Bjorkman et al., 2002). In the current study also, the average number of drugs prescribed and the average number of potential DDIs per prescription increased with increasing age of the patient. Patients between 61-75 years of age were prescribed most number of drugs per prescription and these prescriptions also had maximum number of potential DDIs per prescription (an average of 15.88). The higher number of potential DDIs in this group can be attributed to higher number of drugs prescribed per prescription. Whether the higher number of drugs is necessary in these age groups depends on the clinical diagnosis, however a caution must be exercised while selecting drugs in these patients to avoid the risks associated with potential DDIs. A total of 615 pharmacodynamic potential DDIs (92 serious and 523 significant) were detected. These had the potential to increase or decrease the therapeutic effect, alter the serum potassium levels and increase possibility of ADRs like prolongation of QTc interval.

An increased risk of rhabdomyolysis was detected due to a potential DDI between niacin and statins. Clinically significant rhabdomyolysis can be life threatening (Schreiber DH and Anderson TR, 2006) and the actual incidence of statin-induced rhabdomyolysis is believed to be higher than that reported in the clinical trials as high risk subjects are usually excluded in such trials (Antons et al., 2006). Also, less severe symptoms are often underreported and they can occur in 1-5% of patients receiving statins (Dirks and Jones, 2006). The risk of statin induced myopathy is increased by niacin (Bersot TP, 2011). Multivitamins are frequently used as placebos despite of the fact that they have the potential to cause ADRs and DDIs (Tripathi, 2010). These were frequently prescribed in the present study also, thereby increasing the risk of DDIs. Unnecessary use of multivitamins should therefore be restricted. Also, monitoring for symptoms of myopathy is advisable in such patients .

Ondansetron was also a frequently prescribed drug in the present study. It is known to increase QTc interval (Williams et al., 1991; Charbit et al., 2008) and can lead to serious interactions when co administered with other drugs which can increase QTc interval. QTc prolongation is an important adverse event with some commonly used drugs like fluroquinolones, quinidine, choloroquine, haloperidol etc (University of Arizona Center for Education and Research on Therapeutics, 2013) and many drugs have been withdrawn from the market due to this effect e.g. Grepafloxacin (Ball, 2000) and Mibefradil (SoRelle, 1998). In the present study, a potential for QTc prolongation was detected due to co prescription of ondansetron with certain antimicrobials and antidepressants. Here, either ondansetron or the interacting drug can be advised to be withdrawn or replaced with safer drug. This type of combination therapy should strongly be avoided in patients prone to arrhythmias. Also, close monitoring for development of arrhythmia is warranted. A similar recommendation can be made for prescription of other drugs with a potential for QTc prolongation.

A potential increase in the risk of toxicity of one or more drug was common when antitubercular drugs were prescribed together. Also, a possible increased risk of renal toxicity of aspirin was detected when co prescribed with drug groups like ACE inhibitors and AR blockers. This type of interaction can be particularly important in elderly patients with compromised renal function. Proton pump inhibitors were detected to increase the risk of toxicity of cardiac glycosides by producing hypomagnesemia. These problems can be overcome by avoiding or minimizing the co-administration of drugs likely to increase the toxicity of other drug. In cases where this may not be possible e.g. anti tubercular drugs, close monitoring with individualization of doses is essential for early detection of potential adverse effects. Certain DDIs in the study had the potential to increase the therapeutic effect of the concomitant drugs. These interactions included beta blockers with combined alpha plus beta blockers or calcium channel blockers; ACE inhibitors with diuretics; diuretics with cardiac glycoside, anticoagulants with cephalosporins or anti platelet agents and aspirin with other anti platelet agents. While these types of interactions can beneficially increase the therapeutic effect, the risk of ADRs may also be increased. E.g. antihypertensives are known to be associated with orthostatic hypotension in elderly patients and patients with symptomatic postural changes in blood pressure (Verhaeverbeke and Mets, 1999) and exaggerated hypotension may occur when antihypertensives are combined together. Similarly, an increased risk of bleeding may be present in interactions involving anticoagulant drugs. While it may not be necessary to withdraw these drugs, an awareness of these potential interactions can help optimize the drug therapy by decreasing the individual dose and monitoring for development of ADRs. An individualized patient approach, close monitoring of doses and laboratory investigations e.g. coagulation parameters are also required in such cases. Antagonism i.e. a decrease in the effect of one or both drugs was detected between drugs like NSAIDs with aspirin, aspirin with ACE inhibitors or Beta blocker or ARB, beta blockers and beta agonists, aspirin with vitamin K_1 and steroids with anticoagulants**.** Interaction of such nature can result in

potential therapeutic failure and a careful titration of doses is required to prevent this risk. Clinical and laboratory monitoring and an increased awareness among prescribers is required to ensure optimal drug therapy in such cases. A potential risk of alteration of serum potassium levels was also commonly detected in the present study when different drug groups were co prescribed. Commonly involved drug groups in such interactions were beta blockers, diuretics, ACE inhibitors, aspirin and cardiac glycosides. Close monitoring of serum potassium levels in these patients is recommended to minimize risk of hypokalemia or hyperkalemia and the serious consequences associated like arrhythmias (Weiner and Wingo, 1997), paralytic ileus (John et al., 2011) etc. Also, minimizing or avoiding the use of drug groups prone to alter serum potassium level is recommended. A total of 462 potential pharmacokinetic DDIs were observed in this study. Increased absorption of drug results in higher plasma concentration of the drug, which increase the risk of ADR and toxicity. A potential for increased absorption of cardiac glycoside was observed with H_2 blockers, proton pump inhibitors, potassium sparing diuretics and statins. Increased levels of cardiac glycosides are known to cause ventricular fibrillation (Tripathi, 2010). Considering the serious nature of these interactions; use of alternate drugs was suggested. Also, minimal use of drugs which reduce the gastric acid secretion is recommended. Other common potential interactions leading to increased absorption of drug were detected with K^+ sparing diuretics, statins, corticosteroids and macrolide antibiotics. Careful titration of doses of these drugs is required to minimize the risk in these patients. Potential interactions leading to decreased absorption of one drug by another was commonly detected with macrolides, vitamin B complex, PPIs, iron salts, antiepileptics, RL, fluoroquinolones, AKT, corticosteroids, aminoglycosides and statins. Decreased absorption of the drug may result in low plasma concentration and therapeutic failure. This factor is even more so important in cases of antimicrobials as sub-therapeutic concentration of these drugs can lead to development of drug resistance.

Drug displacement reactions are common between drugs having high amount of plasma protein binding. In the present study, a potential alteration in distribution of one drug by another by competing for plasma protein binding was common between drug groups like NSAIDs, β lactam antibiotics and antiepileptics**.** All these drugs show high plasma protein binding. Accordingly, interactions with drugs that compete for the same plasma protein binding site were evident. Drug displacement reactions can result in toxicity of the drug**,** which can be particularly important with drugs like antiepileptics, having a low therapeutic index and a potential for serious ADRs. Therapeutic drug monitoring is recommended for these drug groups if interacting drugs are co-prescribed.

FDA has issued an alert that ceftriaxone should not be administered with calcium containing solutions within 48 hours of one another, as there had been cases of serious cardiopulmonary events associated with the precipitation of ceftriaxone-calcium salt in the lungs and kidney in neonates (Drug Safety Newsletter, 2009). Ringer's lactate contains calcium chloride (http://www.lavoisier.com/fic_bdd/pdf_en_fichier/12133485550_Ringer_Lactate_En.pdf, 2013). Ceftriaxone and Ringer's lactate are commonly prescribed drugs. A potential interaction between RL and ceftriaxone was detected in five cases. Although the number of cases in which these drugs were co prescribed were less, considering the serious nature of the interaction, an increased awareness of this potential interaction is warranted among prescribers.

A possible risk of increased metabolism was detected between antitubercular drugs; AKT with antiemetic; K^+ sparing diuretics with cardiac glycosides and nitroimidazole antibiotics with antiepileptics and statins. Similarly, some drug groups were detected to have the potential to decrease the metabolism of other drugs e.g. AKT decreasing the metabolism of steroids, benzodiazepines, antiemetic, PPIs and statins; antiepileptics reducing the metabolism of antiemetic, benzodiazepines and statin and macrolide and nitroimidazole decreasing the metabolism of anticoagulants. Increased metabolism of a drug requires an increase in the dosing and close monitoring of the patient. On the other hand, reduced metabolism of a drug may warrant a decrease in dose to avoid toxicities. This has to be supplemented by suitable laboratory tests to ensure optimum treatment of the patients. The CYP450 enzymes implicated in these interactions were CYP3A4, CYP2C9/10, CYP1A2, CYP2C19 and CYP2E1.

Altered excretion of one drug by another was detected as a potential DDI between several drug groups e.g. CCBs with cardiac glycosides, β lactam antibiotics with NSAIDs and vitamins and potassium sparing diuretics with cardiac glycosides. The common mechanisms involved in these interactions were one drug affecting reabsorption or renal tubular secretion of the other drug. The drugs that are predominantly secreted by renal tubules or are reabsorbed in kidney are primarily involved in these reactions e.g. β lactam antibiotic, cardiac glycoside, NSAIDs, diuretics etc. Altered excretion of a drug can manifest as therapeutic failure or drug toxicity. A close monitoring of renal function and individualization of doses is indicated in patients who are co-prescribed these drug groups, to prevent such complications.

CONCLUSION

Polypharmacy was frequent in the present study. The number of potential DDIs increased with an increase in the number of drugs prescribed. The number of drugs prescribed increased with age. Nearly one third of potential DDIs were clinically significant. These DDIs have a potential to increase or decrease the therapeutic effect or to increase the risk of ADRs. An increased awareness of potential DDIs, rational co-prescription of drugs and a close monitoring of patients in whom these drugs are prescribed is recommended.

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