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Drug-Drug Interaction and Drug Induced Abnormalities Studies in the Hospitalized Patients of Private Hospital

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ABSTRACT

Objective: To evaluate incidence, severity and types of drug-drug interactions and drug induced abnormalities in hospitalized patients.

Material and methods: A prospective observational study was carried out in In-patient department of surgical and medical department in private hospital. Study conducted after the approval of Ethics committee. Data were collected for 6 months and drug interactions were identified using standard references. Drug induced abnormalities were observed from patients file.

Results: Total 201 cases collected within 6 months and mean age was 62.5 ± 17.3 years. Most of patients are in age between 61 and 80 years (4.47%) The average incidence rate of DDIs was 66.6%. The most frequently prescribed drug in was aceclofenac (2.3%) and aspirin (78.33%) in surgical and medical department, respectively. The most common DDI was reported between clopidogrel and aspirin (67%). Mechanism of drug-drug interaction was pharmacokinetic (44%) and pharmacokinetic and pharmacodynamic (71.4%) in medical and surgical department. In medical department, the minor drug interaction was higher (40%) and in surgical department, significant and minor drug interactions were at 61%. Out of 201 cases, 16 cases (7.96%) showed drug induced abnormalities. Most of patients are in age between 61 and 80 years (4.47%).

Conclusion: The incidence rate of DDIs was in the range of 64-70%. The majority of DDI were minor type with no clinical significance. Total 16 cases out of 201 cases showed drug induced abnormalities.

Keywords: Drug-drug interaction, Drug induced abnormalities, Clopidogrel, Aspirin

INTRODUCTION

A drug interaction occurs when the effects of one drug (the object drug) are altered (increased or decreased) by the effects of another drug (the precipitant drug) [1]. Drug-drug interaction can increase hospitalization, increased length of hospital stay, morbidity, mortality and increased financial costs [1].

There are three types of drug interactions: pharmacodynamic, pharmacokinetic and pharmaceutical. Pharmacodynamic interactions usually result from combining two drugs with similar mechanisms of action and pharmacokinetic occurs due to effect of one drug altering the effect of another drug by alteration of absorption, distribution, metabolism and excretion [1]. A pharmacokinetic interaction takes place when a drug alters the absorption, distribution, metabolism and/or excretion of another drug. Pharmacokinetic interactions via metabolic effects most often occur via drug interactions with cytochrome P450 enzymes [1].

In 2004 in the United States, more than 3500 drugs were prescribed and found that more than 81% of persons in a given week at least one medication and 25% take at least five such medications so obviously, the potential for an interaction between two or more agents is large [2]. The Boston collaborative drug surveillance program reported 83,200 drug exposures in almost 10,000 patients and shown 3,600 adverse drug reactions, of which 6.5% was resulted from drug interaction [2].

A toxic reaction to or morbid condition resulting from the administration of a drug is called drug induced abnormalities

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[3]. In 1993, the incidence rate of drug related hospital admissions was reported to range from 0.2% to 21.7%, with the median rate of drug related hospitalization at 4.9% [4]. The factors that affect the drug induced abnormalities are pharmacokinetic, pharmacodynamic, co-morbidities, physiological condition, life style factors, drug-drug interaction and genetic variabilities [3].

In developing countries, very few organizations look after the problems related to drug interactions and its harm to patients and safety monitoring. The Uppsala Monitoring Centre is the one of the reference for providing information on drug interaction and also concerned on safety monitoring of medicinal product. In India, very limited activities are focusing on such type of studies. Therefore, the present study was planned to identify drug interactions and drug induced abnormalities in hospitalized patients.

METHODOLOGY

A prospective observational study was carried out for a period of 6 months (15th July 2014 to 15th January 2015) at private hospital in western part of Gujarat. The study was conducted after approval taken from Human Ethics Committee. Prescriptions from surgical and medical ward of Inpatient department were selected and considered for data collection. Patients data was collected for 3 days of hospitalization or till discharged, whichever is earlier. Written prescriptions were evaluated for drug-drug interaction with the help of Medscape multidrug interaction software and Stockley's drug interaction checker [4,5]. On the other hand, reported laboratory data, medication history, past history, co-morbidities of patients were additional evaluated for drug induced abnormalities. After collection of data, the result was prepared by using MS-Excel. Data are expressed as percentage. Descriptive statistic analysis was used to present the data results.

RESULTS

Demographical characteristics

Total 470 prescriptions were reviewed from 201 patients including both medical and surgical Inpatient department of the hospital. The mean age was found to be 62.5 ± 17.3 years. Female dominance was observed in the study (female=58%, male=42%) The majorities of female patients were in age group of 61 to 80 years of age. Arthritis (77, 38.30%) was the common associated condition found in patients **(Table 1)**.

Table 1. Demographical characteristic of patients.

S. No.	Characteristics	Total number (%)
Age (years)		
1	Below 20 years	11 (5.47%)
2	20-40	29 (14%)
3	41-60	64 (31.8%)
4	61-80	92 (45%)
5	Above 80 years	5 (2.48%)
Gender		
6	Male	84 (41.79%)
7	Female	117 (58.20%)
Diagnosis		
8	Arthritis	77 (38.30%)
9	Fracture	13 (6.46%)
10	Injury	9 (4.47%)
11	Other disease such as cvs disorders, respiratory disorders and diabetes	102 (50.74%)

Out of 201 cases, 100 cases were taken from medical department and 101 cases from surgical department during the time period. For the ease of analysis, two departments were separately analyzed.

Medical department

The incidence rate of DDIs in medical department was found to be 64%. The mean age of 55.23 ± 18 years was found including 54% males and 46% females. The most common

presenting complains was arthritis and 42.5% DDIs were observed. Hypertension (32%) was found as the most common co-morbidity among the group of patients.

Looking at prescribing trend in medical department, total 1721 drugs were prescribed and most frequently prescribed drug was aspirin 235 (78.33%). Potential DDI was observed in patients received Aspirin+clopidogrel 43 (67%). Maximum 9 DDIs were found in four prescriptions, while 36 prescriptions showed no drug interactions. Total 64 cases showed DDIs, out of this, 48 (44%) and 39 (35%) cases showed pharmacokinetics (PK) and pharmacodynamics (PD) type of DDIs respectively. Metabolism (28%) was the most common type of PK interaction followed by absorption and excretion **(Figure 1)**. The most frequently occurring drug interaction at metabolism was between barbiturates and pantoprazole (13, 50%).

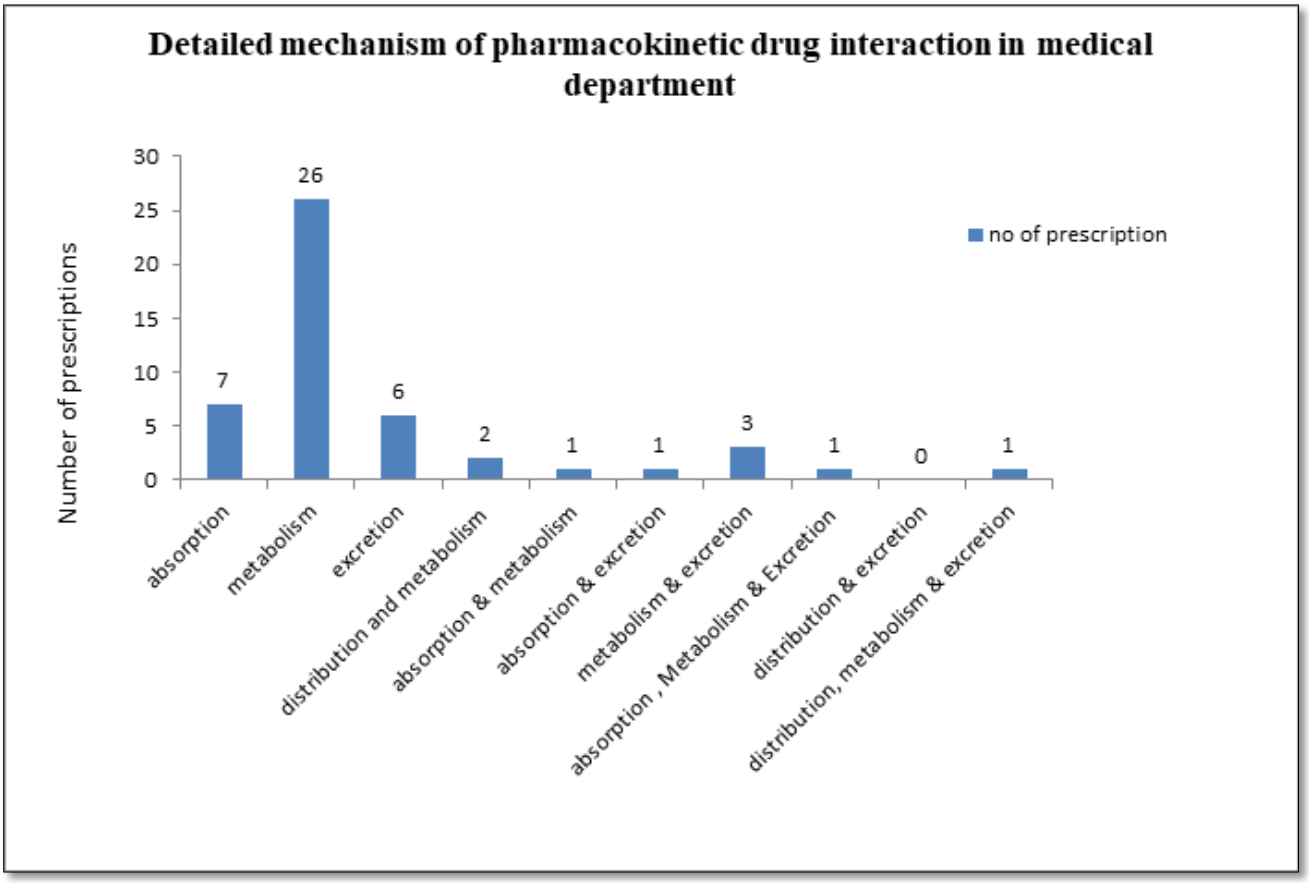

Figure 1. Type of pharmacokinetic drug interactions.

Inter-day incidence of DDIs was observed whereas, high number of prescriptions (116) showed DDIs on 2nd day of hospitalization as compared to the day of hospitalization. On the 3rd day DDIs ratio was gradually decreased.

Out of total cases, 27% cases showed serious DDIs followed by 39% significant and 40% minor type.

Table 2 showed representation of serious type of DDIs.

Table 2. Representative list of serious type of DDIs.

S. No.	Example of DDI n (%)	Effect/Outcome	Measures to prevent/Recommendations
1	Levofloxacin+Ondansetron 10 (37%)	Both increase QTc interval	Ciprofloxacin can be given instead of levofloxacin because it is safer than levofloxacin
2	Telmisartan+Potassium chloride 1 (3.7%)	Increase potassium level in the blood	Serum K level should be monitored and dose adjustment telmisartan-80 mg and Kcl 40-100 mEq once a day
3	Olanzapine+levodopa 2 (7.4%)	Olanzapine decrease effect of levodopa by pharmacodynamic antagonism	Clonazapine should be given instead of olanzapine
4	Phenobarbital+Enoxaparin 2 (7.4%)	Phenobarbital decrease effect of enoxaparin by increasing metabolism	Dose adjustment of Phenobarbital (2 mg/kg)
5	Ivabradine+Amiodarone 2 (7.4%)	Ivabradine enhances toxicity of amiodarone and enhance QT prolongation	Ivabradine should be given at dose 5 mg twice daily
6	Pantoprazole+Digoxin 3 (11.11%)	Pantoprazole increase level of digoxin by increasing gastric pH	Rabeprazole should be given instead of pantoprazole
7	Amiodarone+Digoxin 7 (25.92%)	Amiodarone increase level of digoxin by cationic drug competition	Decrease the dose of digoxin by 25-50% (<2 mg/ml)

Surgical department

The incidence rate of DDIs in medical department was found to be 70%. The mean age of 59.73 ± 17.83 years was found in all together in 29.6% males and 70.4% females. Majority of the patients (56%) were above the age 61 years. The most common presenting complains was knee joint pain observed.

Total 1523 drugs were prescribed to surgical ward included highest prescribing of antibiotics 97 (97.6%). Total 70 cases out of 100 showed potential DDIs. Total 13 (18.57%) prescriptions showed pharmacokinetic (PK) type, 7 (10%) prescriptions showed pharmacodynamics (PD) type of DDIs, while, 50 (71.42%) prescriptions showed both PK and PD types. Metabolism and excretion type of DDIs were common in surgical department, examples includes sulfamethoxazole with losartan (10%), ascorbic acid with aspirin (25%) and furosemide with folic acid (10 %). Aceclofenac with diclofenac is the DDI observed with pharmacodynamic.

Out of total cases, 34 cases showed serious DDIs followed by 61cases of significant and 61 minor type.

Table 3 showed representation of serious type of DDIs.

Table 3. Representative list of serious type of DDIs.

S. No.	Example of DDI n (%)	Effect/Outcome	Measures to prevent/Recommendations
1	Tramadol+Pentazocine	Tramadol may reinitiate opiate dependence in pts. Previously addicted to other opiates; it may also provoke withdrawal Sx. in pts. Who are currently opiate dependent.	Instead of tramadol, Acetaminophen or aspirin should be given.
2	Aceclofenac+Diclofenac	Aceclofenac and Diclofenac both increase anticoagulation and serum potassium.	Use other NSAIDs like acetaminophen, meloxicam. Avoid the use of same class of drugs.
3	Diclofenac+Furosemide	Diclofenac decreases effects of Furosemide by pharmacodynamics antagonism.	Dosing adjustment of diclofenac (50 mg orally 2 to 3 times a day) furosemide (20-80 mg).
4	Ranitidine+Cefuroxime	Ranitidine will decrease the level or effect of cefuroxime by increasing gastric PH.	Discontinue ranitidine and replace with cimetidine.
5	Tramadol+Prochlorperazine	Tramadol and prochlorperazine both increase sedation.	Use acetaminophen alternative to tramadol and instead of prochlorperazine, meclizine or famotidine may be used.
6	Cefuroxime+Furosemide	Cefuroxime increases toxicity of furosemide by pharmacodynamic synergism.	Instead of furosemide, atenolol or amlodipine or metoprolol may be used.

Day wise incidence of DDIs was compared and it showed high number (n=239) prescriptions with DDIs on 2nd day of hospitalization as compared to the day of hospitalization. On the 3rd day DDIs ratio is gradually decreased (n=109).

Drug induced abnormalities

Out of 201 cases, 16 (8%) cases showed drug related problems. Majorities of the abnormalities (66%) were observed at medical department. Details of the drug induced abnormalities are represented in **Table 4**.

Table 4. Details of the drug induced abnormalities.

Drugs	Abnormality	Number of Cases	Concomitantly Prescribed drugs	Mechanism
Aspirin	GI bleeding	4	Ampicillin, Potassium chloride, Torsemide, Cefazolin, Warfarin, Metoprolol, Mineral oil	The back diffusion of H^+ ions across the gastric barrier seems to bear primary responsibility, with physical erosion, prolonged platelet bleeding [31]
Acute overdose of Digoxin (1.5 mg)	Hyperkalemia	4	Ivabradine, Amiodarone, Calcium carbonate, Furosemide, Torsemide, Aspirin, Clopidogrel, Ferrous fumarate, Pyridoxime, Folic acid	The Sodium/Potassium ATPase pump normally causes sodium to leave cells and potassium to enter cells. Blocking this mechanism results in higher serum potassium levels [30]
Pantoprazole	Raised SGPT level	2	Clopidogrel, Aspirin, Clopidogrel, Amoxicillin	Idiosynchratic Reaction [33]
Furosemide	Hyponatremia	3	Folic acid, Aceclofenac, Diclofenac, Ranitidine, Aceclofenac, Diclofenac	Affect Na/K/Cl co-transport system so increased sodium and potassium excretion. [31]
Metoprolol	Raised SGPT level	1	Cefazolin, Warfarin, Aspirin, Mineral oil	It can cause liver necrosis and so increase SGPT level [31]
Antibiotics (Sublactum β-lactamase)	Raised SGPT level	1	Ciprofloxacin, Ondansetron, Diclofenac, Enoxaparin, Aspirin, Dextran, Levothyroxine, Telmisartan, Aspirin, Ranitidine	Idiosyncratic reaction [32]
Lactulose	Hypernatremia	1	Enoxaparin, Aspirin, Dextran, Levothyroxine, Telmisartan, Aspirin, Ranitidine	Lactulose works on osmolarity so water adsorbed and sodium excreted.

DISCUSSION

Our study aim was to analyze prescription for possible drug-drug interaction in medical and surgical ward of Inpatient department. Total 470 prescriptions were reviewed from 201 patients including both medical and surgical Inpatient department of the hospital. The mean age was found to be 62.5 ± 17.3 years. Out of 201 cases, 100 cases were taken from medical department. In our study, out of 100 patients, mean age was 55.7 ± 18 years. The majority of patients in the present study belong to age group of 61-80 years. The incidence rate of DDIs in medical department was found to be 64%. In another study by Patel et al. [2], out of 350 prescriptions were taken from medical department; mean age was 52.45 ± 14.49 years. The incidence rate of drug interactions was found to be 83.42%. [2] In our study, sixty four (64%) prescriptions had the potential for drug interaction out of 100 prescriptions. Our study findings are similar with previous reported study.

In our present study, out of 201 prescriptions, 134 prescriptions show drug-drug interaction. Out of 134 prescriptions, 111 (82.83%) prescriptions showed pharmacokinetic drug interaction and 23 (17.16%) prescriptions showed pharmacodynamic drug interaction. The study carried out by Patel et al. [2], the

pharmacodynamic drug interaction was 68.92% and 26.76% prescriptions had shown pharmacokinetic drug interaction, which differs from us.

In our study, total 43 (67%) cases were found with aspirin and clopidogrel combination and cause serious problem and need monitoring. Reported data says that, aspirin and clopidogrel resistance are emerging clinical entities with potentially severe consequences such as recurrent myocardial infarction, stroke, or death [6]. Additionally we found that four prescriptions with nine types of DDIs and on contrary, 36 prescriptions showed no drug interactions. Total 64 cases showed DDIs, out of this, 48 (44%) and 39 (35%) cases showed pharmacokinetics (PK) and pharmacodynamic (PD) type of DDIs respectively. Metabolism (28%) was the most common type of PK interaction followed by absorption and excretion. The most frequently occurring drug interaction at metabolism was between barbiturates and pantoprazole (13, 50%) in the present study. Study by Shetty et al. [7] reported majority of the drug interactions were pharmacokinetic in nature.

Out of total cases, 27% cases showed serious DDIs followed by 39% significant and 40 % minor type in present study whereas the study carried out by Patel et al. [2], out of 500 prescriptions, only 3.67% showed serious drug interaction, 73.37% significant drug interaction and 22.94% minor drug interactions.

Interday incidence of DDIs was observed in medical ward where, high number of prescriptions (116) showed DDIs on 2nd day of hospitalization as compared to the day of hospitalization. On the 3rd day DDIs ratio was gradually decreased. Study done by Gupta et al. [8] reported that as stay prolonged the rate of DDIs occurrences increased.

In the surgical department, the incidence rate of DDIs in medical department was found to be 70%. The mean age of 59.73 ± 17.83 years was found in all together in 29.6% males and 70.4% females. Majority of the patients (56%) were above the age 61 years. The most common presenting complains was knee joint pain observed. Out of 101 prescriptions of surgical department, 70 (70.1%) showed drug interaction. While in other study carried out by Patel et al. [2] in India, 50 prescriptions were from surgical department. 40 prescriptions shown pharmacokinetic interaction and 27 had pharmacodynamic drug interaction [2].

In this study, highest prescribing of antibiotics 97 (97.6%) was found in surgical department. Total 70 cases out of 100 showed potential DDIs. Total 13 (18.57%) prescriptions showed pharmacokinetic (PK) type, 7 (10%) prescriptions showed pharmacodynamics (PD) type of DDIs, while, 50 (71.42%) prescriptions showed both PK and PD types. Metabolism and Excretion type of DDIs were common in surgical department, examples includes sulfamethoxazole with losartan (10%), Ascorbic acid with aspirin (25%) and Furosemide with folic acid (10%). Aceclofenac with diclofenac is the DDI observed with pharmacodynamic.

Out of total cases, 34 cases showed serious DDIs followed by 61cases of significant and 61 minor type. This was consistent with other studies in which severity range was from 64%-70.4% in moderate category [9-11]. Additional day wise incidence of DDIs was compared and it showed high number (n=239) prescriptions with DDIs on 2nd day of hospitalization as compared to the day of hospitalization. On the 3rd day DDIs ratio is gradually decreased (n=109).

In our study, the digoxin induced hyperkalemia occurred in 1 case out of 201 prescriptions. The study carried out by Khanagavi et al. [12] in USA, it was studied that out of 15,608 hospitalizations, the digoxin induced hyperkalemia was in 408 patients. In our study, drug used like pantoprazole, metoprolol and antibiotic - Sublactum β-lactamase caused raised SGPT level. Whereas drugs like furosemide and lactulose caused fluctuation of sodium level. Additionally Aspirin showed case of GI bleeding in the present study. Gastrointestinal bleeding due to NSAID, acetylsalicylic acid and warfarin were the most common DIDs reported by Brvar et al. [13].

CONCLUSION

The incidence rate of DDIs was in the range of 64-70%. Nearly 50% of DDIs were minor type in both the department with no clinical significance. Total 16 cases out of 201 cases showed drug induced abnormalities. In medical department the drug interaction of aspirin+clopidogrel 43 (67%) was most common on the other side interaction between aceclofenac+diclofenac and antibiotics were major. Majority of the interactions were pharmacokinetics types with metabolism site. In both the department higher number of DDIs reported on 2nd day of hospitalization as compared to the day of hospitalization. Total 16 (8%) cases showed drug induced abnormalities and 66% of them were observed at medical department.

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