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Research Article

A Study On Drug-Drug Interactions Among Hospitalized Patients At Private Hospital

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ABSTRACT

Background: An interaction occurs when the presence of a different drug, herbal remedy, food, beverage, or chemical factor in the environment modifies the effects of a particular substance. Results may be negative if the interaction causes a rise in drug concentration

Aim: To evaluate prevalence, types, and severity of potential drug-drug interaction in in-patient department of CHARUSAT Hospital.

Materials and Methods: An observational prospective study was carried out in patients admitted to CHARUSAT Hospital. Demographic details, drug treatment, medical history, presenting complains and diagnosis were recorded in CRF and follow-up was done for 2 days, for the day of admission and for the 2nd day.

Results: In total, 160 patients were observed for this study. Of 160, 84 (52.5%) had pDDIs. Of 84 patients, 43 (26.8%) were male and 41 (25.6%) were female patients. Total 716 pDDIs were identified for both days. Inter-day variability was found to be 70. 195 (27.23%) were mild, 431 (60.19%) moderate, 86 (12.01%) severe and 4 (0.55%) contraindicated. Risk factors that were identified in patients were polypharmacy (51%), age (21%), comorbidities (22%), decreased renal and hepatic function (3%) and metabolic/endocrine function (3%). Polypharmacy and comorbidities were found significant predictors for DDIs with $P<0.05$. There was highest occurrence of pharmacodynamic interactions (63.12%), pharmacokinetic (33.65%) and unknown mechanism interactions (3.21%).

Conclusion: Prevalence of pDDIs was found to be 46.29% and 52.5% on day – 1 and day – 2 respectively. Total 70 DDDIs recoded in Inter-day and this showed that as the number of prescribed drugs increased, pDDIs also increased. Polypharmacy and comorbidities were significant predictors for pDDIs.

Keywords: Drug – Drug Interactions, Risk factors, Polypharmacy, Comorbidities, Pharmacokinetic pDDIs, Pharmacodynamic pDDIs.

INTRODUCTION

When the effects of one drug are altered by the presence of another drug, herbal medicine, food, drink, or a chemical element in the environment, it is referred as an interaction. If the interaction leads to increase in drug concentration (i.e., drug toxicity), the results can be detrimental [1]. But these harmful effects can also be prevented by considering prescription modifications, that is for potential drug interaction as well as when making a differential diagnosis of symptoms that is for the interactions that already took place.[2]

Every year, millions of people are affected by adverse medication events, which account for up to 5% of all hospital admissions, which leads to enormous financial burden on patient like about more than $ 16000 per admission in hospital. While some adverse reactions are unforeseeable (for example, anaphylaxis due to an undiagnosed allergy), many others can be predicted and avoided. Some adverse drug reactions are life-threatening, and thus popular medications may indeed be pulled from the market. [3] [4]

Because polypharmacy is more frequent in modern medicine, determining the severity of drug-drug interactions is a critical issue. Accurate assessment of clinically relevant DDIs for novel drug candidates is a major task in today's drug research and development, and it is crucial for healthcare practitioners.[5] Although

the clinical literature discusses a large number of potential drug-drug interactions (DDIs), only a small percentage of them are clinically significant.[6] On a national basis, prescribers are less aware about prescribing of drugs involved in these clinically significant DDIs.[7] The clinical pharmacist, being an important member of the multidisciplinary team, can help in reducing drug interactions. Pharmacist also have the right to optimize drug therapy by going through the treatment prescribed at the discharge of the patients leading in minimizing the DDIs.[8]

Polytherapy increases the complexity of therapeutic management and, as a result, the likelihood of potential clinical drug interactions, which can lead to the development of ADRs, as well as lowering or raising clinical efficacy. As a result, those who take a variety of medications are at the greatest risk of drug interactions. In a study of geriatric patients, the prevalence of drug- drug interactions (DDIs) were 90.3%. The key contributing variables for DDI were polypharmacy and several related diseases in the elderly. The vast majority of DDIs reported were clinically insignificant.[9] Acute medical problems, age (very young [5 years] and elderly), impaired renal and hepatic function, medications with limited therapeutic ranges, gender, metabolic or endocrine diseases (e.g.: fatty liver, obesity, hypothyroidism), and polypharmacy are all risk factors for drug-drug interactions.[10]

In India, the area of drug – drug interaction is not given much importance, rather it is being ignored. The outcomes of DDIs are rarely observed by the healthcare members. There are many drug – drug interaction occurring in patients, but very few are clinically significant. Looking at this background, we have planned this study to put insight on different types of DDIs, its severity and its prevalence in the in-patient department.

MATERIALS AND METHOD

An observational prospective study was carried out in CHARUSAT Hospital after obtaining approval from Ethics Committee for a period of 5 months from September 2021 to January 2022. A total of 160 patient's prescriptions were studied from the in-patient department of CHARUSAT Hospital.

Data Collection Procedure

Patient's relevant information such as demographic data, clinical history, and complete prescription details were recorded in Case Record Form (CRF), for the day of admission and for the 2nd day. (Figure – 1) The drug-drug interactions were identified through Medscape drug-drug interaction checker and WebMD drug- drug interaction checker.

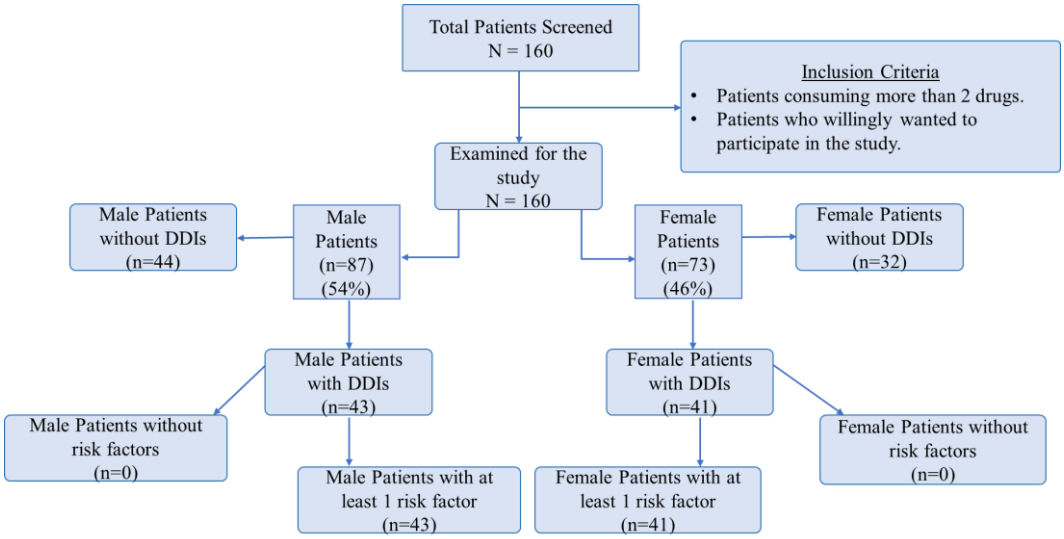

Figure – 1 Patient Enrolment Flow Chart

RESULTS

In the present study, total 160 patients were observed for Drug - Drug Interactions for two days of which there were 87(54.3%) male and 73(45.7%) female patients. The mean age was found to be 43.96 ± 20.61 years. The maximum number of patients were of age group 21 to 30 years. Of 160 patients, 59 patients had co-morbidities and the most common co-morbid conditions were diabetes and hypertension.

Drug – Drug Interactions

On Day – 1, 76 prescriptions had DDIs which were accounted to 323, where 1096 drugs were prescribed to 160 patients. On Day – 2, 84 prescriptions had DDIs and number of DDIs accounted to 393, where 1392 drugs were prescribed to 160 patients. As compared to day 1, there were increased DDIs n=70,(9.7%) on day 2. It

concluded that as the number of drugs increased it also increased the occurrence of DDIs. On day – 1, 24 prescriptions had 1 DDI, 14 prescriptions had 2 DDIs, and so on. The number of DDIs in a prescription on day – 1 and 2 are shown in Figure – 2 and Figure – 3 respectively.
The most commonly occurring Pharmacodynamic DDI were Azithromycin + Ondansetron and Pantoprazole + Theophylline, Pharmacokinetic DDI were Dexamethasone + Ondansetron, Dexamethasone + Pantoprazole and Dexamethasone + Theophylline.
The pharmacokinetic DDIs were also distributed according to its mechanism: 36 (15.1%) Absorption, 9 (3.7%) Distribution, 149 (62.8%) Metabolism and 42 (18.1%) Excretion mechanism.

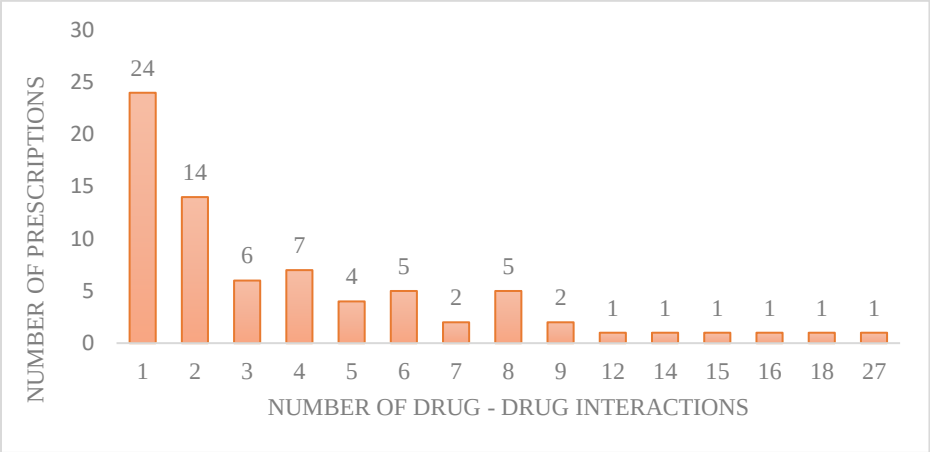

Figure 2: DDIs on the day of admission

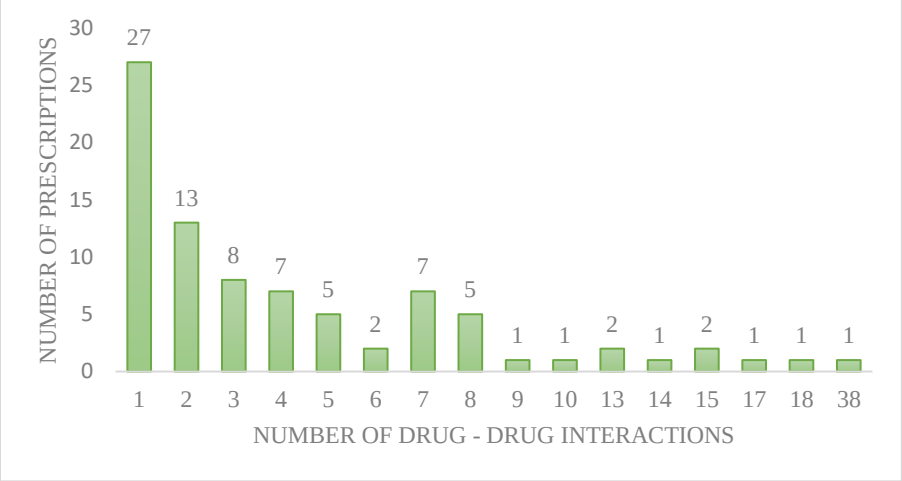

Figure 3: DDIs on Day – 2

Of 160, 43 male patients and 41 female patients had DDIs. On basis of severity of DDIs, of total identified DDIs, 195 were minor, 431 were moderate, 86 were serious and 4 were classified as contraindicated DDIs. On basis of mechanism, drug-drug interactions were classified as 452 pharmacodynamic, 241 pharmacokinetic and 23 DDIs of unknown mechanism.

Inter-day, Intra-day variability.

Inter-day Variability was found in the study with total 70 DDI reported on day 2. Inter-day Intra-day variability is shown in the following table categorized as minor, moderate and severe interactions. (Table – 1)

Table – 1: Inter-day and Intra-day Variability

Severity	Number of DDIs on Day-1 (n=323)	% Of DDIs	Number of DDIs on Day-2 (n=393)	% of DDIs
Mild	89	27.55%	106	26.97%
Moderate	194	60.06%	237	60.30%
Severe	39	12.07%	47	11.95%
Contraindicated	1	0.30%	3	0.76%
Total	**323**		**393**	

The Prevalence of DDIs on Day - 1 and Day – 2 was 46.25% and 52.50% respectively. (Table-2)

Table – 2: Prevalence Rate of DDIs

Total Patients (N=160)	Patients having DDIs	Prevalence Rate
Day - 1	74	46.25%
Day - 2	84	52.50%

Risk factors responsible for DDIs.

The most common and frequent risk factor among the patients with DDIs was polypharmacy, co-morbidities, Age, Metabolic and endocrine conditions and Decreased renal or hepatic function. (Table-3)

Table – 3: Risk factors for DDIs (N = 169)

Risk Factors	Number of Patients (n, %)
Age	22 (13.01%)
Comorbidities	32 (20%)
Decreased Renal/Hepatic Function	4 (2.36%)
Metabolic or endocrine conditions	29 (17.1%)
Polypharmacy	82 (48.52%)

Statistical Analysis:

A Logistic Regression Analysis was performed between dependent variable (Drug-drug interactions) and independent variables (age, comorbidities, metabolic and endocrine conditions, decreased renal or hepatic functions and polypharmacy).

Two independent variables, polypharmacy and comorbidities were found significant predictors of DDIs (Table – 4) The resulting equation is:

$$Odds = \frac{P(DDI)}{1-P(DDI)}$$

Table – 4 Predictors of pDDIs.

Sr. No	Risk Factors	B (constant)	S.E. (Standard Error)	Wald	df	Significant value P
1	Age	-0.461	0.541	0.728	1	0.393
2	Comorbidities	2.281	1.139	4.010	1	0.045*
3	Decreased Renal or Hepatic Function	19.599	23111.107	0.000	1	0.999
4	Endocrine or Metabolic Conditions	-0.327	1.182	0.077	1	0.782
5	Polypharmacy	3.632	1.098	10.942	1	0.001*
	Constant	-3.660	1.107	10.937	1	0.001

*P<0.05 are significant predictors of pDDIs

Risk factors like polypharmacy (P = 0.001) and comorbidities (P = 0.045) have shown significant predictors for DDIs.

DISCUSSION

Our study was conducted in the In-Patient Department of CHARUSAT Hospital that included patients of General ward and ICU ward and total of 160 patients were observed for the study. In our study out of 160 patients enrolled, the patients age ranged from 11 years to 85 years with mean age of 43.96 ± 20.61 years, and a median age of 42 years. Rashid K et al, had observed 100 patients, with patients having age ranging from 13 years to 84 years and a mean age of 49.52±17.5 years. Our study had 87(54.3%) male and 73(45.7%) female patients, where as in the study conducted by Rashid K et al, there were 52 (52%) male, and 48 (48%) females.[11] The most common comorbidities present in patients in our study were hypertension (32.2%), diabetes mellitus (30.5%), hypothyroidism (6.7%), chronic pulmonary disease (8.4%), ischemic heart disease (6.7%), bronchitis and renal inefficiency (3.4%) and chronic liver disease and epilepsy (1.4%), where as in the study conducted by Schneider J et al, the most common comorbid conditions were hypertension (78.4%), congestive heart failure (41.3%), diabetes mellitus (32.1%), coronary heart diseases (26.9%), chronic pulmonary diseases (25.1%) and dementia (27.2%).[12]

We identified 323 DDIs on day 1 and 393 DDIs on day 2 out of 160 prescriptions. Here on day-2 the number of prescribed drugs increased than day – 1 and so the number of DDIs were also increased. A study by Mousavi S et al identified 3350 DDIs from 448 prescriptions.[13] Rabba AK et al conducted study in Birzeit, State of Palestine, reviewed prescription of 502 patients and identified 1114 potential DDIs.[14] Study by Upreti AR et al found 219 drug – drug interactions in 100 patients.[15]

Of 716 total DDIs that were identified in our study, majority of the DDIs were moderate interactions which were found to be 431 (60.1%), followed by minor drug - drug interactions 195 (27.2%), followed by severe interactions 86 (12.01%) and only 4 (0.55%) contraindicated interactions were identified. Similarly in the study by Rashid K et al found 246 (61.5%) moderate, and 124 (31%) were minor, 28 (7%) were serious and 2 (0.5%) DDIs were contraindicated.[11]

Also, Rabba AK et al identified 587 (52.7%) major DDIs, 451 (40.5%) moderate DDIs, 71 (6.4%) minor DDIs and 5 (0.5%) contraindicated DDIs in their study.[14]

According to our study, the risk factor that was most significant predictor for pDDIs were identified using logistic regression analysis and the most significant predictors were found to be polypharmacy (≥ 5 medications is polypharmacy according to the reference of WHO [16] and co-morbidities whose value were <0.05. According to the study by Mousavi S et al, there was a strong association between the prevalence of pDDIs and seven or more prescribed drugs (OR: 0.048; 95% CI:0.02-012, p0.0001), according to logistic regression analysis.[13]

Our study had identified inter day variability as 323 drug – drug interactions on day- 1 and 393 drug - drug interactions on day – 2. Similarly, the study conducted by Suthar J et al, the inter day variability was found to be 984 DDIs on 1st day, followed by 1057 on 2nd and 1125 on 3rd day. [09] This shows that as the number of medicines increases, the more the occurrence of DDIs.

The prevalence of DDIs on day 1 was 46.25% and on day 2 it was found to be 52.5% in our study. In the study by Mousavi S et al, the prevalence rate of pDDIs was accounted to 86.2%.[13] Study by Rashid K et al found prevalence of 77% for pDDIs.[11] Whereas studies from the USA had 25% prevalence rate of pDDIs and Europe show a prevalence rate of 46%.[17][18]

The mechanisms of DDIs were classified as pharmacodynamic, pharmacokinetic and unknown mechanism interactions. Our study identified 452 (63.1%) pharmacodynamic mechanism interactions, 241 (33.65%) pharmacokinetic mechanism interactions and 23 (3.21%) unknown mechanism interaction. Study by Upreti AR showed similar findings with highest mechanism of interactions being pharmacodynamic interactions, followed by pharmacokinetic mechanism interactions and lastly being unknown mechanism accounting to 44.7%, 33.3% and 21.9% respectively.[15] Also the study by Suthar J et al, 2962 (62.91 %) were pharmacodynamic mechanism interactions and 1835 (37.08 %) were of pharmacokinetic mechanism.[09] Similar results were also seen in the study carried out by Rana D et al at 1 Smt. NHL Municipal Medical College, Ahmedabad, that identified pharmacodynamic mechanism interactions were 1424 (68.92%), 553 (26.76%) pharmacokinetic and 89 (4.30%) having an unknown mechanism. All the studies showed majority of DDIs being of pharmacodynamic mechanism, followed by pharmacokinetic and lastly DDIs with unknown mechanism.

Further, the pharmacokinetic interactions were divided into 4 categories, absorption, distribution, metabolism, and excretion. Our study identified 36 (15.1%) absorption pharmacokinetic interactions, 9 (3.7%) distribution pharmacokinetic interactions, 149 (62.8%) metabolisms pharmacokinetic interactions and 43 (18.1%) excretion pharmacokinetic interactions. Similarly, the study by Upreti AR et al, also identified highest PK interaction in absorption category which accounted to 35 (47.9%), followed by absorption 28 (38.3%), excretion 6 (8.2%) and distribution 4 (5.4%).[15] Apparently, the study conducted by Rana D et al, had the highest PK DDIs in the category of absorption 217 (10.5%), followed by metabolism 145 (7.01%), excretion 106 (5.13%) and distribution 32 (1.05%).[19]

Conclusion

Days one and two showed a 46.25% and 52.5% prevalence of DDIs, respectively. Seventeen drug-drug interactions were found; of these, four were contraindicated, four were moderate, sixteen were dangerous, and fifty-five were minor. Every drug-drug interaction that was found out of 716 was clinically non-significant. Days 1 and 2 had 323 and 393 intraday interactions, respectively. It emerged that there was 70 inter-day variability in the DDIs for Days 1 and 2. With a significant value of P <0.05, Polypharmacy and Co-morbidities were the risk factors that contributed significantly to DDIs.

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