



Drug–drug Interactions in Hospitalized Cardiac Patients

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ABSTRACT

Drug–drug interactions (DDIs) are defined as two or more drugs interacting in such a manner that the effectiveness or toxicity of one or more drugs is altered. DDI in patients receiving multidrug therapy is a major concern. The aim of the present study was to assess the incidence and risk factors of DDIs in patients admitted in cardiology unit of a teaching hospital. A prospective, observational study was carried out for a period of 3 months (April–July 2009). During the study period, a total of 600 prescriptions were analyzed and it was found that 88 patients had at least one DDI. The percentage of DDIs was higher in females compared to males (56.82% vs. 43.18%). DDIs were observed more in the age group of 60 years and above (57.96). Patients with more than 10 prescribed drugs developed DDIs more frequently [58 (65.91%)]. Heparin [55 (62.25%)] and aspirin [42 (47.72%)] were the most common drugs responsible for DDIs. Bleeding was the commonest clinical consequence [76 (86.63%)] found in this study population. On assessment of severity of DDIs, majority of the cases were classified as moderate in severity (61.36%). Aging, female gender and increase in concurrent medications were found to be associated with increased DDIs. Patients having these risk factors can be actively monitored during their stay in the cardiology department to identify DDIs.

Key words: Cardiology, drug–drug interactions, hospitalized patients

INTRODUCTION

Drug therapy is growing more complex, thus making appropriate decision on drug therapy increasingly challenging. Drug interactions are most important in this context and proper handling of drug–drug interactions (DDIs) may prevent harmful events.^[1] DDIs are defined

thus: “two or more drugs interacting in such a manner that the effectiveness or toxicity of one or more drugs is altered”.^[2-5] DDI in patients receiving multidrug therapy is a major concern. Such interactions may lead to an increased risk of hospitalization and higher health care costs.^[6] The incidence of actual occurrence of drug interactions has been reported to be much smaller, ranging from 0 to 1.3%.^[7,8] Some studies have found that up to 11% of patients experience symptoms associated with DDIs and that DDIs are responsible for up to 2.8% of hospital admissions.^[9,10] Research has also shown that DDIs are associated with increased health care use.^[11] According to a recently published study, 1% of all hospital admissions are caused by DDIs, and 0.05% emergency department visits, 0.6% of the hospital admissions and 0.1% of

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re-hospitalizations are caused by adverse drug reactions (ADRs) due to DDIs.^[12,13]

The incidence of cardiovascular diseases (CVDs) has increased in recent decades. It has been estimated that CVDs are the most common cause of death in India and as a result cardiovascular drugs have moved to the second place among all drug classes prescribed in the country.^[14]

Patients with cardiovascular diseases are particularly vulnerable to DDIs due to their advanced age, polypharmacy and the influence of heart disease on drug metabolism. The DDI potential for a particular cardiovascular drug varies with the individual, the disease being treated, and the extent of exposure to other drugs.^[15]

Potential for drug interaction is higher with cardiac drugs^[16] and there are reports on potential DDIs in cardiology department from India.^[17] There are no studies reporting actual incidence of DDIs in the Indian setting. Hence, the present study was designed to assess the incidence and pattern of DDIs in hospitalized cardiac patients in a tertiary care hospital, with the assessment of reaction characteristics, outcome and causality.

MATERIALS AND METHODS

Study design, population and data collection

A prospective observational study was carried out for a period of 3 months (April–July 2009) in a tertiary care teaching hospital. Ethical approval was obtained from Institutional ethics committee prior to initiation of the study (UEC/19/2009). Patients who were admitted consecutively to cardiology unit were included in the study. Prescriptions with two or more drugs prescribed during the hospitalization were only selected for the study. The study population comprised all patients aged 18 years or older admitted to the hospital and had a length of stay greater than 24 hours. Patients referred to the cardiology unit for evaluation, patients visiting on outpatient basis and patients who died during hospital stay were excluded from the study. Demographic information (age and gender), number of drugs taken, length of hospital stay, main diagnosis (ICD-10) and the number of additional diagnoses and laboratory investigations made were obtained from the clinical records.

All the prescriptions of the study population were screened for DDIs by using computerized DDI database system.^[18] For determining the ADRs, both the medications added and as well as discontinued were considered. All drugs were classified as per Anatomical Therapeutic

Chemical Classification (ATC code, level one).^[19] Certain demographic characteristics were studied to find out the predictors of DDIs, such as patient characteristics [gender, age (more than 18 years old), concurrent morbidities and length of stay], drug characteristic (number of drugs) and laboratory investigations [International Normalized Ratio (INR), bleeding time, serum creatinine and serum potassium level].

The patient's medical records were screened for the presence of ADRs and the numbers of DDIs were calculated from the total number of DDIs. To classify the causality of the hospital admission to the drug, the Naranjo algorithm was used. The Naranjo algorithm or Naranjo Scale is a questionnaire designed by Naranjo *et al.*, for determining the likelihood of whether an ADR is actually due to the drug rather than the result of other factors. Probability is assigned via a score termed definite, probable, possible or doubtful. Values obtained from this algorithm are sometimes used in peer reviews to verify the validity of author's conclusions regarding ADRs.^[20] The interactions observed were classified into mild, moderate and severe according to severity and undesirable effects. The data on severity was obtained from the DDI data of the drug database.^[18]

Statistical analysis

Frequencies with percentage were used to summarize sex, diagnosis, number of drugs dispensed, frequency of DDIs, drugs involved in the DDIs and severity of DDIs. Mean with 95% confidence interval was used to summarize age and length of stay. Chi-square test was used to find the association between sex, number of drugs and DDIs. Spearman's correlation was used to find the correlation between numbers of drugs, length of stay with DDIs. A “*P*” value of <0.05 was considered statistically significant. All analyses were performed using SPSS v. 15.

RESULTS

Patients, drug characteristics and DDIs

A total of 600 prescriptions were analyzed during the study period and it was found that 88 patients were confirmed with minimum of one DDI (14.66%). A significant proportion of patients with DDIs was females numbering 50 (56.82%), followed by males [38 (43.18%)]. The age group of more than 60 years had 51 (57.96%) DDIs, and was followed by other age groups. Patients who had taken more than 10 drugs developed higher number of DDIs [58 (65.91%)]. Patient characteristics and statistical significance of the results are summarized in Table 1. The patients who stayed

for 5–10 days developed DDIs more frequently than other groups [48 (54.55%)]. On an average, each patient had 3 coded diagnosis in which anterior wall myocardial infarction was the most common condition [16 (18.18%)], followed by inferior wall myocardial infarction [14 (15.91%)], atrial fibrillation [9 (10.23%)], hypertension [4 (04.54%) and others [45 (51.14%)]. The most common drug classes involved in ADRs were the anti-platelets [67 (76.13%)] and anticoagulant drugs [64 (72.72%)]. Heparin [55 (62.25%)] and aspirin [42 (47.72%)] were the most common drugs responsible for DDIs. Clinically important DDIs among the prescribed drugs are summarized in Table 2. Bleeding was the commonest clinical consequence in 76 (86.63%) cases. Clinical consequences of DDIs are summarized in Table 3. The data evaluated for the specific systems affected by DDIs are summarized in Table 4.

Causality and severity of DDIs

All of the DDIs were assessed to have the “probable” causality by using Naranjo algorithm. The interacting drugs were withdrawn in 70 cases (79.54%) and dose was altered in 12 cases (13.63%). Sixty (68.18%) patients improved after withdrawal of interacting drugs. Rechallenge was performed in 65 patients and recurrence of symptoms occurred in 8 patients. Upon causality assessment, majority of the DDI reports were rated as probable [46 (52.27%)] followed by possible rating for 24 (27.27%) reports. These DDIs were assessed for severity in which 54 cases (61.36%) were classified as moderate followed by 33 severe cases (37.50%) and 1 mild case (1.14%).

DISCUSSION

This study revealed the overall incidence of clinically important DDIs in cardiology department to be 14.66%. The incidence compared with another study published from the same setting on potential DDIs which reported an incidence of about 30%. This study focused on the

incidence of actual DDIs compared to the reported study on potential DDIs which was about the possible DDIs which may arise out of the given combination.^[17] Findings

Table 2: Clinically important DDIs among the prescribed drugs

Objective drug	Precipitant drug (n, %)	Clinical consequences	
Heparin C05BA03	Aspirin (33, 37.54%)	Bleeding	
	B01AC06	Bleeding↓	
	Streptokinase (3, 3.40%) B01AD01	Bleeding	
Aspirin B01AC06	Warfarin (8, 9.09%) B01AA03	Bleeding	
	Diltiazam (3, 3.40%) C08DB01	Bleeding↑	
	Eptifibatide (1, 1.13%) B01AC16	Bleeding	
	Insulin (1, 1.13%) A10AE01	Hypoglycemia	
	Captopril (1, 1.13%) C09AA01	Captopril effect↓	
	Furosemide (1, 1.13%) C03CA01	Furosemide effect ↓	
	Warfarin B01AA03	Clopidogrel (2, 2.27%) B01AC04	Bleeding
		Amoxicillin (1, 1.13%) J01CR02	Bleeding
		Aspirin (1, 1.13%) B01AC06	Bleeding
		Atenolol (1, 1.13%) C07AB03	Bleeding
Phenytoin (1, 1.13%) N03AB02		Bleeding	
Clopidogrel B01AC04		Heparin (11, 12.5%) C05BA03	Bleeding
	Torsemide (11, 12.5%) C03CA04	Torsemide toxicity	
	Enoxaparin (8, 9.09%) B01AB05	Bleeding	
	Aspirin (1, 1.13%) B01AC06	Bleeding	

↓ - decrease, ↑ - increase

Table 3: Clinical consequences of DDIs

Clinical consequences	No. of DDIs (%)
Bleeding	76 (86.63)
Torsemide toxicity	11 (12.50)
Hypoglycemia	01 (01.13)
Furosemide effect ↓	01 (01.13)
Captopril effect ↓	01 (01.13)

↓ - decrease, DDI - Drug–drug interactions

Table 4: Organ systems affected by the DDIs

Organ system	Documented complications of DDIs	Number (%)
Platelet, bleeding and clotting disorders	Bleeding	76 (86.63)
Body as a whole – General disorders	Therapeutic effect increased (drug toxicity)	11 (12.50)
Heart rate and rhythm disorders	Bradycardia	9 (2.31)
Urinary system disorders	Acute renal failure	5 (1.28)
Central and peripheral nervous system disorder	Headache	2 (0.51)

Table 1: Patient characteristics

Patient characteristics	Number (%) of ADRs	P value
Gender group		
Male	38 (43.18)	$\chi^2=12.69$, df=3, $P<0.05$
Female	50 (56.82)	
Age (years)		
<45	10 (11.36)	$\chi^2=15.23$, df=3, $P<0.05$
45–60	27 (30.68)	
>60	51 (57.96)	
No of drugs taken		
<5	1 (1.14)	$\chi^2=11.98$, df=3, $P<0.05$
5–10	29 (32.95)	
>10	58 (65.91)	

of the present study showed that the patterns of incidence of DDIs are positively associated with patients' age, gender, number of drugs prescribed and length of hospital stay. A higher rate of DDI was present in women and patients who were more than 60 years of age. This corresponds to results of other studies reporting that DDIs are common in elderly people who are on multiple drug regimens.^[6,21,22]

The results showed that higher rate of DDIs seen in elderly patients was due to the increased number of medications prescribed to this population. These results are in accordance with the observation of reported studies.^[23] Positive association was observed between the number of drugs prescribed and length of stay with DDIs.

In fact, some of these drug combinations are used for therapeutic benefit in clinical practice and others are introduced internationally despite the increased risk of DDIs. Some of the most common drug classes involved in DDIs were anti-platelets (76.13%) and anticoagulants (72.72%). Among these drug classes, heparin and aspirin (37.54%), clopidogrel and heparin (12.5%), clopidogrel and torsemide (12.5%) and heparin and warfarin (9.09%) were the most commonly observed drug pairs resulting in DDIs, and bleeding was the most common clinical consequence observed in the present study. This result correlates with the results of similar studies.^[24] In 2006, the NPSA risk assessment of anticoagulation therapy highlighted co-prescribing of nonsteroidal anti-inflammatory drugs (NSAIDs) and other interacting medicines in anticoagulated patients as one of 15 key high-risk prescribing practices.^[25] The potential consequences of such prescribing practice are an increase in the risk of bleeding complications, which have been reported to affect between 7 and 26% of warfarinized patients annually. Of these bleeds, 6–15% were reported to be minor, 1–8% were major, and 0.25–4.8% were fatal.^[26,27]

Caution must be exercised in comparing the exact rates of each DDI by maintaining the normal range of activated partial thromboplastin time (aPTT) and INR value because even slight increase or decrease in plasma drug concentration can have profound clinical effects. On the other hand, for this same reason, patients using heparin and warfarin are often subject to rigorous monitoring of aPTT or INR and doses might be adjusted according to lab reports.

DDIs were reported from cardiology department. Concurrent use of many drugs and frequent addition of new drugs makes this group of patients vulnerable to DDIs. Despite all this, there is a need to increase the

awareness of possible DDIs in all hospital departments, as a sizeable number of DDIs have been recorded in all of them. The age, gender, number of drugs taken and multiple disease states were identified as the risk factors for developing DDIs ($P < 0.0001$). There was an extremely significant linear relationship ($r = 0.98$; $P < 0.01$) between the number of drugs prescribed and the DDIs in patients. Similarly, a significant linear relationship ($r = 0.96$; $P < 0.0001$) was observed between length of stay and DDIs. These results are in accordance with previous reports available in the literature.^[28]

Consistent with previous research, it was observed in this study that the use of multiple medications was associated with significantly increased risk of being prescribed potentially harmful drug–drug combinations; in fact, the odds of being prescribed potentially interacting drug more than doubled for each additional medication prescribed, after controlling for other factors.^[29,30] With regard to management approach for DDIs, drug withdrawal or dose reduction is usually the first step to be employed for the management of DDIs. In present study, in 70 cases (79.54%) the suspected drug was withdrawn, and in 12 (13.63%) cases the dose of the suspected drug was altered. Drug withdrawals and dose alterations of suspected drugs have been reported in the literature.^[25]

On causality assessment of DDIs by using Naranjo algorithm, DDIs were confirmed to have the probable causality. Considering the severity assessment of the reactions, majority of the reactions were categorized as moderate in nature, followed by severe and mild severity, and these findings are different when compared with the reports of spontaneous reporting studies.^[21,31]

The usefulness of computerized screening depends on the quality, including proper validation, of data held in the software. Furthermore, updating such systems requires knowledge, judgment and continuous effort by specialists maintaining the drug interaction database.^[31]

Limitation of this study is its short duration without any intervention component. Controlled study to evaluate whether good clinical management of DDIs can reduce drug-related morbidity or mortality is needed in the future in this discipline.

CONCLUSION

This study reports the incidence of DDIs in the cardiology department in a hospital from Indian setting. This study also examined patient, drug characteristics, causality and

severity of DDIs. This study shows that DDIs are frequent among hospitalized cardiac patients. The factors influencing DDIs are age, gender, number of prescribed drugs and length of hospital stay and cost. Thus, development and implementation of cautionary guidelines and computer-based screening might help to prevent potentially harmful drug interactions.

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