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RESEARCH ARTICLE

Potential drug-drug interactions among ischemic heart disease patients at a tertiary care hospital

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ABSTRACT

Background: Drug-drug interactions (DDIs) often pose a greatest challenge to health-care providers in patient care, hence their prediction, identification, and prevention are of prime importance. **Aims and Objectives:** The aims of the study were to evaluate the potential DDIs (pDDI) and factors influencing clinically relevant pDDI in ischemic heart disease (IHD) patients. **Materials and Methods:** An analytical cross-sectional study conducted from April to September 2018 to analyze the pDDIs among the outpatients of the Cardiology Department at Bangalore Medical College and Research Institute. All patients with a history of IHD on at least two drugs were included in the study. Patient demographic data and prescription details (drugs prescribed, duration of therapy, and number of drugs) were collected in a case record form. Drug data were analyzed for interactions using a drug interaction software (Lexicomp version 4.1.1) by risk rating scale (category A, B, C, D, or X). **Results:** Of 520 IHD patients, 489 had 3217 pDDIs. The average number of drugs prescribed per patient was 6.4±1.6 and most commonly prescribed drugs were aspirin (93%), atorvastatin (88%), clopidogrel (60%), metoprolol (57%), and ramipril (43%). Aspirin and clopidogrel (54%), aspirin and ramipril (40%) were the most commonly interacting pairs. The majority of the interactions were of category C, i.e. which requires monitoring of therapy. Number of drugs prescribed and hypertension was found to be the factors significantly influencing clinically relevant pDDIs. **Conclusion:** Antiplatelets and statins were the most commonly prescribed drugs in IHD and contributed to most of the pDDIs in particular categories C and D. In addition to number of drugs, comorbidity also influences pDDIs. Awareness regarding DDIs should be raised among prescribers which will enable them to recognize potentially harmful drug combinations and avoid them or to monitor therapy if such drugs are deemed essential.

KEY WORDS: Aspirin, Clopidogrel, Ischemic heart disease, Potential drug-drug interactions

INTRODUCTION

Drug interaction is said to occur when the effects of one drug are changed by the presence of another drug, herbal medicine, food, drink, or by some environmental chemical agent.[1] Likewise, drug-drug interactions (DDIs) imply the ability of a drug to modify the action or effects of another drug administered successively or simultaneously.[2] The detrimental effects of prescribing multiple drugs include adverse effects, DDIs, and non-compliance and may lead to higher health-care costs and an increased risk of hospitalization.[3] DDIs account for 27% of adverse drug reactions (ADRs) and 15.6–17.4% of hospital admissions.[2,4]

Ischemic heart disease (IHD) is one of the major contributors to cardiovascular disease mortality in India, together with

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stroke it is responsible for one-tenth of the years of life lost. Indicating premature deaths in younger individuals.[5] Patients with cardiovascular diseases are particularly vulnerable to DDIs due to multiple drug prescriptions, comorbidities, and the influence of heart disease on drug metabolism.[6] The prevalence of potential DDI (pDDI) in cardiology is reported to be high (83–91%) and the chance of identifying interacting drug pairs per prescription was 8 times higher among these patients as compared to other medical specialties.[3] Besides, number of co-morbidities are observed to be more in IHD patients, leading to an increase in the number of cardiovascular drugs prescribed ranging between 5.5 and 16.2.[7]

Various factors such as age, gender, genetic make-up, comorbidity, concomitant medication, food components, smoking, and environmental factors can influence the outcome of prescribed medicines. Hence, this study intends to determine the frequency of pDDIs and explore additional factors associated with it in patients with IHD and to provide relevant and useful feedback to physicians regarding high-risk pDDIs.

Objectives

The objectives of the study were:

- To evaluate the pDDIs among patients with IHD
- To determine the factors influencing clinically relevant pDDIs in IHD patients.

MATERIALS AND METHODS

After obtaining approval from the Institutional ethics committee (Ref No. BMC/PS/25/2018-19), a total of 567 patients with IHD visiting cardiology outpatient department (OPD) of BMCRI for follow-ups were screened. Based on the previous study,[8] considering a proportion of pDDI as 87.2% in patients with IHD, the sample size calculated was 496; considering 5% non-responders, the total sample size came up to 520 and was included in the current study after fulfilling inclusion and exclusion criteria. This cross-sectional study was conducted from April to September 2018. Patients of either gender aged >18 years, who were taking at least two drugs and willing to give written informed consent, were included in the study. Patients with other than IHD as their primary diagnosis were excluded from the study.

The demographic data, history, and clinical examination findings, relevant data on drug prescription that is, number of drugs, dosage form, dose, route, and duration of drugs prescribed to each patient were recorded in the case record form. The collected prescriptions were evaluated for potential DDIs using drug interaction software Lexicomp, version 4.1.1.

Based on the severity, DDIs are categorized into major (life-threatening or permanent damage), moderate (deterioration of patient's status), and minor (bothersome or little effect). Based on how rapidly one should respond to the drug interaction, a risk rating scale exists in Lexicomp software. Each interacting pair assigned a risk rating of A, B, C, D, or X. The progression from A to X is accompanied by increased urgency for responding to the data. In general, A and B monographs are of academic importance, not a clinical concern. Monographs rated C, D, or X always requires the user's/clinician's attention.[9]

Clinically Relevant pDDIs

According to a recent expert group consensus report, "clinically relevant potential" DDI is defined as "A potential DDI with safety concerns related to either toxicity or loss of efficacy that warrants the attention of health-care professionals and/or systems involved in the medication therapy process."[10] Since DDIs with the risk rating category of C, D, and X reasonably fit into the above definition, we considered them as clinically relevant and included them in analysis for evaluationg factors influencing pDDIs.

Statistical Analysis

The data were analyzed using descriptive statistics. Results were expressed as percentages or proportions where applicable and as mean ± standard deviation (SD) for continuous parametric variables. Binary logistic regression analysis was performed to determine the factors such as age, gender, comorbid conditions, number of drugs, and duration of IHD, influencing clinically relevant potential DDIs. About 95% confidence interval with $P < 0.05$ was considered as statistically significant. Patient characteristics and other relevant data were computed using Microsoft Excel and SPSS statistical package version 20.0.

RESULTS

A total of 520 IHD patients were included in the study, 354 (68%) were males and 166 (32%) were females. The average age was 57.7 ± 11.6 years. Three thousand three hundred forty-nine drugs were prescribed with an average 6.44 drugs/patient. Number of cardiovascular and non-cardiovascular drugs prescribed was 2878 and 471, respectively [Table 1]. Hypertension (66%) was the most common comorbidity followed by and type 2 diabetes mellitus (T2DM), cerebrovascular accident, epilepsy, hypothyroidism, peripheral neuropathy, and chronic kidney disease [Table 1].

The most commonly prescribed drugs were aspirin (93%), atorvastatin (88%), clopidogrel (60%), metoprolol (57%), and ramipril (43%) [Table 1 and Figure 1]. Of 520 patients, 489 had a total of 3217 pDDIs, with an average of 6.18 per patient. The majority of the interactions were of Risk category C [Figure 2]. Two thousand six hundred fifteen

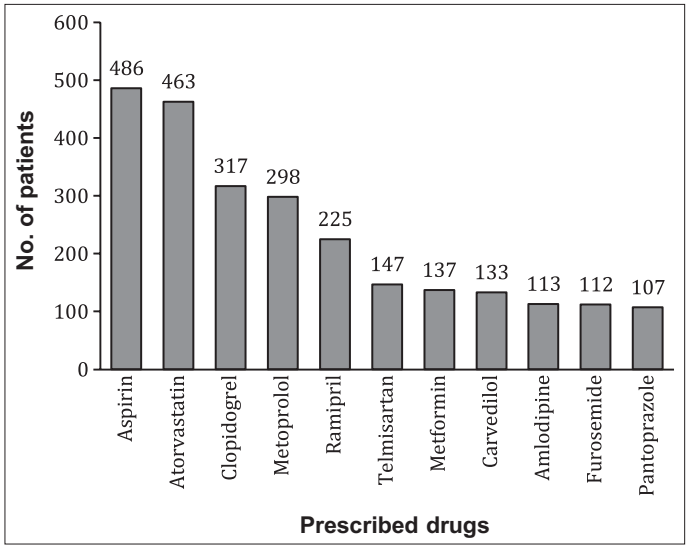

Figure 1: Most commonly prescribed drugs

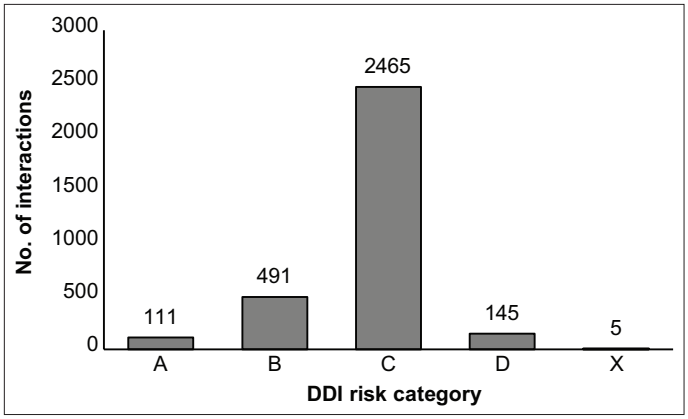

Figure 2: Potential drug-drug interactions

clinically relevant pDDIs were identified. Aspirin and clopidogrel (54%), aspirin and ramipril (40%) were the most commonly interacting pairs [Table 2]. Five pDDIs of category X were identified [Table 3].

On binary logistic regression analysis, number of drugs prescribed and hypertension was found to be significantly associated with clinically relevant pDDIs with an odds ratio of 4.71 and 5.25, respectively. With the increase in the number of drugs prescribed, the chance of occurrence of clinically relevant pDDI increases by 4.71 times and in patients with hypertension, the chance of occurrence of clinically relevant pDDI increases by 5.25 times [Table 4].

DISCUSSION

DDIs are one of the well-recognized medication-related problems encountered due to multiple drug prescriptions. Cardiovascular drugs have emerged as the most common class of drugs contributing to DDIs.[2,3] DDIs often pose the greatest challenge to health-care providers in patient care, hence their prediction, identification, and prevention are of prime importance.[11] A potential DDI is defined as, "The co-prescription of two drugs known to interact, and therefore a DDI could occur in the exposed patient." While several studies have assessed pDDIs using various resources, there are no gold standard tools to evaluate pDDIs. Drug compendia and knowledge base vendors such as Micromedex, Lexicomp, and Drugs.com differ in their approach with respect to identification, classification of pDDIs based on the clinical evidence with the limited agreement between the systems.[10] In our study, we used Lexicomp software to predict DDIs.

The average age of the study population was 57.7 years which is similar to previous studies, i.e., 57.27 years and 56.9 years by Patel *et al*. and Zachariah *et al*., respectively.[12,13] Male

Table 1: Patient characteristics

Variables	Value
Total number of patients	520
Age in years (Mean±SD)	57.7±11.6
Males (%)	354 (68)
Females (%)	166 (32)
Comorbidities	
Hypertension	344
Diabetes mellitus	182
CVA	20
Others	45
Total number of drugs prescribed	3349
Anti-platelets	
Aspirin	486
Clopidogrel	317
Statins	
Atorvastatin	463
Cardiovascular drugs	
Metoprolol	298
Ramipril	225
Telmisartan	147
Carvedilol	137
Amlodipine	133
Furosemide	113
Antidiabetic agents	
Metformin	112
Proton pump inhibitors	
Pantoprazole	107
Average number of drugs per patient (Mean±SD)	6.44±1.63
Number of cardiovascular drugs prescribed	2878
Average number of cardiovascular drugs per patient	5.53
Patients with pDDIs (%)	489 (94)
Total number of pDDIs	3217
Average pDDI per patient (Mean±SD)	6.18±4.52
Average duration of treatment in years (Mean±SD)	3.87±4.07

pDDI: Potential drug-drug interaction, SD: Standard deviation

Table 2: Most common clinically relevant pDDIs

Most common interactions	Number of pDDIs (%)	Risk rating	Severity	Type of DDI	Mechanism of interaction
Aspirin + Clopidogrel	281 (54)	C	Moderate	Pharmacodynamic	Enhanced anti-platelet activity
Aspirin + Ramipril	212 (41)	C	Moderate	Pharmacodynamic	Aspirin may enhance the nephrotoxic effect and diminish the therapeutic effects of ACEIs
Atorvastatin +Carvedilol	115 (22)	C	Moderate	Pharmacokinetic	P-GP/ABCB1 inhibitor may increase the serum concentration and enhance the distribution of P-GP substrates
Aspirin + Furosemide	102 (20)	C	Moderate	Pharmacodynamic	Aspirin may diminish the therapeutic effects of loop diuretics and loop diuretics may increase serum concentration of aspirin
Clopidogrel + Pantoprazole	75 (14)	D	Moderate	Pharmacokinetic	PPI increase serum concentration of active metabolite of clopidogrel

pDDIs: Potential drug-drug interaction, DDI: Drug-drug interaction, ACEIs: Angiotensin-converting-enzyme inhibitors

Table 3: Category X* drug interactions

Drug combination	Number of pDDI	Severity	Mechanism of interaction
Ramipril + Telmisartan	3	Major	Telmisartan enhances the toxic effect of ramipril Telmisartan enhances the serum concentration of ramipril Concentration of the active metabolite – ramiprilat may be increased
Sildenafil + Nitroglycerine	1	Major	PDE-5 inhibitor enhances the vasodilatory effect of nitrates
Sildenafil + Nicorandil	1	Major	PDE-5 inhibitor enhances the vasodilatory effect of nitrates

*Avoid combination; the risks associated with concomitant use of these agents usually outweigh the benefits,[8] pDDI: Potential drug-drug interaction

Table 4: Factors associated with clinically relevant pDDIs

Variables	Odds ratio*	Confidence interval	*P*-value
Age	1.020	0.983–1.058	0.297
Gender	0.496	0.221–1.114	0.09
Duration of IHD	0.945	0.848–1.051	0.297
Number of drugs prescribed	4.713	2.921–7.604	0.0001#
Hypertension	5.254	2.043–13.508	0.001#
Diabetes mellitus	2.228	0.702–7.068	0.174

*Binary logistic regression analysis: #$P<0.05$ considered significant.
IHD: Ischemic heart disease, pDDIs: Potential drug-drug interaction

preponderance (68%) was observed and is in accordance with other studies, indicating the fact that the prevalence of IHD is slightly high among males.[14,15] Cardiovascular disease develops 7–10 years later in women than in men, as exposure to endogenous estrogens during the pre-menopausal period is said to delay the manifestation of atherosclerotic disease.[16]

The frequency of occurrence of pDDI among IHD patients was 94% which is similar to previous studies conducted by Murtaza *et al*. (91.6%) and Patel *et al*. (87.2%).[8,15] In the present study, we observed that hypertension (66%) and T2DM (35%) were the frequently associated comorbidities which is attributed to a higher prevalence of such lifestyle diseases in India.[17] Dumbreck *et al*. in their review evaluating National institute for health and care excellence (NICE) guidelines for the treatment of various diseases including IHD reported that potentially serious DDIs were relatively common as they often have multiple comorbidities and that the guideline developers should consider measures to identify and highlight the potential for various interactions between recommended drugs.[18]

The NICE guidelines and the American Heart Association guideline recommends dual antiplatelet therapy, angiotensin-converting-enzyme inhibitors (ACEI), beta-blockers, and statins for all stable IHD patients.[19,20] The prescribing trend in the present study complies with guideline recommendations and is in line with previous studies.[12,21] A total of 3349 drugs were prescribed with an average of 6.18 pDDI per patient. About 77% of pDDIs belonged to moderate severity which is in agreement with Patel *et al*., namely, 60.3% pDDIs in cardiology inpatients.[12]

The most common interacting pair was aspirin and clopidogrel (54%) and is in concordance with a study by Al-Amin (46.85%).[22] Dual antiplatelet therapy (DAPT; aspirin with P2Y12-inhibitor) is essential in primary and secondary prevention of IHD and for the maintenance of stent patency as recommended by the Association of Physicians of India and NICE.[17,19] Drug interaction between aspirin and clopidogrel is a pharmacodynamic one, i.e., aspirin inhibits platelet activation through TXA2 pathway, whereas clopidogrel acts by inhibiting P2Y12 receptor leading to synergistic anti-hemostatic effect.[23] Although this combination therapy may offer additional benefit over monotherapy, physician should monitor for the risk of bleeding as it belongs to risk category C. Aspirin is also noted to have PD interaction with ramipril (41%) which is similar to the study conducted by Aswani *et al*.[7] Prostaglandins are essential for the pharmacological action of ACEIs, whereas aspirin irreversibly inhibits synthesis of prostaglandins leading to attenuation of therapeutic effects of nearly all antihypertensives, including ACEIs.[24]

Clopidogrel and PPIs are frequently co-prescribed due to the fact that PPIs reduce the risk of GI bleed in high-risk patients.[25] Different PPIs are known to inhibit CYP2C19 to a variable extent and thereby reduce the formation of the active metabolite of clopidogrel accordingly.[26] In the present study, pDDI with clopidogrel and pantoprazole was noted which belonged to risk category D meaning modification of therapy is required after risk versus benefit assessment. USFDA recommends concomitant use of clopidogrel and omeprazole or esomeprazole to be avoided.[27] Guidelines recommend that patients who are on DAPT and high risk for GI bleed should receive PPIs, either pantoprazole or rabeprazole, due to their lesser affinity for CYP2C19.[28] In the current study, although this interaction was predicted as risk category D, there is insufficient data yet as to whether it is clinically significant.[29]

Potential DDIs of risk category X were also noted in the present study, mainly between ramipril with telmisartan and sildenafil with vasodilators. Telmisartan augments the toxic effect of ramipril by increasing the serum concentration of the latter and its active metabolite ramiprilat. PDE-5 inhibitor (sildenafil) enhances the vasodilatory effect of nitrates, causing dangerous fall in blood pressure and may precipitate myocardial infarction.[23] Patients with pulmonary arterial hypertension were prescribed sildenafil as it is the drug of choice, but the fact that these patients were also on glyceryl trinitrate for IHD was over-looked. High patient load in cardiology OPD may have imposed time constraint in reviewing all the previous medications and anticipate any risk due to multiple drug prescription. Physician was informed about the seriousness of such combinations. In patients with multiple disease conditions, mere application of guideline recommendations developed for individual disease without accounting for comorbidities can result in complex drug regimens with an unanticipated risk of drug interaction leading to adverse outcomes.[18]

Number of drugs prescribed and hypertension was significantly associated with clinically relevant pDDI with an odds ratio of 4.71 and 5.25, respectively, similar to a study by Patel *et al*.[8] Multiple drug prescription is a well-known factor for the occurrence of DDIs, in turn contributing to ADRs.[4] Incidentally, ramipril and carvedilol are among the commonly prescribed antihypertensives in this study and contribute to most of category C interactions owing underlying to PK and PD interactions. Irrespective of their well-documented status, clinical outcomes of pDDIs may vary individually due to patient-related factors. Hence, drug-interaction software may be considered as an effective and valuable tool in patient care in predicting dangerous drug combinations provided, it factors in both patient-related data and clinical evidence.[3] Educating the physician about rational prescribing, usefulness, and accessibility of drug interaction software can aid in promoting good prescribing practices.[30]

The limitations of the study being a cross-sectional design which does not allow for assessment of outcomes of pDDIs.

CONCLUSION

The present study demonstrated a higher frequency of potential DDIs among patients with IHD attending cardiology OPD due to the complexity of pharmacotherapy. Antiplatelets and statins were the most commonly prescribed drugs in IHD and contribute to most of the pDDIs in particular categories C and D. Number of drugs prescribed and hypertension emerged as the factors significantly influencing clinically relevant pDDI. Exposure to harmful DDIs (category X) can be prevented instantaneously by supporting clinical decision with the aid of electronic DDI prediction software.

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