

Assessment of drug-drug interactions in the prescription of elderly patients on cardiovascular drugs

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ABSTRACT

Background: Cardiovascular disease is one of the major causes of mortality and morbidity in a developing country like India. These patient's prescription contains multiple drugs to reduce the mortality and morbidity and they also contain drugs for treatment of co morbidities leading to polypharmacy. The main objective of the study was to identify the pattern of drug- drug interaction (DDI) in patients on cardiovascular drugs with various co existing morbidities.

Methods: This study was conducted in the Department of General Medicine of a tertiary care center. Prescription of 200 patients were analysed for demographic details like gender, age, comorbidities and drugs prescribed. DDI were assessed using Micromedex software.

Results: In this study, conducted on the prescription of 200 elderly patients, 13 (66%) prescription had 408 DDI, of which 158 (39%) were major, 246 (60%) were moderate and 1 (0.02%) was contraindicated and 3 (0.007%) were minor.

Conclusions: It can be concluded from the present study that the risk of DDI increases with the increase in number of drugs in the prescription and there is increase in number of drugs in the prescription with the increase in number of co morbidities. The antiplatelet and anticoagulant group of drugs were responsible for majority of DDI, followed by antihypertensives and hypoglycaemic agents. Most of these DDI could be avoided with slight modification in the dosage regimen based on the pharmacokinetics and pharmacodynamics of the drug.

Keywords: Cardiovascular drugs, Drug-drug interaction, Major interaction, Moderate interaction

INTRODUCTION

Drug-drug interaction (DDI) refers to modification of response to one drug by another drug when they are administered simultaneously. The modification is mostly quantitative where the response is either increased or decreased in intensity but sometimes it is qualitative, hence abnormal or a different type of response is produced. The possibility of DDI arises whenever a patient receives more than one drug and chances increase with number of drugs taken.¹ There are numerous potential DDIs that can

result in toxicity, alteration of the desired therapeutic effects and even can lead to life threatening condition. Drug-specific factors like dose, route of administration, drug formulation and the sequence of drug administration can be determinants of DDI.²

As per National Policy on older persons adopted by Government of India, elderly or geriatric is defined as a person who is of age 60 years or above. According to official population projections, the number of Indian elderly will raise to approximately 140 million by 2021.³

Polypharmacy is defined as concomitant use of more than two medication.⁴ Polypharmacy practice is common in elderly as they are usually having comorbid illnesses. Polypharmacy and complicated drug regimens used for treating the comorbidities in an elderly lead to DDIs and adverse drug reactions. Studies have confirmed polypharmacy as one of the major risk factors in precipitation of DDIs.⁵ The elderly population are at increased risk because of decreased functioning of the systems, more number of medications due to comorbidities and multiple drug regimes. Sometimes inappropriate prescribing patterns may lead to poly pharmacy.⁶

DDI are classified as⁷

- Contraindicated- drugs contraindicated for concurrent use.
- Major- interaction may be life threatening and or require medical intervention to minimize or prevent serious adverse events.
- Moderate- interaction may result to exacerbation of patient’s condition and or require an alteration in the therapy.
- Minor- interaction would have limited clinical effects, may include increase in frequency or severity of side effects but generally would not require major alteration in the therapy.

METHODS

In this cross-sectional study, the data was collected from 200 geriatric inpatients prescriptions admitted to M.S. Ramaiah Hospital, Bangalore, Karnataka, India. Institutional ethics committee approval was obtained. Study period was from March 2015 to March 2016. This study included all elderly in patients on cardiovascular drugs, who were admitted to medicine ward. The critically ill patients in the intensive care were excluded from the study. The out patients were not included in the study. Patient’s demographics, pre-existing diseases and drug history were recorded. Drug-Drug interactions were assessed using Micromedex software on reviewing patient’s case records. All the quantitative variables like age were expressed as mean and standard deviation. All the qualitative variables were expressed as proportion.

This study was conducted by analysing all the prescriptions of geriatric inpatients admitted in MS Ramaiah Hospital, Bangalore, Karnataka, India. The prescriptions were assessed on the basis of demography and drugs prescribed. All the prescriptions will be evaluated for polypharmacy and drug interactions. Drug-drug interactions was assessed through Micromedex software.⁸

In the present study, expecting 95% confidence level 10% relative precision, the study requires a minimum of 181 subjects. Descriptive statistics were analysed and presented in terms of mean, standard deviation and

percentage. Chi-square test was used to study the association of age and gender with polypharmacy and DDIs. SPSS version 20 was used to analyse the data.

RESULTS

A total of 200 prescriptions of elderly patients were analysed. All the quantitative variables like age were expressed as mean and standard deviation. All the qualitative variables were expressed as proportion. There were 73% (n=126) male patients and 37% (n=74) female patients in this study (Table 1).

Table 1: Age distribution.

Age (years)	n (number)
60-69	139(70%)
70-79	52(26%)
80-89	08(4%)
>90	01(0.5%)

In these 200 prescriptions, 408 interactions were found. The age of this population ranged from 60 to 93 years. The mean age of the patients was 69.19±6.99 years. The number of drugs used per patient ranged from a minimum of 1 to a maximum of 10 drugs. The patients were on various groups of drugs acting on the cardiovascular system as follows:

- Antihypertensives- calcium channel blockers, beta blockers, ACE inhibitors, angiotensin receptor blockers, alpha blockers,
- Diuretics- loop diuretics, thiazides, potassium sparing diuretics, osmotic diuretics,
- Drugs with positive inotropic effects- digoxin,
- Antiplatelet agents- aspirin, clopidogrel,
- Hypolipidemics- statins, fibrates,
- Vasodilators- nitrates, potassium channel activators,
- Electrolytes,
- Thyroid and antithyroid agents,
- Anticoagulants.

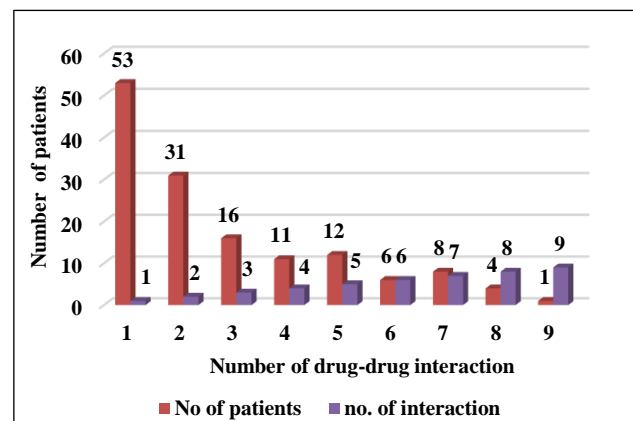
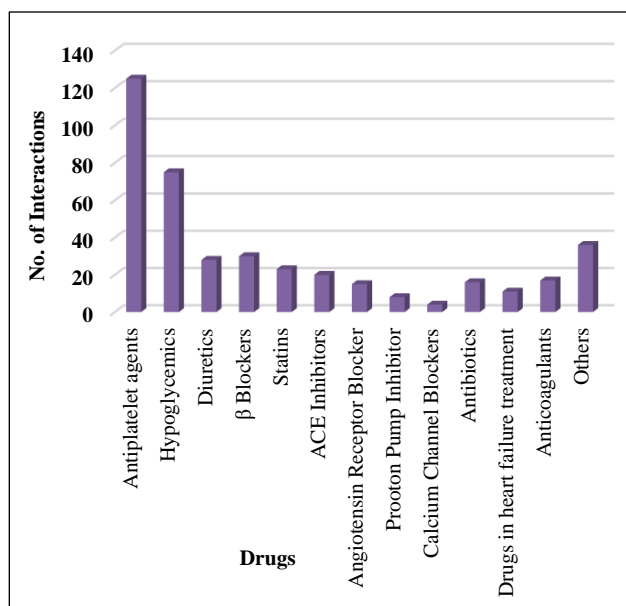


Figure 1: Number of interactions.

Table 2: Frequency and effects of DDIs due to cardiovascular drugs.

Drugs	Interactions	No. of patients (n)
Aspirin+Clopidogrel	Increases risk of bleeding	38
Atorvastatin+Clopidogrel	Decreases antiplatelet effect	32
Aspirin+ Insulin	Increases hypo/hyperglycaemia risk	17
Aspirin+Furosemide	Decreases diuretic efficacy	16
Aspirin+Metoprolol	Decreases antihypertensive efficacy	16
Metoprolol+Insulin	Masks symptoms of hypoglycaemia	07
Telmisartan+Insulin	Increases risk of hypoglycaemia	04
Aspirin+Ramipril	Decreases antihypertensive efficacy	10
Aspirin+Cilostazol	Increases risk of bleeding	07
Amlodipine+Clopidogrel	Decreases antiplatelet efficacy	04
Ramipril+Metformin	Increases risk of hypoglycaemia	04
Aspirin+Enalapril	Decreases antihypertensive efficacy	08
Ramipril+Spironolactone	Increased risk of hyperkalaemia	07
Ramipril+Insulin	Increases risk of hypoglycaemia	04
Insulin+Metformin	Increases risk of hypoglycaemia	06
Insulin+Levofloxacin	Impaired glycaemic control	06
Insulin+Losartan	Increases risk of hypoglycaemia	04
Other combination with cardiovascular drugs with less than or equal to frequency of 4 DDI		218
Total DDIs		408

**Figure 2: Different group of drugs involved in the interaction.****Table 3: Classification of DDI.**

Category	n	Percentage
Contraindicated	1	0.002%
Major	158	39%
Moderate	246	60%
Minor	3	0.007%
Total	408	

Figure 1 shows the number of interactions per prescription. At least 53 (27%) prescriptions were found to have at least one interaction.

On statistical analysis of age of patient and number of drugs by Pearson's Chi Square test, p was significant at less than 0.0001, hence there was statistically significant difference between the age and the number of drugs in the prescription, and the number of drugs increased with the increase in age. As the age increased the risk of co-morbid illness also increased, so the number of drugs in the prescription also increased. But there was no statistically significant difference in the occurrence of DDI among male and female ($p=0.3$). The drugs that were prescribed for co morbid illness like diabetes mellitus, bronchial asthma, seizure disorder, gastro oesophageal reflux disorder, peptic ulcer disease, peripheral vascular disease, acute infections etc. would often interact with different groups of drugs acting on cardiovascular system. The interacting drugs belonged to various pharmacological classes like- proton pump inhibitors, H2 blockers, beta agonists, antiepileptics, oral hypoglycemics, insulin, prokinetic agents and antibiotics. It was found that the antiplatelet agent, aspirin (33%) was the most common drug to be involved in DDI, followed by insulin (20%). Aspirin would interact with antihypertensives and diuretics and blunt their therapeutic efficacy.

The drugs would interact with insulin and would either increase the risk of hypo/hyperglycemia. These DDI might reduce the quality of life and also add on to the disease burden. Table 2 shows the different DDI caused by various

drugs. Figure 2 shows the different group of drugs involved in DDI. Majority of the interactions were moderate in nature. Table 3 depicts the classification of 408 interactions found in the prescription.

DISCUSSION

This study involved 200 prescriptions of elderly patients on cardiovascular drugs, of which 74 were female and 126 were male. In this study, the prescription contained minimum of one drug to a maximum of 11 drugs. These prescriptions contained more than 70 different types of drugs of them about 40 drugs were acting on the cardiovascular system which belong to the following classes: antiplatelet agents like aspirin, clopidogrel and cilostazol, antihypertensives like CCBs amlodipine and clindipine, ARBs- telmisartan, olmesartan and losartan, ACEIs- enalapril and ramipril, β blockers- atenolol, metoprolol, propranolol, carvedilol and α blockers like prazosin, α agonists- clonidine, moxonidine, diuretics- thiazides, furosemide, torsemide, spironolactone, metolazone, antianginals like nitrates and drugs like digoxin, ivabradine and ranolazine were used in heart failure. More than 65 pairs of DDI were found. The minimum number of DDI per patient was 1 in 53 patients and the maximum was 9 in one patient who was on 11 drugs (Figure 1). 246 (60%) of the DDI were moderate in nature and 158 (39%) were major DDI, Table 3 illustrates the effects of these DDI. Antiplatelets were the most common drugs responsible for the DDI where they increased the risk of bleeding when used with other anticoagulants and also diminished response of various other drugs (Figure 2). In a study conducted by Sharma S et al, a total of 48 DDI was identified in 150 patients. Among them 32 were identified with at least one interacting combination. 20 (65.5%) were identified with single interacting combination, this was followed by the patients who encountered two DDI in 8 (25%) patients and three interactions in 4 (12.5%) patients.⁹

Polypharmacy is a major cause of DDI. According to the analysis of SAGE (Study on global aging) data by Dutta M et al, the prevalence of polypharmacy was 4.2% among elderly in India. This study also showed higher proportion of polypharmacy among male, aged 70-79 years.¹⁰ But in present study polypharmacy was more prevalent in the age group 60-69 years. Ahmad A et al, have concluded in a study that out of 404 records reviewed, 78 (19.3%) patients had potential DDI and out of these 74 (54%) were moderate in nature.¹¹ According to Pelliccia F et al study, states that DDI contributed for the inconsistency in the efficacy of clopidogrel to prevent atherothrombotic events.¹² According to Corsonello A et al, infections in elderly have increased rate of mortality and morbidity because of the polypharmacy regimens which increase the risk of DDI. Additionally, changes in the body composition occurring with advance in age, reduced liver function and perfusion, reduced renal excretion affects the pharmacokinetics and pharmacodynamics.¹³ Hence, DDI and ADR contribute to a significant health issue worldwide.¹⁴ Polypharmacy may

indirectly lead to hospital readmissions increasing the morbidity and mortality.¹⁵ Over the counter medication and non-prescription drugs significantly contribute to polypharmacy and DDI.¹⁶ Lesser the number of drugs prescribed, lesser the chance of inappropriate medication and DDI.¹⁷ Additionally, there is a controversial role of alternative system of preventive medicine, where yoga can help treat insomnia, stress and control of blood glucose and blood pressure may reduce the number of drugs and their frequency of administration in the elderly patients, hence may reduce the risk of DDI.¹⁸⁻²¹ The alternative system of herbal medicines further poses the risk of herbal-drug interactions by altering the pharmacokinetics and pharmacodynamics of the drugs. These herbal medications however have intrinsic variation amongst themselves in active drug composition.²² The drug-gene interaction is the newest concept that requires further reasoning on its impact on pharmacokinetic variations in the absorption, metabolism and excretion of the drug. Therefore, thorough understanding of P450 isoenzymes and drug transporters may lead to new methods to prevent clinically relevant drug interactions.^{23,24} Tailor made drug therapy, based on the pharmacogenomics of individual patient may be the solution to eliminate such drug-gene interaction.²⁵

CONCLUSION

Polypharmacy increases the risk of drug-drug interactions, most of these can be minimized by pharmacokinetic and pharmacodynamic modification of the drug regimen. This also reduces the incidence of adverse drug reactions due to drug-drug interactions and also reduces the morbidity and mortality. Coordination between the clinician and the clinical pharmacologists plays an essential role in optimized prescription.

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