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Drug Related Problems and Reactive Pharmacist Interventions for Inpatients Receiving Cardiovascular Drugs

Rani Reema Abraham

Department of Pharmacy Practice, College of Pharmacy, Sri Ramakrishna Institute of Paramedical Sciences, Sri Ramakrishna Hospital Campus, Coimbatore-641 044, India

Email: ranireema09@gmail.com

Abstract – Although pharmacotherapy in cardiovascular diseases can improve the well-being, its benefit can be compromised by drug-related problems (DRPs). The objectives of the present study were to examine the number and nature of drug related problems in patients with cardiovascular diseases and to demonstrate the role of pharmacist in ensuring safe and efficient use of medicines in daily practice in the inpatient settings. A prospective cross sectional study was carried out for 8 months in the general medicine department of a 640 bedded multi-specialty private corporate hospital. The nature, prevalence and incidence of DRPs were studied and documented using the PCNE (Pharmaceutical Care Network Europe Foundation) classification system. A total of 1051 drugs were prescribed during the study period. Most commonly prescribed categories of drugs were antihypertensives (21.05%), anticoagulants and antiplatelet drugs (11.13%), antiulcers (8.84%), insulin and oral hypoglycemic agents (6.95%) and anti infectives (5.42%). Drug interactions (46.19%), drug overdosage (17.26%) and drug duplication (11.17%) were the most frequently occurring DRPs. Most common clinical risk factors identified were polypharmacy (66.21%) and diabetes mellitus (20.31%). Antihypertensives presented the highest drug risk ratio. Statistical analysis showed positive correlation between age and number of DRPs in the study population. Pharmacist interventions were mostly on drug interactions, dosing and drug choice and 59% of them were accepted, resulting in prevention of DRP occurrence. The current study demonstrated the importance of routine medication review and the need of a pharmacist in a multidisciplinary team in treating cardiovascular diseases.

Keywords – Drug related problems, cardiovascular diseases, drug interactions, clinical risk factors

1. Introduction

Cardiovascular diseases (CVDs) remain the biggest cause of deaths worldwide**.** A WHO report (2011) estimated that 17.1 million people die of CVDs each year representing 30% of all deaths. Of these, about 7.3 million are due to coronary heart disease and 6.2 million due to stroke. By 2030, an estimated 23.6 million people will die from CVDs mainly from heart disease and stroke. These are projected to remain the single leading causes of death [1].

According to the WHO, cardiovascular diseases will be the major cause for death and disability in India by 2020 [2]. The number of CVD related cases is projected to be 64 million in 2015 [3]. CVD related deaths are estimated to be about 4.6 million by 2020 [4].

Although pharmacotherapy in cardiovascular diseases can improve the well-being, its benefit can be compromised by drug-related problems (DRPs). A drug-related problem is any event or circumstance involving drug treatment that interferes with the patient achieving an optimum outcome of medical care [5]. They pose as a significant risk, leading to significant morbidity and mortality. In a review of international studies, it was found that about 28% of all emergency department visits were related to DRPs and 24% of them resulted in hospital admission. In a study conducted by Blix et al in 2004, it was seen that about 87% of hospitalized patients have drug related problems [6]. In another study conducted by Nascimento et al in 2009, the incidence of DRPs was reported as 91.7% [7]. An Indian study reported that the incidence of DRPs was found to be greater than quoted in developed countries. High incidence of inappropriate dosage and improper drug selection observed in the study was attributed to lack of standard treatment protocols and the differing treatment patterns between the medical wards in each Indian hospital [8]. Cardiovascular drugs are one of the drug categories frequently involved in drug related problems. A study by Andreazza et al in 2011 reported cardiovascular drugs to account for the majority of all DRPs [9]. Detection and prevention of DRPs can save lives along with enhancing patients' quality of life and optimizing healthcare costs.

Many studies have proven the significance of pharmacists in identifying and resolving potential DRPs through timely interventions. Gattis et al in 1999 observed that including a pharmacist as a member of a multidisciplinary heart failure (HF) team significantly reduced mortality and HF events [10]. Studies assessing the prevalence of DRPs in hospitalized patients and the significance of pharmacist intervention in such cases are lacking in India. Little is known about the extent of drug related problems in cardiovascular diseases. Hence the objectives of the present study were to examine the incidence and prevalence of drug related problems in patients with cardiovascular diseases, to carry out reactive interventions to reduce their incidence and to demonstrate the role of pharmacist in ensuring safe and efficient use of medicines in daily practice in the inpatient settings.

2. Materials and Methods

The study was conducted in the General medicine and Cardiology departments of a 640 bedded multispecialty

tertiary care hospital at Coimbatore. All inpatients receiving cardiovascular drugs were included in the study. The outpatients, intensive care patients, those not willing to participate and patients with insufficient medical records were excluded from the study. Medication chart review for each patient was conducted and recorded in customized data entry form. DRPs were identified by evaluating the appropriateness of prescriptions in terms of indication, dosage, duration of therapy, adverse drug reaction (ADR), appropriateness of drug choice, safety and efficacy. Available clinical guidelines were used as standards for drug therapy. Problems identified and recognized were documented and discussed with the concerned physician. The review took about one hour per patient. DRPs were categorized using PCNE classification (Pharmaceutical Care Network Europe Version 6.02). These included drug overused, drug underused, contraindication, inappropriate drug, inappropriate duplication of therapeutic group, no clear indication of drug, adverse drug reactions, therapeutic drug monitoring and drug interaction.

The number of DRPs per patient and medications most frequently associated with DRPs was determined to estimate the incidence of DRPs. Drug risk ratio was calculated as the number of DRPs in relation to how often the drug was used (DRP/Times used). Some common clinical/pharmacological risk factors of DRPs such as polypharmacy, reduced renal function (calculated creatinine clearance < 50 ml/min or serum creatinine above normal range), reduced liver function (aspartate aminotransferase three times above normal range) and confirmed diabetes mellitus were identified through systematically performed case review.

2.1. Statistical analysis

Descriptive statistical analysis was performed using SPSS (version 19.0) statistical software. Categoric variables were described by frequencies and percentages, and continuous variables were described by means and standard deviations. ANOVA tests were used to study differences between groups for variables of age, number of drugs prescribed, number of clinical/pharmacological risk factors and number of DRPs. A p value less than 0.05 was considered statistically significant. Association between the number of drugs prescribed, clinical/pharmacological risk factors and DRPs was found out by Pearson's correlation coefficient.

3. Results and Discussion

The study included 80 patients with a mean age of 59.31 ± 12.46 (range 13-84years). In the total population, 66% were males. The mean number of drugs prescribed in the study population was 9.595 ±3.53 (range 6-16). The major diagnoses included systemic hypertension (SHT) 47.5%, ischemic heart disease (IHD) 16.25%, congestive cardiac failure (CCF) 10%, and cerebrovascular accident (CVA) 7.5%. Diabetes mellitus (46.25%), chronic renal failure (18.75%) and peptic ulcer (8.95%) were the most common concomitant diseases present in patients with cardiovascular diseases.

A total of 1051 drugs were prescribed during the study period. Most commonly prescribed categories of drugs were antihypertensives (21.05%), anticoagulants and antiplatelet drugs (11.13%), antiulcers (8.84%), insulin and oral hypoglycemic agents (6.95%), anti infectives (5.42%), antidyslipidemics (4.56%) and analgesics (2.94%). Drugs commonly prescribed in SHT were amlodipine, clopidogrel, pantoprazole, torsemide, aspirin and insulin. Clopidogrel, pantoprazole, amlodipine, atorvastatin and heparin were the drugs normally prescribed in IHD. In patients with CCF the commonly prescribed drugs were furosemide, carvedilol, ramipril, clopidogrel, heparin and pantoprazole. Pantoprazole, clopidogrel, aspirin, ramipril and atorvastatin were the drugs commonly prescribed in CVA patients.

Table 1. Patient characteristics (n=80)

Types of cardiovascular diseases	No: of patients (%)	Age (mean ± SD)	Drugs (mean ± SD)	DRPs (mean ± SD)
SHT	38	62.77±13.06	10.083±2.28	4.77±0.683
IHD	13	64.96 ±10.70	9.86 ± 2.45	4.64±0.71
CCF	8	63.79±11.25	9.21±2.359	4.21±0.745
CVA	6	58.86 ± 20.21	10 ± 3.16	4.69 ± 0.49
MI	5	52.17 ± 14.03	9.83± 2.32	4.593 ± 0.82
DCM	3	61.5 ± 7.937	7.75 ± 1.5	3.42 ± 0.577
RHD	3	44.25 ± 18.23	7.75 ± 0.96	3.37 ± 0.5
Dyslipidemia	2	62 ± 8.72	7.24 ± 2.65	2.91 ± 0.577
CAD	1	55.5 ± 18.38	12 ± 3.36	5.13 ± 0.577
Angina	1	60 ±19.798	7.5 ± 0.71	3.4 ± 0.707

Patient characteristics of different cardiovascular diseases are described in table 1. Three hundred and ninety four DRPs were identified in 80 patients, which correspond to 4.9 DRPs per patient. Characteristics of DRPs identified are summarized in table 2. Table 3 and 4 illustrates the details of ADRs and potential drug interactions recorded during the study period.

DRPs were found to be high in drug categories like antihypertensives, antiplatelet drugs, anticoagulants, antihyperlipidemics and antiulcers. An analysis of nature and frequencies of DRPs revealed that drug interactions (46.19%), drug overdosage (17.26%), drug duplication (11.17%) and drug underdosage (10.41%) were the most frequently occurring DRPs. These findings are in agreement with that of Al-Hajje et al (2012) [11] who reported drug interactions (37%), overdosage (28%) and non-conformity to guidelines and contra-indications (23%) as the most frequent DRPs.

Patients with SHT were prescribed with 494 drugs

Table 2: Frequencies of DRPs with various cardiovascular diseases (n=394)

Cardiovascular disease	Dosing problem		Drug Choice problem							
	Drug Overused	**Drug underused**	**Inappropriate Group**	**Drug duplication**	**No clear indication**	**Contra Indication**	**Adverse Drug Reaction**	**Therapeutic Drug Monitoring**	**Drug interactions**	**Drug related problems**
SHT	14	9	6	10	2	4	4	2	61	112
IHD	8	5	4	6	1	4	2	0	41	71
CCF	7	8	2	5	1	1	1	0	22	47
CVA	8	4	2	6	0	2	1	0	10	33
MI	6	3	0	5	1	1	0	1	12	29
DCM	7	4	1	3	0	0	1	0	10	26
RHD	5	3	0	3	1	1	2	0	5	20
Dyslipidemia	6	2	1	2	0	1	1	0	6	19
CAD	4	1	1	2	1	0	1	1	7	18
Angina	3	2	0	2	1	2	1	0	8	19
Total (n)	68	41	17	44	8	16	14	4	182	394

(10.083 ±2.28). A total of 112 DRPs (28.43%) were identified in these patients (4.77 ± 0.683). Among the IHD patients who received a total of 217 drugs (9.86 ± 2.45), 71 DRPs (18.02%) were recognized with a mean of 4.64 ± 0.71. About 129 drugs were prescribed in patients with CCF with a mean of 9.21 ± 2.359 and a sum of 47 (11.93%) DRPs (4.21 ± 0.745) were observed. In patients with CVA, 70 drugs (10 ± 3.16) were prescribed and 33 (8.38%) DRPs (4.69 ± 0.49) were identified.

In patients with SHT and IHD, the most frequently identified DRPs were drug interactions (54.46% & 57.75%), drug overdosage (12.5% & 11.27%) and drug duplication (8.93% & 8.45%). Figure 1 and 2 represents the details of DRPs observed in these patients. In CCF patients, drug interactions (46.81%), drug underuse (17.02%) and drug overuse (14.89%) were frequently observed while in CVA patients, drug interactions (30.30%) was the most common DRP followed by drug overuse (24.24%) and drug duplication (18.18%). The results are represented in figure 3 and 4. DRPs identified were discussed with the concerned physician on the same day and necessary changes were made in the prescribing pattern.

Table 3. ADRs identified (n=14)

Class	Drug	ADR	No. of patients (%)
Antidiabetics	Insulin & OHA	Hypoglycaemia	5 (35.7)
Fluoroquinolones	Levofloxacin	Allergic reaction	3 (21.42)
Ca-Channel Blocker	Amlodipine	Pedal Edema	2 (14.29)
Diuretic	Torsemide	Hypokalemia	2 (14.29)
Anticoagulant	Warfarin	Bleeding	1 (7.14)
Beta blocker	Atenolol	Bradycardia	1 (7.14)

Table 4. Potential drug interactions (n=114)

S. No	Interacting Drugs	Effect	Severity	No. of patients (%)
1	Pantoprazole + Clopidogrel	An increased risk of thrombosis	Major	57 (30.98)
2	Heparin/ Aspirin+ Clopidogrel	An increased risk of bleeding	Major	22 (11.96)
2	Ramipril + Spironolactone	Hyperkalemia	Major	17 (9.24)
3	Insulin + Levofloxacin	Increased risk of hypo (or) hyperglycemia	Major	11 (5.98)
4	Furosemide + Amikacin	Nephrotoxicity	Major	6 (3.3)
5	Digoxin + Spironolactone	Digoxin Toxicity	Major	5 (2.72)
6	Levofloxacin + Theophylline	Theophylline Toxicity	Major	5 (2.72)
7	Cinnarizine + Alprazolam	Increased CNS depressant effect	Major	4 (2.17)

Table 5. Clinical risk factors (n=118)

Type of cardiovascular disease	Polypharmacy (%)	Diabetes Mellitus (%)	Reduced renal & hepatic function (%)
SHT	74.19	58.06	48.38
IHD	84.61	46.15	7.69
CCF	85	25	12.5
CVA	83.33	16.67	14.10
MI	85	20	7.09
DCM	66.67	16.67	2.56
RHD	66.67	8.33	3.84
Dyslipidemia	50	2.77	2.56
CAD	33.33	5.86	5.86
Angina	33.33	3.55	2.38

Table 6. Types of pharmacist interventions to prevent DRPs (n=251)

Types of interventions	Number	Total (%)
Drug choice		
a. Drug discontinuation	37	52 (20.71%)
b. Addition of a new drug	11	
c. Change of dosage form	4	
Dosing		
a. Decrease the dose	31	60 (23.90%)
b. Increase the dose	20	
c. Appropriate duration	9	
Adverse drug reactions	5	5 (1.99%)
Drug interactions	134	134 (53.38%)

Table 7. Result of pharmacist interventions (n=251)

Recommendations	Result (%)
Suggestion accepted and therapy changed	151 (59.7%)
Suggestion accepted but therapy not changed	66 (26.4%)
Neither suggestion nor therapy changed	34 (13.4%)

The most frequently documented major interactions were heparin which causes increased risk of bleeding when administered along with aspirin/clopidogrel. It should only be used concurrently when the potential benefit outweighs the significant risk of bleeding. If used, partial thromboplastin time must be monitored closely [12]. Clopidogrel is highly contraindicated in patients with recent surgery, myocardial infarction or peptic ulcer as it increases the risk of bleeding. Therapy with clopidogrel can be avoided in such patients [13]. Co-administration of ramipril (2.5 mg) and spironolactone (25 mg) in 17 patients which can cause first dose hypotension was another drug related problem observed. Either ramipril dose reduction (recommended dose 1.25 mg) or discontinuation of diuretic therapy 2 to 3 days before initiation of ramipril was recommended. Blood level monitoring of theophylline was suggested in those patients receiving fluoroquinolones simultaneously to avoid theophylline toxicity. The present study has documented several cases of overdosage of clopidogrel. The normally recommended dosage of clopidogrel is 75mg OD. An overdosage can cause bleeding disorders, GI disturbances such as dyspepsia, nausea and vomiting etc [14]. A lower dose of amlodipine (2.5 mg once daily) was recommended by the pharmacist in renally impaired patients with hypertension.

Atorvastatin is contraindicated in hepatically impaired patients as it can lead to accumulation of drug and eventually drug toxicity [14]. Bile acid sequesterants

or ezetimibe was recommended in those patients. Some inappropriate drug choices observed were the use of spironolactone in hyperkalemic patients, metolazone in gout patients and torsemide in renally impaired patients. In hyperkalemic patients spironolactone can lead to further increase in the serum potassium levels leading to arrhythmia. In gout patients metolazone is reported to aggravate hyperuricaemia and reduce uric acid excretion [15]. Such patients were monitored for symptoms and drug was discontinued if symptoms persisted. Torsemide increases urea and creatinine levels in renally impaired patients, owing to delayed excretion and thus worsens the condition [16]. Dosing interval was increased along with dose reduction to counteract these effects.

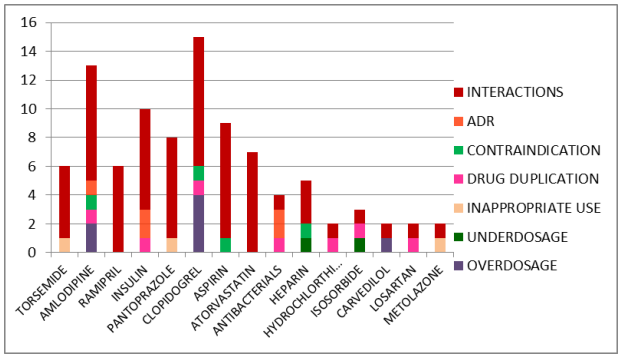

Figure 1. DRPs in systemic hypertension

Either drugs dechallenge or dose reduction was recommended by pharmacist for all moderate to severe ADR observed. Treatment was continued with amoxicillin and ceftriaxone after levofloxacin induced allergic rashes in 3 patients. Warfarin induced gastrointestinal (GI) bleeding was another ADR observed in the study period. The dose was reduced and the international normalized ratio (INR) was frequently monitored to prevent further complications and worsening of the patient's condition [17]. Insulin, metformin, glimepiride and glibenclamide induced hypoglycaemia in diabetic patients was a common ADR observed. In such patients, either their dose was reduced or any one OHA was stopped. Since amlodipine (5mg) caused hypotension and pedal edema in elderly patients, a reduction of dose (2.5mg) was advised for patients with hypertension [18]. The study has documented 2 cases of torsemide induced hypokalemia. The drug was dechallenged and treatment with a potassium sparing diuretic (spironolactone) was initiated in these patients after pharmacist interventions. Potassium level was continuously monitored until discharge.

Drug duplication was another type of DRPs identified. This problem was noted especially with antihypertensive, antidiabetic and antiulcer group of drugs. Administration of pantoprazole and rabeprazole concurrently was seen in few cases leading to duplication as both of these drugs belong to the same class. Overdosage may lead to an increased risk of GI disturbances such as nausea, vomiting, diarrhea and stomach pain, headache and dizziness [14]. Few prescriptions were found to contain lasix and lasilactone, both of which contained furosemide. Overdosage due to furosemide may cause acute toxic symptoms like dehydration, electrolyte imbalance, hypotension, hypokalemia and hypochloremic alkalosis [14].

The number of clinical/pharmacological risk factors significantly increases the risk of DRPs. The various clinical risk factors observed in the current study were polypharmacy (≥ 5 drugs), diabetes mellitus and reduced hepatic (aspartate amino transferase or alanine amino transferase three times above normal range) or renal function (creatinine clearance below 50ml/min or serum creatinine above normal range). Polypharmacy (74.19%), diabetes mellitus (58.06%) and reduced renal or hepatic function (48.38%) were high in patients with SHT while in other CVDs, reduced renal/hepatic function was found to be a less significant factor. The clinical risk factors seen in this study are summarized in table 5. Polypharmacy was the most common clinical/pharmacological risk factor seen in IHD followed by CVA and SHT. It is a common reason for drug duplication and interactions. As it is known, elderly uses more drugs due to multiple illnesses. Polypharmacy can be controlled by simplification of the medication regimen through decreased dosing frequency, eliminating pharmacologic duplication and regular review of the treatment regimen [19].

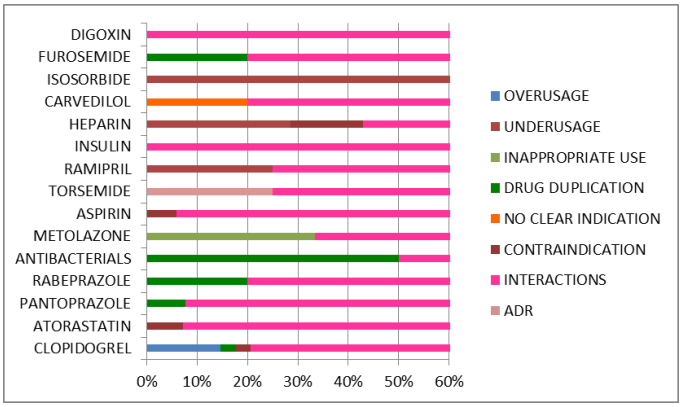

Figure 2. DRPs in ischemic heart disease

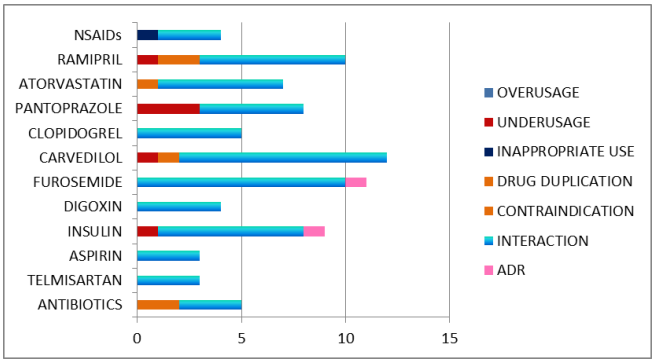

Figure 3. DRPs in congestive cardiac failure

Antihypertensives were found to show the highest drug risk ratio (2.6) followed by antiplatelet drugs (0.95), anticoagulants (0.66), antihyperlipidemics (0.64) and antiulcers (0.62).

Of the 251 interventions proposed, the most frequent suggestion was on drug interactions (53.38%) followed by dosing (23.90%). Change in drug choice accounted for 20.71% of the recommendations. 59.7% of interventions

were accepted and therapy was changed. Various interventions provided by the pharmacist and their result are presented in table 6 and 7.

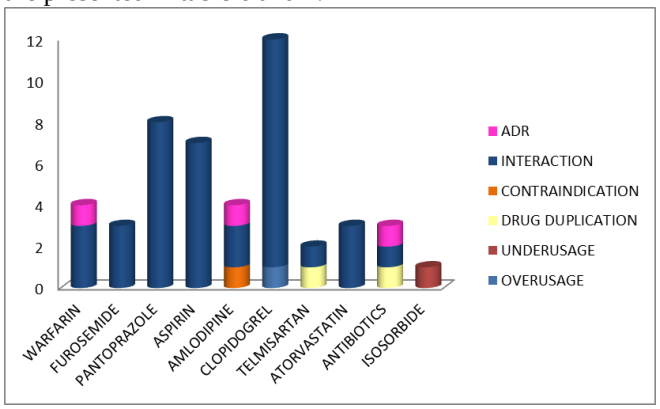

Figure 4. DRPs in cerebrovascular accident

ANOVA test revealed that age, total number of drugs used, total number of DRPs and clinical/pharmacological risk factors were not significantly different between the groups with various cardiovascular diseases ($p>0.05$). Pearson's correlation coefficient (r) was calculated to find out the association between DRPs and various patient factors such as age, number of drugs prescribed and number of clinical/pharmacological risk factors. In the present study, a positive correlation was observed between number of DRPs and age (r = 0.402), number of drugs prescribed (r = 0.261) and number of clinical / pharmacological risk factors (r = 0.103).

The present study has the following limitations. First, it remains unknown to changes in medication which leads to improvement in the health and well-being of the patients because such outcome data was methodologically difficult to obtain, especially after discharge. Secondly, other experts did not validate the quality of interventions. However, decisions about pharmacotherapy in this area are difficult as current guidelines rarely address the complexity of multiple chronic conditions of patients with cardiovascular diseases. Thirdly, a relatively large number of DRPs remains unresolved, because more time was needed for implementing changes. Therefore, additional follow-ups for such patients are suggested. Repetition of the interventions and medication review by pharmacist in daily practice are also recommended.

4. Conclusion

The present study demonstrated that patients with cardiovascular diseases suffer from a large number of DRPs that may be solved or prevented by pharmacist intervention. DRPs were more common in patients with SHT, IHD and CCF. The most frequently identified DRPs were drug interactions followed by overdosage and drug duplication. Polypharmacy and diabetes mellitus have been identified as important clinical risk factors for DRPs. Routine medication review and reactive pharmacist intervention are strongly recommended to improve the treatment outcome of patients with cardiovascular diseases.

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