Research Paper

Assessment of Adverse Drug Reactions in Patients on Cardiovascular Drugs: A Prospective Study

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Abstract

Objectiv: To quantify ADRs in patients on cardiovascular drugs and to assess their severity. **Materials and Methods:** Based on inclusion and exclusion criteria, 265 inpatients on cardiovascular drugs from a tertiary care center were included in this prospective study. All patients were assessed for occurrence of ADR and followed up till the recovery of the ADR. Causality assessment of ADR was done, severity of ADR was graded, and preventability of ADR was assessed. **Results:** In the present study, descriptive statistics were used to analyze the data. Out of 265 patients screened, 137 (51.69%) had 245 ADRs. About 175 (71%) ADRs were due to antihypertensives, 175 (71%). On causality assessment of these ADRs, 230 (94%) were found to be possible and 15 (6%) probable. Two hundred and nine (85%) ADRs were mild, 34 (14%) were moderate, and 2 (1%) were severe. The most common ADR encountered in the study was giddiness due to various classes of antihypertensives in 26% about patients. **Conclusions:** Among the cardiovascular system drugs, antihypertensives were the most common group of drugs to cause giddiness as ADR. Majority of the ADRs had a score of "possible" because of concomitant medications.

Keywords: Adverse drug events, adverse drug reaction, cardiovascular drugs, causality assessment

Introduction

Drug is defined as "any substance or product that is used or intended to be used to modify or explore physiological systems or pathological states for the benefit of recipients. They are used for diagnostic, prophylactic, or therapeutic benefits on the biological system."[1] Drug safety is a major concern in the health-care system. Adverse drug reactions (ADRs) are associated with significant morbidity, mortality, and cost burden to the health-care system. It has been estimated that 5% of hospitalized patients experienced an ADR during their hospital stay and that ADRs cause 197,000 deaths annually throughout Europe.[2] Cardiovascular diseases are the most common noncommunicable diseases contributing to significant morbidity and mortality. It claims the lives of 17.9 million people every year, accounting for 31% of all global deaths.[3]

Patient compliance decreases with the occurrence of ADR. An adverse event or experience is any negative or harmful occurrence that takes place during treatment, which may or may not be associated with a medicine. There is a coincidence in time without any suspicion of a causal relationship. While an ADR is "a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man."[4] Multiple factors may play an important role in causation of ADR.

ADRs are of major concern in patients with complex therapeutic regimens. In European hospitals, up to 10% of patients experience an ADR during their stay.[5] There is an increase in the incidence of ADR with underlying systemic diseases, drug polymorphism, and long duration of therapy. The risk of ADR with cardiovascular drugs is about 2.4 times higher, compared to other drugs.[6] The increasing prevalence of polytherapy with aging may lead to an increased risk of inappropriate drug use and medication errors.[7-9] Assessment of patient's case reports for likelihood of involvement of suspected drug in a particular event for establishing causal

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relationship is called causality assessment. Various methods for causality assessment includes the WHO-UMC assessment scale, Naranjo's scale, European scale, and many others. The major limitations for assessment of ADR are highly subjective to physician's attitude toward ADR. Sometimes, the ADR may occur because of the drug–drug interactions.[10,11] ADRs constitute a significant health-care issue for the elderly in the critical care setting, suggesting that more than one in every ten older patients in the hospital setting experiences an ADR.[12]

In the Indian population, the incidence of ADRs range between 1.7% and 25.1%, with 8% of them resulting in hospitalization, and the ADRs due to cardiovascular drugs are major contributors to morbidity in patients with cardiovascular diseases. They can lead to electrolyte imbalance, bleeding episodes, or tachyarrhythmia.[13] The Indian data on ADRs due to cardiovascular drugs are inadequate. Hence, this study was taken up with an objective to quantify ADRs in patients on cardiovascular drugs and to assess their severity.

Materials and Methods

The data for this prospective study were collected from the inpatients of the department of medicine of a tertiary care center. The ethical clearance from the institutional ethics committee was obtained before the study commencement, EC certificate number STD-1/EC/0372/2014. The study period was for 2 years, from January 2015 to December 2017. Patients who fulfill the inclusion criteria were explained clearly about the purpose and nature of the study in the language they understand, and written informed consent was taken. Patient demographics, pre-existing diseases, and drug history were recorded and also evaluated for ADRs.

Sampling technique

The patients were interviewed, their case records were reviewed, and ADRs detected were collected. The patients were followed till recovery of ADR. The time of onset and duration of the reaction, suspected drug, outcome, and actions taken for managing the reactions were precisely recorded.

Causality assessment of ADRs was done using the WHO-UMC scale and Naranjo's scale.[14,15] Severity of ADRs was assessed using the Hartwig's scale, and preventability of reactions was assessed by the Schumock and Thornton scale.[16]

Inclusion criteria

Male and female patients aged above 18 years of age on cardiovascular drugs were included in the study.

Exclusion criteria

Outpatients on cardiovascular drugs were excluded from the study.

Based on previous study conducted in a tertiary care hospital in India, it was found that the incidence of ADR was 21.5% in the present study, with absolute precision of 4% and with the desired confidence level of 95%, and the minimum sample size required for the present study was estimated to be 263.[17]

Statistical analysis

All the quantitative variables such as age were expressed as mean and standard deviation. All the qualitative variables were expressed as proportion. Chi- square test was used to compare the difference in proportion of ADR occurrence between male and female, and risk of occurrence of ADR with number of drugs. Causality assessment of ADR were expressed as percentage.

Results

Out of 265 patients on cardiovascular drugs in this study, 164 were male and 101 were female. On causality assessment of these 265 patients, 137 patients had ADR [Figure 1]. The age and gender distribution are depicted in Table 1. There was no statistically significant gender difference in ADR distribution ($P = 0.1$). Patients were prescribed a minimum of one drug and a maximum of 11 drugs acting on the cardiovascular system (CVS). A total of 72 different types of drugs were taken by 265 patients. Chi-square test was performed to establish the relationship between the number of drugs and the risk of occurrence of ADR. There was statistically significant occurrence of ADR when the patient was on more than two drugs ($P < 0.00001$).

In this study, a total of 277 ADRs were noticed among 137 patients. Out of these 277 ADRs, about 245 ADRs were due to drugs acting on the CVS, and 32 ADRs were attributed to antidiabetic medication, antibiotics, analgesics, and antipyretics. Out of the 137 patients with ADR, 64 (47%) patients experienced at least one ADR, and 4 (7%) patients had a maximum of five ADRs [Table 2].

The patients in the study were prescribed with the following drugs acting on CVS[Figure 2]: antiplatelet agents such as clopidogrel, aspirin, and cilostazol; antihypertensives such as calcium channel blockers (CCBs) – amlodipine and clinidipine; angiotensin receptor blockers (ARBs) – telmisartan, olmesartan and losartan; angiotensin-converting enzyme inhibitors – enalapril and ramipril; β-blockers – atenolol, propranolol, carvedilol and metoprolol; α-blockers – prazosin; α agonists – clonidine and moxonidine; diuretics – thiazides, furosemide, torsemide, spironolactone, and metolazone; antianginals – nitrates; and drugs such as digoxin, ivabradine, and ranolazine, which were used in heart failure [Table 3].

In this study, the most common ADR encountered was giddiness in 64 (26%) patients due to diuretics, β-blockers,

Table 1: Age and gender distribution of cardiovascular disease patients

Variable	N/years
Total number of patients	265
Total number of females	101
Age range (years)	41-87
Mean age (years)	62±10.2

CCBs, drugs acting on renin–angiotensin system, and α-blockers. The second most common ADR was generalized weakness in 47 (19%) patients due to hypolipidaemics and antihypertensive drugs. About 16 (7%) patients on diuretics had electrolyte disturbance like hyponatremia. Among the patients on β-blockers, about 4% patients experienced giddiness and 2% had bradycardia. The most common ADR with CCBs was giddiness 4% [Table 3]. According to the system organ classification, the most common ADR was classified under the nervous system disorder, followed by general disorder and gastrointestinal system [Table 4].

According to this study, the most common diagnosis of patients on various cardiovascular drugs was hypertension (64%), followed by ischemic heart disease (16%) and chronic kidney disease (6%). The rest were admitted for miscellaneous provisional diagnosis such as acute exacerbation of bronchial asthma, viral fevers, and gastroenteritis and were on treatment for the underlying comorbid conditions.

This study revealed that majority of the ADRs 230 (94%) had a score of possible according to Naranjo's scale, followed by probable 15 (6%) because of multiple concomitant drugs and comorbid conditions [Table 5].

Based on the Hartwig's and Siegel's ADR severity scale, the severity of ADR was mild in 209 (85%), moderate in 34 (14%), and severe in 2 (1%) patients [Table 6a]. On analysis of preventability of ADR using the Schumock and Thornton scale, about 16 (7%) ADRs were preventable [Table 6b].

Table 2: Number of adverse drug reactions experienced in patients

Number of ADR/patient	Number of patients, *n* (%)
1 ADR	64 (47)
2 ADR	25 (18)
3 ADR	30 (22)
4 ADR	14 (10)
5 ADR	4 (3)

ADR=Adverse drug reaction

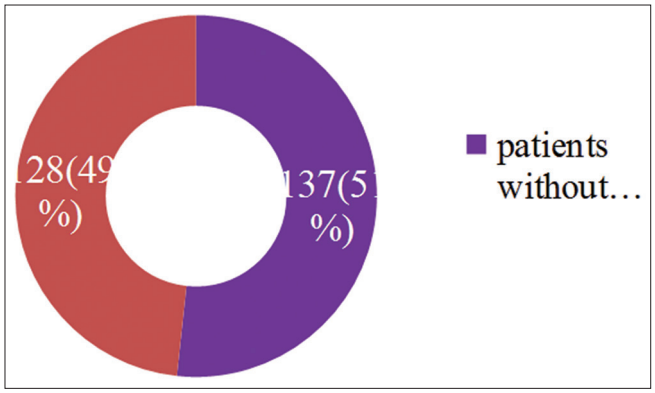

Figure 1: Adverse drug reaction frequency in cardiovascular disease patients

Discussion

This study showed no gender difference in occurrence of ADR in patients on cardiovascular drugs ($P = 0.1$). This was similar to a ADR study conducted by Kunnoor *et al*.[18] Chen *et al*. compared characteristics of adverse drug even between older and younger adults presenting to a Taiwan emergency department. Out of 452 patients, 295 elderly patients and 157 young patients had adverse drug event (ADE). Preventable ADEs in older adults were due to antithrombotic agents, antidiabetic agents, and cardiovascular agents. Out of 452 patients, 295 elderly patients and 157 young patients had ADE. Preventable ADEs in older adults were due to antithrombotic agents, antidiabetic agents, and cardiovascular agents.[19] Venkatesan *et al*. monitored the pattern of ADRs, their frequency, severity, and preventable of ADRs from a medicine ward at a tertiary care hospital for a period of 6 months. One thousand two hundred and twenty patients were monitored. The average number of drugs taken by patients was 10 ± 4.50. Using the Naranjo's algorithm, 60.93% of the ADRs were defined as "probable," whereas 38.12% were defined as "possible" and 0.93% were classified as "definite" in relation to the suspected drug.[20]

According to a study conducted by Palaniappan *et al*., at a tertiary health-care center in India, on pattern of ADR reported with cardiovascular drugs revealed 463 ADR in 397 patients. Among them, cough 77 (18%) due to enalapril was the most common ADR. However, according to this study, giddiness 64 (47%) was the most common side effect, and it was attributed to the drugs acting on the adrenergic system.[6]

There was an incidental finding in the study that among 72 patients on ARBs, about 15 (4.8%) were found to have anemia. Among them, eight patients were on telmisartan and

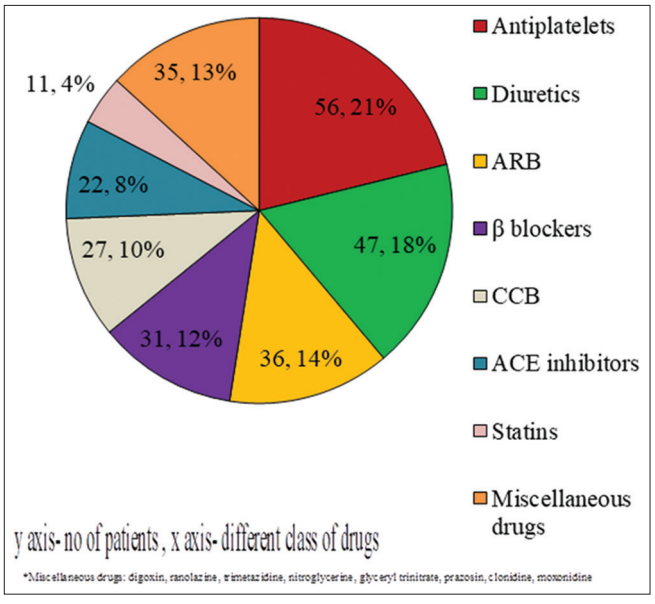

Figure 2: Different classes of drugs causing adverse drug reaction

Table 3: Adverse drug reactions distribution according to different drugs

Drug	ADR	Total ADRs, *n* (%)
Amlodipine	Giddiness (8), generalized weakness (6), headache (5), pedal edema (4), hypotension (2)	25 (10.2)
Cilnidipine	Giddiness (1)	1 (0.005)
Verapamil	Constipation (1)	1 (0.005)
Telmisartan	Giddiness (12), anemia (8), generalized weakness (3), insomnia (2)	25 (10.2)
Losartan	Anemia (7), giddiness (4), generalized weakness (2)	13 (0.053)
Olmesartan	Giddiness (2)	2 (0.008)
Ramipril	Dry cough (7), giddiness (5), hyponatremia (4), generalized weakness (2)	18 (0.073)
Enalapril	Giddiness (1)	1 (0.005)
Furosemide	Polyuria (9), loss of appetite (9), giddiness (4), hyponatremia (2), bradycardia (2)	26 (10.6)
Torsemide	Hyponatremia (3), polyuria (3)	6 (0.024)
Metolazone	Hyponatremia (3), giddiness (3)	6 (0.024)
Spironolactone	Giddiness (3), hyponatremia (3), gastritis (2)	8 (0.033)
Hydrochlorothiazide	Hyponatremia (1)	1 (0.005)
Metoprolol	Generalized weakness (6), giddiness (5), insomnia (4), bradycardia (3), headache (2)	20 (0.082)
Carvedilol	Giddiness (3), insomnia (2), bradycardia (1)	6 (0.024)
Propranolol	Hypotension (1)	1 (0.005)
Atenolol	Giddiness (2), bradycardia (1), generalized weakness (1)	4 (0.016)
Aspirin	Gastritis (23), minor bleeding (5)	28 (11.4)
Clopidogrel	Gastritis (14), minor bleeding (5)	19 (7.76)
Cilostazol	Giddiness (5), generalized weakness (4)	9 (3.67)
Atorvastatin	Generalized weakness (10)	10 (4.08)
Rosuvastatin	Generalized weakness (1)	1 (0.005)
Ranolazine	Generalized weakness (1)	1 (0.005)
Nitroglycerine	Headache (2)	2 (0.008)
Digoxin	Nausea (1), loss of appetite (1)	2 (0.008)
Moxonidine	Giddiness (1)	1 (0.008)
Prazosin	Giddiness (6), tachycardia (1), generalized weakness (1)	8 (3.26)
Total		245

ADR=Adverse drug reaction

Table 4: Adverse drug reactions based on system organ classification

System organ classification of ADR due to drugs acting on CVS	Total ADRs, *n* (%)
Nervous system disorder	79 (32.23)
Cardiac disorder	17 (6.94)
Respiratory, thorax, and mediastinal disorder	07 (2.86)
Gastrointestinal disorder	40 (16.33)
Renal and urinary disorder	13 (5.30)
Blood and lymphatics	42 (17.14)
General disorder	47 (19.18)

ADR=Adverse drug reaction, CVS=Cardiovascular system

Table 5: Adverse drug reactions causality assessment

Category	*n* (%)
Naranjo's scale	
Probable	15 (6)
Possible	230 (94)
WHO score	
Probable/likely	15 (6)
Possible	230 (94)

seven patients were on losartan. A case was reported by Shalavadi *et al*. on losartan-induced anemia and vasculitis in India.[21] However, the reason for this is unknown. Australian public assessment report for telmisartan also reported anemia in 0.8% of 8542 patients on telmisartan. There was a drop in hemoglobin by 2 g/dl in these patients. However, this postmarketing surveillance fails to establish the reason for the same.[22]

The strength of the study is that it adds on to the Indian data on ADRs in inpatients on cardiovascular drugs. Limitations of the study were that it cannot be generalizable as the study included only the inpatients on cardiovascular drugs in the department of medicine. The study could have included all department patients on cardiovascular drugs.

Conclusion

This study concludes that there is no difference in gender distribution related to occurrence of ADRs among patients on cardiovascular drugs. Among the CVS drugs, antihypertensives were the most common group of drugs to cause giddiness as ADR. The risk of ADR increased with the number of drugs in the prescription. Majority of the ADRs had a score of "possible" because of concomitant medications. Most of the ADRs were mild in severity and were not preventable. The observations of the present study have generated information about different ADRs due to various classes of cardiovascular drugs. This is

Table 6: Severity and preventability of adverse drug reactions

Severity/Preventability	*n* (%)
(a) Hartwig's severity score	
Mild, *n* (%)	209 (85)
Moderate, *n* (%)	34 (14)
Severe, *n* (%)	2 (1)
(b) Schumock and Thornton ADR preventability score	
Definitely preventable, *n* (%)	16 (7)
Probably preventable, *n* (%)	14 (6)
Not preventable, *n* (%)	215 (87)

expected to sensitize physicians about the safety profile of the drugs when used clinically. Hence, rational prescription without unnecessary multiple drugs should be practiced.

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Conflicts of interest

There are no conflicts of interest.

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