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Research Article

Pattern and incidence of adverse drug reactions observed in cardiac clinic of tertiary hospital, Hakeem Abdul Hameed Centenary Hospital, Jamia Hamdard, New Delhi

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ABSTRACT

Background: The aim of the present study was to monitor the incidence and pattern of adverse drug reactions (ADRs) in cardiac care unit at Hakeem Abdul Hameed (HAH) Centenary Hospital.
Methods: Study was conducted with the permission of Institutional Ethics Committee. Patients visiting medicine outpatient department, cardiac clinic, medical ward, and emergency departments over a period of 15 months were recruited. ADRs were recorded on the prescribed form. Causality assessment was done using Naranjo probability scale. 223 patients of hypertension and stable coronary artery disease were enrolled of which 48.9% were males and 51.1% females. The most common prescribed drugs were ace-inhibitors, angiotensin receptor blocker, and beta-blockers. Other prescribed drugs were calcium channel blockers, statins, nitrates, and antiplatelets.
Results: A total of 44 ADRs were recorded. 26 ADRs were seen in females and 18 in males. Statins were the commonest drug associated with ADRs (29.5%) in our study. The most common organ system associated with ADRs in the present study was central nervous system followed by skin 15.9% each. The incidence of ADRs was about 20% of which 20% ADRs were probable, and 80% were possible. Maximum ADRs occurred in patients prescribed statins followed by beta-blockers and angiotensin receptor blockers.
Conclusion: There is a need for conducting such studies in more and more patients to see the pattern of ADRs in cardiac patients. More information will help in reducing the ADR occurrence and making drug use more rational and safe for patients.

Keywords: Adverse drug reaction, Coronary artery disease, Naranjo's scale, Pharmacovigilance program of India

INTRODUCTION

India is a developing country with an estimated 1.27 billion population of varying socio-economic strata and varying ethnic background.[1] The people practice different systems of medicine, and no drug is completely devoid of risk. Healthcare practitioners have both positive and negative experiences while treating the patients. As a healthcare professional it is their moral duty to report any adverse drug reaction (ADR). Their contribution in this regard

may be very useful in improvement in understanding the disease and its treatment. World Health Organization has defined the ADR as "a response of drug which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis or treatment of disease."[2] The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem is pharmacovigilance.[2] Pharmacovigilance helps in the safety and serves as an indicator of the standards of clinical care practiced within a country. In a country like India with variation in disease prevalence and use of multimodal practices a robust pharmacovigilance system is needed. National Pharmacovigilance Program was launched in India in 2004 and restarted in 2010 as Pharmacovigilance Program of India (PvPI) under Ministry of Health and Family Welfare, Government of India, to monitor the safety of medicines in Indian population.[3,4] Indian Pharmacopoeia Commission is the National Coordination Centre (NCC) which collects the ADR reports and further recommends to Central Drugs Standard Control Organization (CDSCO) and Uppsala Monitoring Center (UMC) for regulatory actions.[5] ADR reporting in India is still below 1% compared to 5% global reporting.[6]

Hypertension and cardiovascular diseases (CVD) remain one of the leading causes of mortality and morbidity all over the world.[7,8] Estimates indicate that of 30 million coronary artery disease (CAD) patients in India, 14 million are in urban, and 16 million are in rural areas and by 2020, the load of the CVD in India will exceed other regions of the world.[9] Every year more than 30% of the deaths are due to CVDs.[10] Number of risk factors tend to increase with the consumption of various medicines. Patients with cardiovascular disease are particularly vulnerable to ADRs due to their advanced age, polypharmacy, longer duration of therapy, and the influence of heart disease on drug metabolism. Since the data on ADRs in cardiovascular diseases in India is limited, the present study aims to see the incidence and pattern of ADRs in cardiovascular diseases at tertiary hospital level.

METHODS

The present study was carried out to monitor ADRs in 233 patients with cardiovascular diseases using antihypertensives drugs for stable coronary artery disease at Medicine outpatient department, cardiac clinic, medical ward, and emergency departments in Hakeem Abdul Hameed (HAH) Centenary Hospital, Jamia Hamdard, New Delhi during the period April 2014 to June 2015. The study was conducted after the approval by the Jamia Hamdard Institutional Ethics Committee and in accordance with the principles of the Declaration of Helsinki. Informed consent was taken from the patients. The disease history and demographic details of all the patients were taken and entered individually in a case report form by the attending researcher. In case of ADR the details, such as time of initiation of ADR, causative drug, dose, and duration as per the CDSCO prescribed Suspected ADR Reporting form were filled. The data were analyzed and causality assessment was done as per the Naranjo's scale (Table 1).[11] Scores were assigned to the set of specific questions. The total scores for an ADR were calculated and were categorized as definite (score >9), probable (score 5-8), possible (score 1-4) or doubtful (score 0). The forms were duly filled and certified by the attending physician/cardiologist and submitted to NCC from where the reporting was done to UMC using VigiFlow software version 5.3. The confidentiality of the patients' identity was maintained by assigning the initials.

Statistical analysis

Binomial logistic regression analysis was used to correlate whether the age and gender is a cofactor for ADR. Statistical significance was determined at 95% level of confidence. The data were analyzed using software STATA version 12.1.

RESULTS

The study involves the spontaneous reporting of the ADRs in patients (causality and ward) and outpatients with hypertension and coronary artery diseases visiting the medicine department of the HAH Centenary Hospital, Jamia Hamdard. In this study, 223 patients of hypertension and stable CAD were enrolled. Out of the total 223 patients 109 (48.9%) were males and 114 (51.1%) were females. Adult (19-60 years) patients were 129 (57.8%) and elderly (more than 60 years) patients were 94 (42.1%). Patients with only hypertension were 113, patients with CAD alone were 50 and patients with both hypertension and CAD were 60. During the study total 44 ADRs were recorded out of which 26 ADRs were seen in females and 18 in males. A total of 14 ADRs were observed in the patient age group of above 60, followed by 13 in 41-50 age groups, 10 in 51-60 age groups and further depicted in Table 2. Patients were prescribed mostly ace inhibitors, angiotensin receptor blockers (ARB), and beta blockers. Other drugs included were calcium channel blockers, statins, nitrates, and antiplatelets. In our study, statins were the commonest drug associated with ADRs (29.5%) (Figure 1). Among 223 patients, 44 patients were treated with beta blockers. Of these 8 patients experienced ADRs (18.8%). A total of 34 patients received treatment with angiotensin converting enzyme inhibitors. Among these a total of 6 patients experienced ADRs (13.6%). Calcium channel blockers were administered to 29 patients. Among these 4 patients experienced ADRs (9.0%). Combination drug therapy was given to 21 patients out of theses 3 patients had ADRs. The combination drug therapy classes causing ADRs were calcium channel blocker with ARB caused 3 ADRs, calcium channel blocker with beta blocker caused 1 ADR and diuretic with beta blocker combination had 1 ADR. Other drugs classes, which were prescribed are depicted in Figure 1.

Table 1: Naranjo adverse drug reaction probability scale.

Question	Yes	No	Do not know	Score
Are there previous conclusive reports on this reaction?	+1	0	0	
Did the adverse event appear after the suspected drug was administered?	+2	–1	0	
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
Did the adverse reaction reappear when the drug was read ministered	+2	–1	0	
Are the alternative causes (other than the drug) that could on their own have caused the reaction?	–1	+2	0	
Did the reaction reappear when a placebo was given?	–1	+1	0	
Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
Was the adverse event confirmed by any objective evidence?	+1	0	0	

Definite ≥9, Probable-5-8, Possible-1-4, Doubtful ≤0

Table 2: Age distribution of patients with ADRs.

Age distribution (years)	HTN	CAD	HTN+CAD	Total number of ADRs
21-30	0	0	1	1
31-40	4	1	1	6
41-50	5	2	6	13
51-60	3	5	2	10
Above 60	8	3	3	14
Total	20	11	13	44

HTN: Hypertension, CAD: Coronary artery disease, ADR: Adverse drug reactions

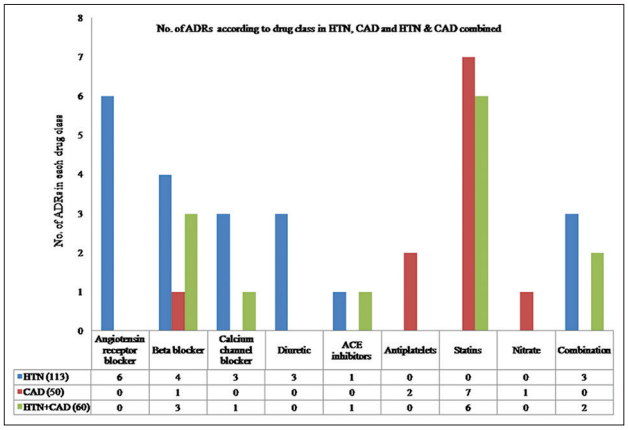

Figure 1: Number of adverse drug reactions according to drug class in patients with hypertension (HTN), coronary artery disease (CAD), and HTN and CAD combined.

The most common organ system associated with ADRs in the present study was central nervous system (CNS) followed by skin 15.9% each (Table 3). Other organ systems involved in ADRs have been depicted in Table 3.

Headache and rashes were the most frequent ADRs reported in cardiac patients. Telmisartan, atorvastatin and glyceryl trinitrate were the most frequent suspected drugs causing headache. Telmisartan, indapamide, losartan, carvedilol, and atorvastatin were most frequent suspected drugs which caused rashes. Other ADRs and the suspected drugs have been listed in Table 4.

Causality assessment

Out of the total 44 ADRs 9 ADRs were categorized as probable and, 35 as possible using Naranjo Probability Scale. Hypertension alone patients had 20 ADRs out of which 4 were probable, and 16 were possible. Patients with CAD were 50 and had a total of 11 ADRs with 2 probable and 9 possible events. Patients with hypertension as well as CAD had 13 ADRs out of which 3 were probable, and 10 were possible.

DISCUSSION

The study relates to the pattern and incidence of ADRs in the cardiac clinic of a tertiary care hospital. Pharmacovigilance plays a role in the scientific understanding of the safety profile of drugs and issuance of advisory to the regulatory authorities.[12] Detecting signal is one of the important aspects of pharmacovigilance. Spontaneous reporting system of ADRs is one of the commonest methods of detecting a signal in pharmacovigilance. According to the WHO, pharmacovigilance signal is "reported information on a possible causal association between an adverse event and a drug, the relationship being unclear or incompletely documented previously."

Out of the 223 patients the total ADRs seen were 44 which were almost about 20% of the patients attending the cardiac clinic.

Our results are in conformity with Kaur et al. 2011[10] and Gholami et al. 2008[13] who reported about 20% ADRs in patients with cardiovascular diseases. Mohebbi et al[14] also reported about 24% ADR due to the use of cardiovascular drugs. The differences in the incidence of ADR may occur due to various factors. It could possibly be because of pharmacological, immunological or genetic factors.[15,16] Besides prescribing pattern, patient's age, gender, weight, past history of ADRs and allergy, multiple drugs, etc. also affect the incidence of ADRs in a patient population.[16] In our study, ADRs were more in females compared to males though marginally. In hypertension alone group of patients, in females the chances of ADR are 4.18 times higher than the males which is statistically significant ($p<0.05$). However, in CAD alone and hypertension with CAD group though the number of females was more but was statistically insignificant.

Ofotokun and Pomeroy (2003) reported that gender plays a role in the effect on ADRs.[17,18] Probably the anatomical and physiological differences of males and females affect the action of many drugs.

Occurrence of ADRs increased with age, they were more in middle-aged persons. In the elderly patients above 60 years the ADRs were comparatively lesser than the persons

Table 3: Organ-systems involved in cardiovascular drug adverse reactions.

Organ-system	Number of ADRs (%)
CNS	7 (15.91)
Cutaneous	7 (15.91)
Gastrointestinal system	6 (13.64)
Cardiovascular system	6 (13.64)
Respiratory system	3 (6.82)
Musculoskeletal	3 (6.82)
Endocrine system	1 (2.27)
Genitourinary	1 (2.27)
Others	10 (22.73)
Total (n)	44

CNS: Central nervous system, ADRs: Adverse drug reactions, n: Number of ADRs

Table 4: Types of ADRs in cardiovascular diseases.

Type of ADRs	Number of ADRs	Suspected drugs
Headache	5	Telmisartan (1), Atorvastatin (3), Glyceryl Trinitrate (1)
Rashes	5	Telmisartan (1), Indapamide (1), Losartan (1), Carvedilol (1), Atorvastatin (1)
Epigastric pain	4	Aspirin (2), Olmesartan (1), Metoprolol (1)
Breathlessness	3	Amlodipine+Atenolol (1), Amlodipine (1), Ramipril (1)
Chest pain	3	Metoprolol (1), Atorvastatin (1), Nebivolol (1)
Swelling all over body	2	Telmisartan (1), Metoprolol (1)
Angioedema	2	Diltiazem (1), Ramipril (1)
Pedal Edema	2	Metoprolol (1), Amlodipine+Losartan (1)
Bodyache	2	Atenolol (1), Metoprolol (1)
Muscle ache	2	Atorvastatin (1), Simvastatin (1)
Insomnia	2	Atorvastatin (2)
General weakness	2	Atorvastatin (2)
Urticaria	1	Indapamide (1)
Pruritus	1	Telmisartan (1)
Flushing over entire face	1	S-Amlodipine (1)
Decreased micturination	1	Furosemide+Metoprolol (1)
Back pain	1	Amlodipine+Losartan (1)
Restlessness	1	Diltiazem (1)
Palpitation	1	Indapamide (1)
Hypotension	1	Telmisartan+Amlodipine (1)
Flatulence	1	Atorvastatin (1)
Constipation	1	Rosuvastatin (1)
Total	44	

Total number of patients: 223; out of which HTN: 113, CAD: 50 and HTN + CAD combined: 60 patients respectively, HTN: Hypertension, CAD: Coronary artery disease

between 41 and 50 years. Using binomial logistic regression it was found that the chances of ADR in age >60 years were higher than those subjects who were ≤60 years, but it was not statistically significant.

With the progression of age number of health problems start occurring and the use of medicines increases. Klotz 2009 reported that due to age-related changes, many drugs tend to stay in an older person's body much longer than they would in the younger person's body, prolonging the drug's effect and increasing the risk of side effects.[18]

Statins were the leading cause of ADR's, followed by the beta-blockers and ARB (Figure 1). Almost 30% of total ADRs were due to statins, 18% due to beta blockers and 13% due to ARB. These were followed by other drugs. Hypertension alone group having 113 patients did not have any statin related ADR the reason being that statins were not prescribed to them. All 50 patients of CAD were prescribed statins and out of 60 patients of CAD with hypertension only 31 were prescribed statins. A total of 24 ADRs were observed in both the groups and among these 54.16% ADRs were because of statins. ADRs like chest pain, insomnia, headache and weakness were reported due to atorvastatin (40 mg); atorvastatin, simvastatin and rosuvastatin in 20 mg doses caused ADRs such as muscle pain, headache, leg pain, and constipation. Atorvastatin 10 mg caused rashes and flatulence. Statins are potent and effective in treating CAD with wide range of physiological, biochemical and biological functions that include hypolipidemic, vasodilative, antithrombotic, antioxidant, antiinflammatory, antiproliferative, anticoagulant, angiogenic, and bone formation inducing functions.[19] Myopathy is the most common side effect of statins some less common side effects are peripheral neuropathy, impaired myocardial contractility and autoimmune diseases. However, the risks are outweighed by the greater reduction of cardiovascular events in statin users.

CNS and skin were the most affected systems in the present study. CNS related ADRs were also prevalent in the study of Karimzedah et al. 2011[20] and Singhal et al.[21] The most frequent ADRs seen in the present study were headache and rashes due to ARB, statins, antianginals, beta-blockers. Singhal et al.[21] and Karimzedah et al.[20] reported headache as the most common ADR. Mohebbi et al.[14] reported the skin hypersensitivity reactions as the most commonly occurring ADR. In present study epigastric pain was the second most frequent ADRs followed by breathlessness and chest pain as depicted in Table 2. In this study, the total percentage of the probable and possible events were 20.45 and 79.55%, respectively.

Most of the ADRs were managed by lowering the dose of drug and changing the suspected drugs by the treating physician.

CONCLUSIONS

The study indicates the incidence and pattern of ADRs in patients of hypertension and coronary artery disease attending cardiac clinic of tertiary care hospital. The incidence of ADRs was about 20%. Maximum number of ADRs occurred in the patients prescribed statins followed by beta-blockers and ARB and so on. Most of the ADRs affected CNS and skin.

The mortality and morbidity due to cardiovascular diseases are increasing at an alarming rate. Since the patients are on polypharmacy for a longer duration, risks of ADRs always exist. There is a need of conducting such studies in more and more patients to obtain more data on pattern and incidence of ADRs. The awareness can be created in the physicians treating the patients to prescribe medicines accordingly and thus help in avoiding the ADRs. The more information we get will help in reducing the ADR occurrence and making the drug use more rational and safe for the patient.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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