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Original Research Article

# A prospective observational study of adverse drug reactions of cardiovascular drugs at tertiary care teaching hospital

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ABSTRACT

**Aims and Objectives:** The aim of the study is to estimate the prevalence of adverse drug reactions (ADRs) in patients on cardiovascular drugs and to assess their occurrence, severity, quantification by clinical and laboratory means, management and possible prevention.

**Materials and Methods:** The present study was conducted over a period of 6 months. Naranjo probability assessment scale was applied to report the causality. Severity assessment was done based on Hartwig and Siegal Severity Scale and preventability assessment based on Schumock and Thornton preventability scale.

**Results:** The most ADRs occurred in the age group 51-60 years. ADRs in patients after hospital admission were 69.3% & patients who presented to the hospital with ADRs 30.6%. All ADRs reported were type-A ADRs i.e. dose-dependent. The cardiovascular system was mostly affected by 29.3%. Anti-hypertensives showed maximum ADRs. Based on Naranjo's scale ADRs reported were, definite 10.6%, probably 85.3%, possibly 4% and doubtful 0%. Hartwig's and Siegal severity assessment scale showed ADRs were mild 37.3%, moderate 56% and severe 6.6%. Schumock & Thornton preventability Scale showed 17.3% of ADRs were definitely preventable. The most potent management in our study was found to be drug discontinuation 61.3% followed by dose reduction and supportive treatment 38.6%.

**Conclusion:** Inter-individual variability is the underlying cause of the ADRs in the majority of the patients. Other causes include factors such as age, polypharmacy, concomitant diseases, availability of newer drugs, underreporting by healthcare professionals and lack of a formal system for monitoring of adverse drug reactions play an important role. Additionally, the association can be made with the use of medication history, medication reconciliation and drug exposure timeline. After identification the offending agent should be discontinued, treatment recommendations should be made and patient education should be provided to prevent future adverse reactions.

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## INTRODUCTION

Many studies have been carried out in several parts of the world on the incidence in hospitalized patients and of hospital admissions that result from adverse drug reactions (ADRs) and other drug-related problems. A

much-cited study from the USA demonstrated that the incidence of serious ADR′s among hospitalized patients was 6.7% and in 0.3% the outcome was fatal. This makes ADR′s between 4th and 6th leading causes of death in the USA (Parthasarthi et al., 2004).

A detailed study from the UK showed that 6.5% of hospital admissions were related to ADR′s. The most commonly implicated medicines were widely used ones like NSAID′s, diuretics, warfarin, and ACE inhibitors Similar study in 2007 carried out in Mumbai, India demonstrated that 6.9% of hospital admissions were caused by ADRs of which 60% deemed avoidable (Parthasarthi et al., 2004).

Studies show that cardiovascular drugs are among the most common cause of adverse events in hospitalized patients (Bates et al., 1995). Some studies report that cardiovascular drugs may cause half of all hospital admissions due to adverse drug reactions (Levy et al., 1980). Another study describes that 4% of adverse events induced by cardiovascular drugs are serious ADEs (Zaidenstein et al., 2002). Almost 10% of all medication-related office visits result from cardiovascular drug reactions, and most of those visits are related to dermatological reactions (Bates et al., 1995).

Knowledge is accumulating to demonstrate that ADRs are a considerable burden to society both financially and in terms of human suffering (Parthasarthi et al., 2004).

The importance of ADR′s is often underestimated. They are common, can be life-threatening and are unnecessarily expensive. Because of the wide range of drugs available, the manifestations of toxicity can be variable and affect any organ system. It is also likely that the pattern of toxicity is going to change with the introduction of new biotechnology products (Andrews and Moore, 2014). Both type A and type B adverse reactions are complex and their prevention for future populations will depend on an understanding of their pathogenesis and exactly how a foreign chemical interacts with macromolecules within the body. Pharmacogenomic strategies have e prevention of these reactions been proposed for the prevention of these reactions in the future by prediction of susceptible individuals (Wiley, 2014).

Despite the relative safety of modern medicines–compared to those used in the past –ADR′s remain an important cause of morbidity and mortality. A study from the UK published in 2004 suggested that about 6.5% of hospital admissions are related to an ADR and estimated the annual cost to the National Health Service to be around 500 million Euros. ADR′s are certainly the most important form of iatrogenic (i.e., doctor-induced) disease. Many of the serious reactions e.g. bleeding with warfarin, the upper gastrointestinal effects of NSAIDs. In public health terms, it is not newly introduced drugs that are responsible for most of the population burden of adverse drug reactions but those whose safety profile is well-established (Patrick, 2011). The World Health Organisation (WHO) initiated a program for reporting all adverse reactions possessed by drugs. Further awareness of adverse drug reactions has resulted in the emergence of the practice and science of pharmacovigilance (WHO, 2006). WHO defines pharmacovigilance as 'the science and activities related to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems (Gupta, 2011). The Pharmacovigilance Programme of India (PvPI) was started by the Government of India. Although, India is participating in this program, due to the lack of awareness among the health care professionals regarding the adverse drug monitoring and reporting system, its contribution to the database is very small.

Cardiovascular diseases are the leading cause of deaths globally (WHO, 2006). Cardiovascular drugs could develop serious and even fatal adverse reactions in CCU patients (Karimzadeh et al., 2011). Most ADRs are observed in older patients with comorbidities and polypharmacy. This population, in general, is very vulnerable for developing ADRs, the stakes of which are very high in this population in particular, and could lead to permanent organ damage or initiate a cascade of events finally terminating with the death of the patient. This warrants the study of such ADRs so that they can be appropriately managed and prevented. Since the study on ADRs related to cardiovascular drugs has not been conducted in Telangana. The primary purpose of the present prospective study was to design and conduct a study profiling the ADRs of drugs used in cardiovascular diseases and the newer drugs which are frequently prescribed in various cardiovascular diseases so that the morbidity and mortality associated with such ADRs can be minimized or limited.

## MATERIALS&METHODS

A prospective observational study was done during the participation in ward rounds at Osmania general hospital, Hyderabad with a sample size of 75 patients. The study was conducted for a period of 6 months.

A modified questionnaire form made from the previous studies and CDSCO-ADR reporting form was used as a data collection tool for this study. Patients who presented with an ADR, as well as patients who experienced ADRs after the admission into the hospital, were taken into consideration in this study. Data was collected based on personally interviewing the patient /

or relative, the clinician's assessment and from the medication chart of the patient.

The following data were analyzed for causality assessment using Naranjo causality assessment scale and documented. Then the severity was assessed using the Modified Hartwig Scale followed by preventability assessment based on Schumock and Thornton scale.

**Table 1.** Selection criteria of patients.

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| Patients of either sex | Patients admitted due to overdose |
| Patients of age group 20-80 year | Pregnant and lactating women |
| Patients with cardiovascular diseases prescribed with cardiovascular drugs and polypharmacy. | Patients with drug administration errors are observed. |
| Patients presenting to hospital due to ADR associated with cardiovascular drugs. | |

### Plan of work

A prospective observational study was conducted in the Department of General Medicine, Osmania General Hospital, Hyderabad; Telangana, India over a period of 6 months. The study protocol was reviewed and approved by the Institutional Ethics Committee (IEC; MCP/IEC/PD/PR/20).

The study was designed to estimate the prevalence of ADRs in patients prescribed with cardiovascular drugs and to assess their occurrence, severity, and preventability. The study included patients prescribed with cardiovascular drugs, who presented to the hospital with an ADR and also all the denovo cases (patients in whom ADR was observed after the hospital admission. During the ward rounds, the ADRs associated with the cardiovascular drugs which the patients have been prescribed was collected through patient's complaints, history taking, medication chart review including over the counter medications or supplements, clinicians assessment and by further interviewing of the patient. A modified Questionnaire with reference to the ADR reporting form of Central Standard Control Organization (CDSCO) and previous studies which include patient demographics like name, age, sex, medication history, diagnosis, name of suspected drug along with route of administration, frequency, dose, duration ,nature of reaction was also mentioned in the form. The data collected were analyzed to characterize the type of ADR and the organ system affected by it.

Naranjo adverse drug reaction probability scale was used in the study to assess the causality of the reaction which classified the reaction as Definite, Possible, Probable or Unknown. Modified Hartwig and Siegal scale were used in the study to assess the severity of the reaction as Mild, Moderate or Severe. Schumock and Thornton scale was applied to the study to evaluate the preventability of the reaction as definitely preventable, probably preventable or not preventable.

All patients were informed about the purpose of the study and were included and registered after obtaining consent. The patient details and registers were kept confidential in accordance with the principles of professional secrecy.

From the analyzed data the frequency, severity, management, and outcome of the ADRs were reported. All the reported ADRs were assessed for their appropriate management and proper steps were taken to prevent such ADR in the future.

## RESULTS

### Population Demographics

A total of 75 cases of ADRs induced by cardiovascular drugs was reported during the study period of 6 months, out of which 39 (52%) were males and 36 (48%) were females. Males experienced a significantly higher incidence of ADRs with cardiovascular drugs than females.

**Table 2.** Distribution of subjects based upon gender.

| Gender | No. of Patients |
|---|---|
| Male | 39 |
| Female | 36 |
| Total | 75 |

### Distribution of patient pool as per age

The study population involved the patients of the age group 20 to 80 years. Maximum patients in whom ADR was observed belong to the age group 51-60 (36%) followed by the age group 61-70 (25.3%).

**Table 3.** Distribution of subjects as per age.

| Age Group | No. of ADRs Seen in Patients | % |
|---|---|---|
| 20-30 | 5 | 6.6 % |
| 31-40 | 7 | 9.3 % |
| 41-50 | 13 | 17.3 % |
| 51-60 | 27 | 36 % |
| 61-70 | 19 | 25.3 % |
| 71-80 | 4 | 5.3 % |

### Distribution of patients in groups

The study population was categorized into two groups. Group 1 included the patients that presented to the hospital with an ADR -23 (30.6%), while group 2 included patients in whom ADR was observed after the hospital admission 52 (69.3%).

**Table 4.** Percentage of ADRS in group 1 and group 2.

| Group | Cases | Percentage |
|---|---|---|
| Group – 1 | 23 | 30.6 % |
| Group – 2 | 52 | 69.3 % |

Group 1: ADR is the reason for hospital admission
Group 2: ADRs occurring after hospital admission

### Cardiovascular Drug Usage

The following table represents the no. of patients who were prescribed cardiovascular drugs for cardiovascular diseases and also the cardiovascular drug that were prescribed for the treatment of other diseases.

**Table 5.** Use of cardiovascular drugs for the treatment of diseases.

| Condition | Cases | Percentage |
|---|---|---|
| **For treatment of cardiovascular diseases(CVD)** | **71** | **94.6 %** |
| **For treatment of diseases other than CVD** **( Grave's disease, anxiety & migrane ) | **4** | **5.3 %** |

**Table 6.** Drugs and their ADRs.

| Drug | Disease | ADR | Cases | Group 1 | Group 2 | Male | Female |
|---|---|---|---|---|---|---|---|
| **Digoxin** | 1. AF<br>2. VA<br>3. CHF | 1 .Hypokalaemia<br>2. Diarrhoea<br>3. VT<br>4. Aplastic anaemia | 4 | 2 | 2 | 2 | 2 |
| **Enalapril** | HTN | 1. Dry-cough<br>2. Orthostatic hypotension<br>3. Angioedema<br>4. Hypotension | 6 | 1 | 5 | 4 | 2 |
| **GTN** | Angina | 1. Headache<br>2.Methhaemaglobinaemia<br>3. Hypotension<br>4. Acute renal failure | 5 | 2 | 3 | 2 | 3 |
| **Atenolol** | 1. CHF<br>2. HTN | 1. Hypoglycaemia<br>2. Agranulocytosis | 2 | - | 2 | 1 | 1 |
| **Ramipril** | HTN | 1. Angioedema<br>2 . Angina<br>3. Dry-cough | 4 | 1 | 3 | 1 | 3 |
| **Amlodipine** | HTN | 1. Gingival hypertrophy<br>2. Edema<br>3. Headache & Fatigue<br>4.Pulmonary edema | 5 | 2 | 3 | 1 | 4 |
| **Adenosine** | PSVT | Hypotension &<br>Chest pain | 1 | - | 1 | - | 1 |
| **Amiodarone** | 1. VT<br>2. AF | 1. Photosensitivity(2)<br>2. Hypothyroidism(2)<br>3. Constipation<br>4. Peripheral neuropathy<br>5. Pulomonary toxicity<br>6.Hyperthroidism | 8 | 4 | 4 | 5 | 3 |
| **Propranolol** | 1.Migrane<br>2.Grave's disease<br>3. Anxiety<br>4. HTN | 1. Hypotension<br>2. Diarrhoea<br>3. Diarrhoea<br>4. Hyperkalaemia | 5 | 2 | 3 | - | 5 |

| Drug | Disease | ADR | Cases | Group 1 | Group 2 | Male | Female |
|---|---|---|---|---|---|---|---|
| **Furosemide** | 1. CRF<br>2. CHF | 1. Hearing impairment<br>2. Hyperurecemia<br>3. Postural hypotension (aggrevated by alcphol)<br>3. Hyperglycemia<br>4. Tinnitus<br>5. Hypocalcemia<br>6. Arrythmias<br>7. Hypokalaemia<br>8. Aplast anaemia | 10 | 1 | 9 | 7 | 3 |
| **Hydrochlorothiazide** | HTN | Hypokalaemia | 1 | 1 | - | 1 | - |
| **Diltiazem** | HTN | Headache | 1 | - | 1 | 1 | - |
| **Telmisartan** | HTN | Allergic skin reaction | 1 | - | 1 | 1 | - |
| **Dobutamine** | CRHD | Phlebitis | 1 | - | 1 | 1 | - |
| **Disopyramide** | AF | Urinary incontinence & constipation | 1 | - | 1 | 1 | - |
| **Isosorbide dinitrate** | Angina | Headache | 1 | - | 1 | - | 1 |
| **Nifedipine** | 1. CCF<br>2. Anigina | 1. Peripheral edema<br>2. Headache | 2 | - | 2 | - | 1 |
| **Pentoxiphylline** | Intermittent claudication | Dyspepsia & Bloating | 1 | - | 1 | 1 | - |
| **Hydralazine** | Resistant HTN | SLE | 1 | 1 | - | - | 1 |
| **Lidocaine** | VT | Nystagmus | 1 | - | 1 | 1 | - |
| **Procainamide** | VT | Hypotension | 1 | - | 1 | 1 | - |
| **Spironolactone** | CHF | 1.Gynecomastia<br>2.Hyperkalaemia | 4 | 2 | 2 | 3 | 1 |
| **Clonidine** | CKD | 1. Postural hypotensioin & Somnolence<br>2. Rebound HTN on withdrawal | 2 | - | 2 | 1 | 1 |
| **Dipyridamole** | Angina | Tinnitus | 1 | - | 1 | - | 1 |
| **Minoxidil** | Severe HTN | 1. Hirsutism<br>2. Peripheral edema & reflex tachycardia | 2 | - | 2 | 1 | 1 |
| **Metoprolol** | HTN | Bronchospasm | 2 | 2 | - | 2 | - |
| **Carvedilol** | LV-dysfunction | Bronchoconstriction | 1 | 1 | - | 1 | - |
| **Lisinopril** | HTN | Pancreatitis | 1 | 1 | - | - | 1 |

"All reactions reported were dose dependent i.e. Type –A ADRs".

**ADR Type**

**Table 7.** The table represents the nature of ADR that was mostly observed i.e. the cardiovascular type 29.3% followed by others 28%.

| Type of ADR | No . ADRs Reported | Percentage (%) |
|---|---|---|
| Allergic | 1 | 1.3 % |
| Cardiovascular | 22 | 29.3 % |
| Dermatological | 4 | 5.3 % |
| CNS/Nervous System | 5 | 6.6 % |
| Haematological | 4 | 5.3 % |
| Renal | 2 | 2.6 % |
| Gastrointestinal | 6 | 8 % |
| Respiratory | 10 | 13.3 % |
| Other | 21 | 28 % |

****Other ADRs include:** Hormonal, Electrolyte Imbalance (like hypokalemia & hyperkalaemia), hypo & hyperglycaemia, hypocalcaemia,hypo & hyperthyroidism, oral (like gum swelling), edema &headache, etc.

**Table 8.** Class of drug with maximum no. of ADR.

| S. No. | Class | No. of ADRs |
|---|---|---|
| 1 | Anti-Anginals | 11 |
| 2 | Anti-Arrythmics | 12 |
| 3 | Anti-Hypertensives | 31 |
| 4 | Drugs of heart failure | 20 |
| 5 | Drugs of peripheral vascular diseases | 1 |

Among all the classes of cardiovascular drugs, Anti-hypertensives was the class of drug with maximum no.of ADRS (31 cases) that were reported followed by drugs of heart failure (20 cases).

**Note***

1. Anti-Hypertensives: include β-Blockers, α+β-blockers, CCBs, ACEIs and ARBs

2. Drugs of heart failure: include Diuretics (furosemide & hydrochlorothiazide), Spironolactone, Digoxin and Dobutamine.

**Drugs with maximum number of ADRs**

These 3 drugs were found to cause the maximum no.of ADRs of which "Furosemide was the drug with maximum no. of ADRs =10 i.e. 13.3% of reported ADRs followed by Amiodarone = 8 i.e.10.6 % and Enalapril = 6 i.e. 8%".

Furosemide = 10; Amiodarone = 8; Enalapril = 6

**Severity assessment based on modified Hartwig & Siegel scale**

After the severity assessment was done based on the Modified Hartwig & Siegael Scale, the percentage was found to be mild 28 cases (37.3%), moderate 42 cases(56%) and severe 5 cases (6.6%).

**Table 9.** Percentage of severity assessment among study population.

| S. No. | Severity Assessment | No. of Patients | Percentage |
|---|---|---|---|
| 1. | Mild | 28 | 37.3% |
| 2. | Moderate | 42 | 56% |
| 3. | Severe | 5 | 6.6% |
| | | **Total**=75 | 100% |

**Probability Assessment Based on Naranjo's Scale**

75 cases of ADR caused by cardiovascular drugs was analysed . After assessment the percentage of definite were 10.6% , probable 85.3%, possible 4% and doubtful 0% according to the application of Naranjo Scale.

**Management of ADRs**

The ADRS reported were managed either by drug discontinuation 46 cases(61.3%) ,dose reduction or through supportive treatment 29 cases(38.6%).

**Table 10.** The percentage of management of ADRs.

| S. No. | Management | No. of Cases | Percentage |
|---|---|---|---|
| 1. | Drug discontinuation | 46 | 61.3% |
| 2. | No action taken | 0 | 0% |
| 3. | Dose reduced and supportive treatment | 29 | 38.6% |
| 4. | Antidote used | 0 | 0% |
| | | **Total= 75** | 100 % |

**Outcome**

The outcome of this study that was conducted in the general department of Osmania General Hospital reported death 4 cases (5.3%), life threatening 1 case (1.33%), hospitalized 41 cases(54.6%) and discharged 29 cases (38.6%).

**Table 11.** The outcome percentage among the study population.

| S. No. | Outcome | No. of Subjects | Percentage |
|---|---|---|---|
| 1. | Death | 4 | 5.3% |
| 2. | Life Threatening | 1 | 1.33% |
| 3. | Hospitalized | 41 | 54.6% |
| 4. | Discharged | 29 | 38.6% |
| | | Total=75 | 100% |

**Preventability Assessment Based on Schumock & Thornton Scale**

Out of 75 cases, 13 cases (17.3%) were definitely preventable, 8 cases (10.6%) were probably preventable and 54 cases (72%) were not-preventable.

**Table 12.** Percentage of preventability assessment among study population.

| Preventability | No. of Cases | Percentage |
|---|---|---|
| Definitely Preventable | 13 | 17.3 % |
| Probably Preventable | 8 | 10.6 % |
| Not-Preventable | 54 | 72 % |

## DISCUSSION

Here we report the results of the prospective observational study conducted for 6 months in the department of general medicine at Osmania General

Hospital, a tertiary care teaching hospital, Hyderabad, Telangana, India. One of the key findings of this study is out of 75 ADR cases reported, in 23 cases (30.6%) ADR is the reason for hospital admission and in 52 cases (69.3%) ADR was observed after the hospital admission which is in contrary to the study conducted by Chan et al. (2016).

Most ADR patients in this study were observed in the age group 51-60 which is partly in accordance with the previous study conducted by Gholami et al. (2008). There is a controversy related to age and prevalence of ADRS. This may be due to the fact that with increasing age the patient is susceptible to concomitant diseases which require therapy through polypharmacy.

The occurrence of ADR in our study showed male predominance 39 cases (52%) over women 36 cases (48%) which is contradictory to the previous study conducted by Rademaker, (2001). Antihypertensives especially Furosemide had the highest rate of ADRs (10 cases i.e. 13.3%) followed by Amiodarone (8 cases i.e. 10.6 %) and Enalapril (6 cases i.e. 8%) which is partly similar to the study conducted by Mjörndal et al. (2002) where the most offending cardiovascular drugs in that study were Metoprolol, Enalapril, Digoxin, , and Furosemide.

Majority of our reported ADRs fall under the Cardiovascular system (22 cases) accounting for 29.3% followed by Other systems types (21 cases) accounting 28% of total ADRs reported which include hormonal, electrolyte imbalances (hypo & hyperkalaemia), hypo & hyperglycaemia, hypocalcaemia, hypo & hyperthyroidism, oral (gum swelling), edema and headache which is contrary to the study conducted by Mjörndal et al. (2002) where Central Nervous and Gastrointestinal System as the most frequent affected system-organ classes by ADRs.

All the adverse drug reactions reported in our study are TYPE A reactions i.e dose dependent which is partly in accordance with the study conducted by Mjörndal et al. (2002) which states that the prevalence of drug-related problems causing or contributing to admission to a clinic of internal medicine is high and is dominated by type A reactions, i.e. reactions in principle predictable and preventable.

The Naranjo algorithm which was established in 1981, is the most widely used assessment tool and consists of 10 simple questions. According to this assessment our study reported, definite were 10.6%, probably 85.3%, possibly 4% and doubtful 0%. The severity assessment was carried out by using Hartwig's and Siegal severity assessment scale. The assessment showed that mild 28 cases (37.3%), moderate 42 cases (56%) and severe 5 cases (6.6%). The outcome of our study reported death 4 cases (5.3%), life-threatening 1 case (1.33%), hospitalized 41 cases (54.6%) and discharged 29 cases (38.6%).

Preventability assessment was done based on Schumock & Thornton Scale and it was found that 17.3% of reported ADRs were definitely preventable which is slightly lower from the similar study conducted by Gholami et al. (1999) where the study design in two internal medicine wards 58.8% of detected ADRs were reported to be preventable based on the same questionnaire.

We evaluated the underlying cause for ADRs and came to the conclusion that maximum no. of ADRs were due to inter-individual variation towards different cardiovascular drug class followed by the lack of awareness among the healthcare professionals and patients. 50% of the total ADRs occurred due to multiple drug therapy, which is the second leading cause of ADRs according to the study carried out previously (WHO, 2004).

The most potent management in our study was found to be drug discontinuation (61.3%) followed by dose reduction and supportive treatment (38.6%) which is in accordance with a previous study (WHO, 2014).

## CONCLUSION

Inter-individual variability is the underlying cause for the ADRs in the majority of the patients. Other causes include factors such as age, polypharmacy, concomitant diseases, availability of newer drugs, underreporting by healthcare professionals and lack of a formal system for monitoring of adverse drug reactions play an important role. Additionally, the association can be made with the use of medication history, medication reconciliation and drug exposure timeline. After identification the offending agent should be discontinued, treatment recommendations should be made and patient education should be provided to prevent future adverse reactions. There is a need to engage healthcare professionals in a well-framed program to build synergies for monitoring ADRs to ensure maximum safety for public health. This warrants the need for clinical pharmacists in hospitals. Pharmacovigilance methods such as passive surveillance, active surveillance and risk-benefit assessment are helpful in preventing adverse drug reactions. Postmarketing surveillance is essential for identification of new signals, yet remains the weakest link in the regulatory process.

## CONFLICT OF INTEREST

None declared.

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