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Original Article

Adverse Drug Reactions Monitoring in New Patients Admitted to the Cardiac Care Unit in a Tertiary Care Hospital

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ABSTRACT

Background: Adverse Drug Reactions (ADRs) are amongst the commonly occurring event in the intensive care unit where patients are mostly on the polypharmacy. They affect the quality of life of patients and increase the burden on the health care system. **Aim and Objectives:** The study aimed to estimate the incidence of ADRs and to assess the causality and seriousness of such ADRs by using the Naranjo probability scale. A prospective, observational, longitudinal study was conducted on patients admitted to the cardiac care unit over a period of 10 months. ADRs profile was noted by spontaneous and intensive monitoring. For analysis, descriptive statistics with 95% CI were used. **Results:** A total of 77 ADRs were reported from the 173 patients, out of which 31 patients suffered from ADRs, with an incidence of 17.9%. The gastrointestinal system was the most common affected system followed by the cardiovascular and respiratory systems. When analyzed on the Naranjo ADR probability scale, the majority of the ADRs (67.5%) were rated as probable followed by possible (32.4%). It was observed that the number of drugs used as well as the duration of stay in the hospital, in patients with ADRs, was significantly higher than those who did not have any adverse effect. The pattern and spectrum of ADRs need to be studied further so that their occurrence can be prevented. **Conclusion:** The study can be useful in identifying and minimizing preventable ADRs and can be an effort to make the use of drugs more rational and safe.

Keywords: Adverse Drug Reactions, Spontaneous and intensive monitoring, Causality assessment.

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INTRODUCTION

Adverse Drug Reactions (ADRs) are known to have a major impact on the national health care system. As per World Health Organization (WHO), an adverse reaction is the harmful and unintentional reaction to the use of drugs that occur at doses normally used in humans for the prophylaxis, diagnosis, or treatment of diseases.[1] The incidence of ADRs varies widely among different studies ranging from 0.86% to 37%.[2] The prevalence of ADRs is higher among the geriatric (5%) population which can be attributed to comorbid diseases, polypharmacy, and altered pharmacokinetic and pharmacodynamic profiles.[3]

Cardiovascular diseases (CVD's) are one of the leading causes of death among many of the non-communicable diseases in India. These patients are prescribed multiple drugs compared to other diseases, leading to the increased number of ADRs.[4] One of the study reported that 4% of adverse effects caused by cardiovascular drugs are serious adverse drug events (ADE). Also about 10% of all medication-related hospital visits result from these kind of drug reactions. It has been observed that cardiovascular drugs have been responsible for 17.9% of preventable adverse drug events.[5]

Although safety and efficacy of a drug are assessed during clinical trials, their post-marketing continuous assessment is still necessary. Spontaneous reporting of ADRs has been the leading method to identify signs relating to drug safety and can be easily reported by health care professionals. However, underreporting of ADRs is the biggest challenge faced by the Pharmacovigilance system.[6] Intensive monitoring in the hospitals which includes prospective recording of demographic and clinical information of hospitalized patients is being routinely done and is a good practice.

The patients in Intensive Care Units are more vulnerable to ADRs than others. The incidence is highly variable in these critically ill patients. It can be as high as 29.7 per 100 admissions in some medical centres. Cardiovascular drugs are commonly prescribed

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in these settings and thus are more prone to medication errors and there is a need to monitor for the ADRs associated with these drugs.[7] However, the data regarding the pattern of ADRs with cardiovascular drugs is sparse and needs more extensive research. The present study analyzed the incidence and pattern of adverse effects reported with cardiovascular drugs, including their causality and seriousness, in a cardiac care unit of a tertiary care teaching hospital.

MATERIALS AND METHODS

Study Design

This research was conducted at a tertiary care hospital which provides medical care to patients in the northern part of Punjab. This was a prospective, observational and longitudinal study. After obtaining ethical approval the study was carried out in the Cardiology Department over a period of 10 months. Informed consent was obtained from the patients before the enrolment, based on the inclusion and exclusion criteria.

Study Participants

All adult patients of age 18 years and above, of either gender, admitted to the cardiac care unit and consenting to participate were enrolled in the study.

Study Setting

During the study, patients were monitored from the day of their admission to hospital to the day of discharge. The investigator visited the Cardiac Care Unit (CCU) daily and collected relevant details and entered them in the proforma designed for the study purpose. The nursing and supporting staff was also explained about the study objectives and were requested to inform the investigator about any suspected ADRs.

Recording of Adverse Drug Effects

Adverse effects were recorded by the investigator himself by self monitoring and intensive monitoring process. Some additional relevant details were collected by reviewing the patient case records. Also, the medical and paramedical personnel helped the investigator in this process. All the adverse effects that were reported through spontaneous reporting and active surveillance were included in the present study. The details that were entered in the proforma included patient demographics, past history, any co-morbid disease, primary diagnosis, medication history, and laboratory investigation reports. Also, the details of suspected ADR, the date of onset of adverse effect, and the number of days of hospital stay were recorded. Additional information, about the system, affected, and alteration of biochemical characters was also collected. All patient's demographic details and ADR related details were also recorded in a Central Drug Standard Control Organization (CDSCO) ADR reporting form.

Assessment of Adverse Drug Effects

The reported ADRs were analyzed using Naranjo Causality Assessment Scale and they were classified into 4 subcategories; definite, probable, possible, and doubtful. The Naranjo criteria consist of a list of weighted questions that helps to classify the probability of relationship of an adverse event to drug therapy.[8] It finds whether there is temporal association of drug administration and event occurrence, or any alternative cause for the event. The ADR is then assigned to a probability category from the total score as follows.

Definite: If total score is ≥ 9
Probable: If total score is 5-8
Possible: If total score is 1-4
Doubtful: If total score is 0

Statistical Analysis

After the collection of data, for analysis, we divided the patients into 2 groups; the patients who developed adverse effects (ADR group), and the other one who did not develop any adverse effects (NON-ADR group). For analysis, we used descriptive statistics with 95% CI. Chi-square test and unpaired *t*-test were used on Microsoft Excel for the analysis, $p < 0.05$ was considered significant. Tables and Figures have been designed in Microsoft Excel 2007.

RESULTS

In the present study, the patients were enrolled from 18 years of age and above. A total of 175 patients were enrolled in the beginning but 2 of the patients dropped out from the study as their data was incomplete. So a total of 173 patients, who were admitted to the cardiac care unit, participated in the study. Out of these patients, 31 patients developed adverse drug reactions (ADRs) during their hospital stay.

Incidence of ADRs

The incidence of ADRs in the admitted patients in this study was 17.9%. The total number of ADRs recorded in 31 patients was 77 so the approximate number of ADRs per patient came out to be 2.4. The incidence of adverse effects in males was 9.2% and in females admitted to the cardiology unit was 8.6%.

Maximum patients i.e 56 (32.3%) were in the age group of 61-70 years. [Table 1] Out of these 13 patients (42%) were in the ADR group and 43 (30%) patients were in the non-ADR group. It was seen that 9 (29%) of the patients suffered from 1 ADR and 3 patients (9.6%) develop more than 5 adverse effects while on medication in the intensive care unit. Among the various types of adverse effects, it was observed that the most common ADRs were related to the Gastrointestinal system i.e, 15 ADRs (19.4%), followed by the cardiovascular system, musculoskeletal system, disturbed liver and Kidney functions [Figure 1].

Table 1: Distribution of patients according to the age groups.

Age groups (years)	ADR patients (N)	Non- ADR patients (N)	Total patients N (%)
21-30	1	3	4 (2.3%)
31-40	4	13	17 (9.85%)
41-50	5	22	27 (15.6%)
51-60	5	44	49 (28.3%)
61-70	13	43	56 (32.3%)
71-80	2	9	11 (6.35%)
81-90	1	8	9 (5.2%)
Total	**31**	**142**	**173**

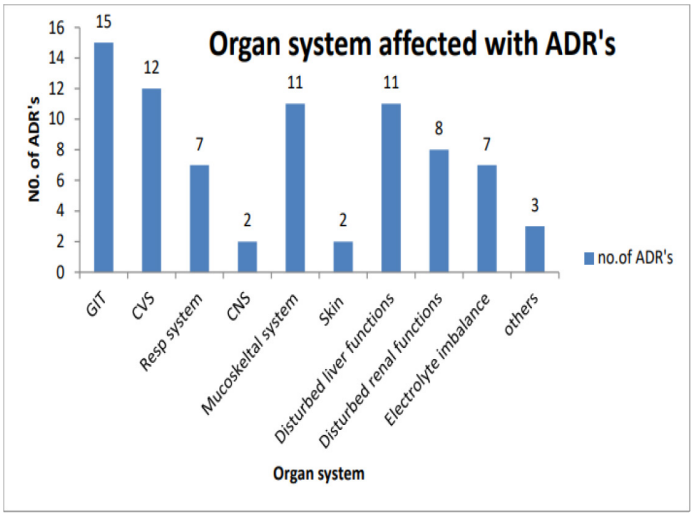

Figure 1: Distribution of Organ system affected with adverse effects.

Table 2: Predisposing factors for Adverse Drug Reactions.

Sl. No	Predisposing factors		ADR patients N (%)	Non-ADR patients N (%)	*p* value
1	**Gender**	Male	16 (51.6%)	94 (66.1%)	0.1263
		Female	15 (48.3%)	48 (33.8%)	
2	**Polypharmacy**	< 10 drugs	13 (42%)	84 (59.1%)	0.080
		> 10 drugs	18 (58.0%)	58 (40.8%)	
3	**Drugs per prescription**		10.74 ± 3.09	8.16 ± 2.53	0.0001
4	**Comorbid diseases**	Present	27 (87%)	57 (80.94%)	0.6023
5	**Mean duration of Hospital Stay (days)**		4.38 ± 3.57	2.51 ± 1.91	0.0001

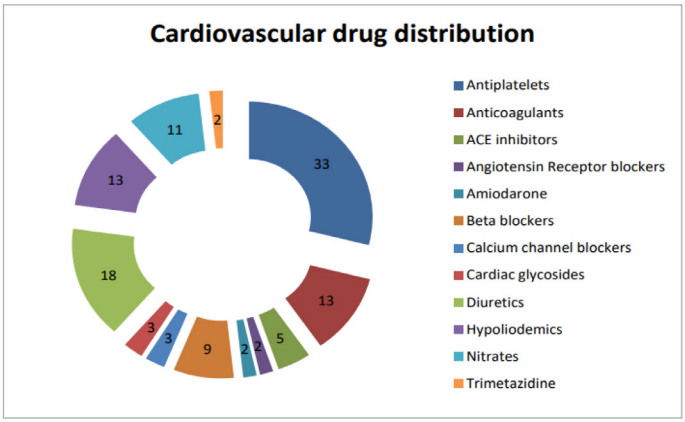

Figure 2: Distribution of durg primarily acting on cardiovascular system in ADR patients.

ADRs and Comorbidity

In the present study, 27 patients (87.0%) from the ADR group had co-morbid disease, whereas 57 (40.14%) patients in the Non-ADR group suffered from co-morbidity. The *p*-value was calculated using chi Square test to see the difference in co-morbidity among the ADR and Non-ADR groups, its value was non-significant (p=0.6023).

ADRs and their effect on hospital stay

In this study, we also compared the average time spent in hospitals in patients who developed adverse effects with those who had no adverse effects. The median number of days spent in the hospital in ADR patients was 3 days and in Non-ADR patients was 2 days. When statistically analyzed we observed a significant difference (p=0.0001).

Drugs Per prescription

As all the prescription of the patients enrolled in the study was extensively analyzed, we found that the total number of drugs used in the patients who reported adverse effects were 333 (22.3%) and the average number of drugs used per prescription came out to be 10.74 ± 3.09. In patients who did not develop any adverse drug effects, the total number of drugs used was 1157 (77.7%) and the average drugs per prescription were 8.16 ± 2. When statistically compared this difference was significant (p=0.0001). It was also observed that ≥ 10 drugs were used in 18 (58%) patients who developed adverse drug reactions [Table 2].

Prescription Analysis

On analysis of prescription of patients who developed adverse drug reactions, it was seen that 114 (34.23%) were the drugs that were primarily acting on the cardiovascular system. Among these maximum were Antiplatelets 33 (28.9%) followed by Diuretics 18 (15.7%), Antianginals, and Anticoagulants. [Figure 2] Out of these 114 drugs, a maximum of 90 drugs (79%) were given by oral route and 24 (21%) were given by intravenous route. Among the other drugs that were used in patients with adverse drug reactions, 52 (23.7%) were antimicrobial, and 61 (27.8%) were drugs acting on the gastrointestinal system. Among the antimicrobial agents, the penicillin group of antibiotics was most

Table 3: Adverse effects caused by suspected drugs.

Sl. No	Drugs	Suspected Adverse Drug Reactions
1	Furosemide	Hypokalemia, electrolyte imbalance
2	Glycerol trinitrate	Bradycardia, hypotension, itching, ventricular tachycardia
3	Ramipril	Cough
4	Aspirin, Clopidogrel	Gastritis
5	Metoprolol	Fatigue
6	Anticholinergics	Dryness of mouth
7	Statins	Myalgias, Arthralgias, discomfort
8	Calcium channel Blockers	Edema
9	Digoxin	Arrhythmia
10	Digoxin + Furosemide	Hypokalemia

commonly used, followed by other groups like fluoroquinolones, Aminoglycosides, Antitubercular drugs, polypeptides, and urinary antiseptics, etc. In a few patients, fixed-dose combinations were also used, like Sulbactam and Cefoperazone, Piperacillin and Tazobactam, Ceftriaxone and Sulbactam. Adverse effects that were suspected because of cardiovascular drugs were studied in detail. It was observed that diuretics, antianginals and antihypertensives were responsible for many ADRs [Table 3].

Assessment of ADRs by Naranjo ADR probability scale

The majority of the ADRs (52 of 77, 67.5%) were rated as probable followed by possible. The incidence of probable ADRs was 2.4% and that of the possible reactions was 2.02% of all the enrolled patients. The probable ADRs were more common in males as compared to females. The most common age group affected because of these ADRs was 61-70 years. According to the Hartwig Scale of severity, adverse drug effects were categorized as mild and moderate. (43 of 77) 56% of ADRs were mild and (34 of 77) 44% of the adverse effects were of moderate severity.

DISCUSSION

The development of new drugs in the past few years has brought tremendous benefits for patients but at the same time, incidence of ADRs has also increased. The Pharmacovigilance program of India gathers ADRs from all health care setups in India and further communicates the important information to the regulatory authorities for necessary action.

In this study from a total of 173 patients, 31 of them reported one or more adverse effects with overall incidence of 17.9 %. Whereas lower incidence of 9.8 % has also been observed in one of the study.[9] A higher incidence reported in the present study may be because the adverse drug effects were reported both by self-reporting and intensive monitoring methods. Also this incidence was higher (9.2%) in males as compared to females (8.6%) and a similar pattern has been previously reported by an author.[10]

Predisposing factors like age, gender, co-morbid diseases, polypharmacy, and length of hospital stay have been reported as important risk factors in the development of adverse effects. In the present study maximum number of patients, 56 (32.3%) were in the age group of 61-70 years. Also one of the study reported that patient's aged ≥ 60 years had a higher rate of polypharmacy and ADR's. It is a commonly observed practice that polypharmacy poses increased risk of adverse effects.[11] In our study, it was observed that ≥ 10 drugs were used in 58% of patients who developed adverse drug reactions and in 40.8 % patients who did not get any ADR. In comparison, the value was insignificant. Similar higher incidence of ADRs, i.e 23.5% in patients taking more than 10 drugs as compared to 8.4% in patients taking less than 10 drugs was observed by another author.[4] In our study, GIT was reported to be the most common organ system affected in terms of adverse effects i.e 15 (19.4%), followed by the CVS 12 (15.5%) and Respiratory system 11 (14.2%).

In this study, we compared the average time spent in hospitals in patients who developed adverse effects with those who had no adverse effects. The median number of days spent in the hospital in ADR patients was 3 days and in Non-ADR patients was 2 days. This difference was statistically significant. Another author in his study observed that the patients who developed adverse effects during hospitalization were hospitalized for an average of 1.2-3.8 days longer than the patients who did not develop any ADR.[12]

Anti-anginals (30.76%) were one of the most common drug classes with which adverse effects occurred followed by anti-hypertensives (26.15%), anti-coagulants (13.84%), and fibrinolytics (13.07%).[13] Similarly in our study Antianginals (9.09%) were the most common drug class followed by antihypertensives (7.07%). The cardiovascular drugs implicated in causing adverse effects were Enalapril, Atorvastatin, and Aspirin.[14] Frequently seen adverse effects were gastritis followed by the respiratory tract, musculoskeletal and connective tissue disorders, the present study also shows similar results with gastritis being the most commonly reported one. Similar results have also been observed in other studies with GI (14.1%) and respiratory disorder (14.1%.) ADRs.[15] Another study shows that headache and dizziness were the commonest ADRs because of cardiovascular drugs.[16] In the present study cardiovascular drugs like Nitrates also show the same type of result.

One of the study reported that Probable ADRs were more, 118 (56.7%) than the Possible adverse effects, 90 (43.3%) with males presenting with more number of probable reactions. These were more common in patients with comorbid conditions.[4] In the present study, Probable ADRs were 52 (67.5 %) and possible ADRs were 25 (32.4%). The Probable reactions were more in males, 29 (37.6%) as compared to 23 (29.8%) in females. Also Probable reactions were common in patients with age less than 65 years, whereas the possible reaction was more in patients aged

more than 65 years. Another study shows a total of 19 (6.8%) Probable ADRs, 80 (62%) possible ADRs, and 6 (28.2%) certain.[14]

One of the author also studied the severity, which reported that 114 (74.4%) ADRs were moderate and 30 (19%) were mild.[17,18] In the present study, 34 (44.1 %) adverse effects were moderate and 43 (55.8 %) were mild in nature.

Limitations of the study

More extensive research is still needed in terms of attribution of adverse effects to the various cardiovascular drugs. Also, more patients from other departments can be enrolled for a better understanding of ADR patterns.

CONCLUSION

Prevention of ADRs and emphasizing patient safety are current priorities for the Accreditation of Health Care Organizations. The study can be useful in identifying and minimizing preventable ADRs and can be an effort to make the use of drugs more rational and safe. ADR monitoring can be done in other clinical departments in the future.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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