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Research Article

REPORTING AND MONITORING OF ADVERSE DRUG REACTIONS WITH CARDIAC DRUGS

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ABSTRACT
Adverse drug reactions are a common medical problem, especially in patients who need multiple therapies. Patients with cardiovascular diseases are mostly on polypharmacy, so adverse effects of drug are quite common. The objective of the present study was to determine the severity and causality of adverse drug reactions in patients with cardiovascular drugs. This prospective and observational study enrolled patients who were on cardiac drugs and experienced adverse drug reaction. Naranjo ADR probability scale was used to establish the causality. A total of 231 ADRs were reported from 148 patients. Of these 148 patients, 39 patients were hospitalized primarily due to the development of ADRs, while 109 patients developed ADRs during hospital stay. Headache was the most frequent detected ADR (24.2%). The systems most commonly affected were the central nervous (33.3%) and gastrointestinal (16.5%). About 23.4% of the reactions were associated with calcium channel blockers followed by nitrates and ACE inhibitors. Assessing the severity and preventability of ADRs revealed that 1% of ADRs were detected as severe and 39% as preventable reactions.
The main treatment of reaction was the withdrawal of the suspected drug(s). Occurrence of adverse drug reactions was common in Indian population and majority of them often were predictable and preventable. Monitoring ADRs in patients using cardiovascular drugs is a matter of importance since this class of medicines is usually used by elderly patients with critical conditions and underlying diseases.
KEY WORDS: Adverse drug reactions, adverse event, cardiovascular diseases, causality, severity, monitoring

INTRODUCTION

A very broad definition of a drug would include "all chemicals other than food that affect living processes". If the affect helps the body, the drug is a medicine. However, if a drug causes a harmful effect on the body, the drug is a poison. The same chemical can be a medicine and a poison depending on conditions of use, dose and the person using it. A person with drug toxicity has accumulated too much of a medication in the bloodstream.[1, 2]

Adverse drug reactions (ADRs) which are officially described as: "a response to a drug which is noxious and unintended, and which occurs at doses normally used for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function".[3]

Adverse drug reactions are one of the leading causes of morbidity and mortality. It has been estimated that approximately 2.9-5.6% of all hospital admissions are caused by ADRs and as many as 35% of hospitalized patients experienced an ADR during their hospital stay.[4] An incidence of fatal ADRs is 0.23%- 0. 41%.[5]

Cardiovascular diseases (CVDs) remain a leading cause of morbidity and mortality worldwide. More than 30% of all the deaths every year are attributed to CVDs. With such a sizeable number of people suffering from these diseases, the number of drugs consumed per patient is relatively predictable and thus the inevitable danger of ADRs, which need to be monitored from time to time. The adverse drug event (AE) prevention study group reported that odds ratio of severe AEs with cardiovascular medicines was 2.4 times that of other medicines.[6]

International Scenario

The incidence of CVDs has been increased in recent decades, it has been estimated that CVDs are the most common cause of death in Iran. With introducing new cardiovascular drugs to the market, Pharmacotherapy of CVDs has improved rapidly during last few years. It has been reported that adverse drug events are considered as 4th to 6th cause of death in the US. Studies show that cardiovascular drugs are among the most commonly cause of adverse events in hospitalized patients. Some studies report that cardiovascular drugs may cause half of all hospital admissions due to adverse drug reactions. Another study describes that 4% of adverse events induced by cardiovascular drugs are serious ADEs.

Almost 10% of all medication-related office visits result from cardiovascular drug reactions, and most of those visits are related to dermatological reactions. In a literature review of ten studies published between 1994 and 2001, cardiovascular drugs were implicated for 17.9% of preventable adverse drug events.[7]

National Scenario

Like many other countries, India claims to have a national registry for collecting, retrieving and disseminating information on adverse drug reaction. The Drugs Controller General of India (DCGI) has established ADR monitoring centers in few hospitals of major cities in India. The national registry is said to be located at All India Institute of Medical Sciences (AIIMS), New Delhi. It has established an ADR reporting and monitoring system during late 1990s.

Indian Council of Medical Research (ICMR) ran a research program for 5 years and had identified six regional centers for monitoring of ADRs. It is reported to have collected around 90,000 reports from 12 centers in the country. However, in a country like India with population of more then one billion, this reported number is significantly low. Although many hospitals across the country claim to have ADR monitoring centers, only few ADR monitoring centers have established a working system. Adding to this, there is no evidence to confirm their present functioning. However, sufficient data pertaining to ADRs in Indian population has still not been generated. Pharmacovigilance has not picked up well in India and the subject is in its infancy.

OBJECTIVE

The objective of this study was to determine the severity and causality of adverse drug reactions in patients undergoing treatment with cardiovascular drugs.

MATERIALS AND METHODS

This was a prospective, observational study, commenced after approval from Independent Ethics Committee and was spread over a period of one year. All patients who were receiving cardiac drugs of either sex who developed adverse drug reaction during hospital stay or hospitalized due to ADR were included in the study. A suitable ADR notification form was prepared and provided at study centers on which treating physicians recorded suspected ADR. World Health Organization (WHO) definition of an ADR was adopted. When an ADR is identified, it was assessed as to whether it could be drug related or not. Demographic details of all the patients who developed ADR were recorded in the ADR notification form. After the initial notification of the suspected ADR by the physician, additional details were collected by review of the patient's case records and interview. The collected data were further analyzed and causality was ascertained. ADRs were characterized into mild, moderate and severe, according to severity scale.[8] The causality relationship between the drug and the effect was established using Naranjo's ADR probability scale.[9]

RESULTS AND DISCUSSION

A total of 231 adverse drug reactions (ADRs) were reported from 148 patients during study period of one year. A maximum of 5 reactions were reported in a single patient and three drugs were suspected in a single reaction. A total of 109 hospitalized patients experienced an ADR, while in 39 patients ADR was attributed to hospital admissions. There was only one fatal ADR was reported during this study. Majority [62.1% (n = 92)] of patients who developed an ADR were male. In 58.1% (n=86) of the cases patients developed single reaction and 57.5% (n=85) of patients were receiving two or more drugs at the time of experiencing an ADR. This finding further confirms the higher risk of developing an ADR if multiple drugs are prescribed. The demographic details of patients who experienced an ADR are presented in Table I.

System associated with adverse drug reaction and suspected reactions

Central nervous system and gastrointestinal system disorders were the most frequent system-organ classes affected with ADRs. In a study carried out by Gholami et al., it was reported that central nervous system and gastrointestinal system was most commonly associated with ADRs. The findings of our study are concurrent with this report. The systems associated with ADRs are shown in Table II. The most common adverse drug reaction reported was headache [(24.2%) n = 56] followed by cough [(13.9%) n = 32], hypokalemia [(9.5%) n=22] and nausea [(8.7%) n = 20]. This finding is consistent with reports of many other studies. The reported adverse drug reactions to suspected drugs are listed in Table III.

Causality of ADRs

When analyzed on Naranjo ADR probability scale, majority of ADRs [n = 149 (64.5%)] were rated as 'probable', followed by 'possible' [n = 76 (32.9%)], 'Unlikely' [n = 4 (1.7%)] and 'Definite' [n = 2 (0.9%)]. The probable reactions were more in males as compared to females. This finding was consistent with other studies; where in majority of reactions were rated as 'probable' and 'possible'.

Severity of ADRs

Majority of reactions, that is 138 (60%) were moderate, 90 (39%) were mild, and 3 (1%) were severe. Mild and severe reactions were more common in males, whereas

moderate reactions were significantly more common in females.

Management and Outcomes of ADRs

Of the 231 reported reactions, the offending drug was withdrawn in 176 (76.2%) of cases. The withdrawal of suspected drug(s) was observed in all cases of both 'severe' and 'moderate' adverse drug reactions and in few cases of 'mild' adverse drug reactions. Dose was altered in 6 (2.5%) cases. Of all, 49 (21.3%) cases required no change with offending drug.

Specific and symptomatic treatment were provided in 28 (12.1%) and 145 (62.8%) of cases respectively, whereas 58 (25.1%) of cases required no treatment. Patients were treated with a specific drug(s) wherever possible for the management of an ADR. In cases where the specific treatment option was not available it was treated symptomatically. In the remaining cases patients were not treated due to the fact that these reactions did not warrant the drug therapy as most patients recovered from adverse reactions after the cessation of suspected drug(s) while few others could tolerate the adverse drug reactions owing to their 'mild' in nature. Of 231 reported events of ADR, 173 (74.9%) recovered fully, whereas 45 (19.5) events were still continuing. Overall, only one reaction (0.4%) proved fatal.

Preventability and predictability of ADRs

Majority [(61%) n = 139] of reported reactions were not preventable. However, 39% (n = 92) of reactions were preventable. Of the total (n = 231) adverse reactions reported, 63% (n = 145) of reactions were predictable and 37% (n = 86) of reactions were not predictable.

Drugs Implicated in ADRs

Of the total reactions reported, the most commonly implicated drug class in causing ADRs was calcium channel blockers [(23.4%) n=54] followed by nitrates [(16.5%) n=38] and ACE inhibitors [(15.6%) n=36]. This finding is consistent with many other studies wherein it was reported calcium channel blockers, nitrates and ACE inhibitors as the most commonly associated drug classes in causing ADRs. Our finding may be due to the fact that in the present population, these classes of drugs are widely prescribed in Indian population. The drug classes commonly implicated in ADRs are shown in Table IV.

CONCLUSION

The reporting of ADR in Indian population is imbalanced with respect to its prevalence. However, European countries, USA and Australia are more vigilant in reporting of ADR when compared with other countries across the world. ADR related hospital admissions are significant problem in the healthcare system. Another reason for increased incidences of ADRs is increased consumption of medicines and co-morbidities. Monitoring adverse drug reactions in patients using cardiovascular drugs is a matter of importance since this class of medicine is usually used by elderly patients with critical conditions and underlying diseases. The frequency of ADRs occurrence can be reduced by decreasing the number of drugs prescribed. ADRs of Cardiovascular drugs mostly occur in first days of treatment, therefore monitoring patients in first days of using cardiovascular drugs could help in preventing ADRs. To determine the rate and nature of adverse events induced by different subclasses of cardiovascular drugs, more studies are recommended in various populations.

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Table I: DEMOGRAPHIC CHARACTERISTICS OF STUDY PATIENTS

Demographic Characteristics	Number (%) of patients (n=148)
Sex	
Male	92 (62.1)
Female	56 (37.9)
No. of Drugs	
Single drug	63 (42.5)
2-4 drugs	76 (51.4)
≥ 5 drugs	9 (6.1)
No of reactions / patient	
One	86 (58.1)
Two	48 (32.4)
More than two	14 (9.5)

Table II: SYSTEMS ASSOCIATED WITH ADVERSE DRUG REACTIONS

System Affected	Number of ADRs (%)
Nervous	77 (33.3)
Gastrointestinal	38 (16.5)
Respiratory	32 (13.9)
Minerals & fluid balance	32 (13.9)
Musculoskeletal	28 (12.1)
Cardiovascular	16 (6.9)
Dermatology	5 (2.2)
Endocrine & Metabolic	3 (1.2)

n=231

Table III: REPORTED ADVERSE DRUG REACTIONS TO SUSPECTED DRUGS

Suspected Reactions	Number of ADRs (%)
Headache	56 (24.2)
Cough	32 (13.9)
Hypokalemia	22 (9.5)
Nausea	20 (8.7)
Weakness	19 (8.2)
Dry mouth	12 (5.2)
Hyperkalemia	10 (4.3)
Hypotension	9 (3.9)
Dizziness	9 (3.9)
Vomiting	8 (3.5)
Bradycardia	7 (3.0)
Myalgia	6 (2.5)
Diarrhea	5 (2.2)
Constipation	3 (1.3)
Rhabdomyolysis	3 (1.3)
Purities	3 (1.3)
Increased liver enzyme	3 (1.3)
Rash	2 (0.9)
Abdominal pain	2 (0.9)

n=231

Table IV: DRUG CLASSES COMMONLY IMPLICATED IN ADVERSE DRUG REACTIONS

Drug Classes	Number of ADRs (%)
Calcium channel blokers	54 (23.4)
Nitrates	38 (16.5)
ACE inhibitors	36 (15.6)
Diuretics	27 (11.7)
Beta blockers	18 (7.8)
Angiotensin receptor blockers	17 (7.3)
Cardiac glycosides	13 (5.6)
Statins	12 (5.2)
Antiplatelets	11 (4.8)
Alpha blockers	5 (2.1)

n=231

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