Pattern of Angiotensin-Converting Enzyme Inhibitors Induced Adverse Drug Reactions in South Indian Teaching Hospital

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Abstract

Background: Adverse drug reactions (ADRs) occur frequently with cardiovascular drugs leading to change in therapy, increasing morbidity, and mortality. **Aim:** The study was conducted to evaluate the incidence of ADRs due to angiotensin-converting enzyme Inhibitors in cardiology department. **Materials and Methods:** A cross-sectional observational study was carried out for a period of 6 months. The data were assessed for the pattern of the ADRs with respect to patient demographics, nature of the reaction, outcome of the reactions, causality, severity, and preventability. **Results:** Among 692 patients, 51 (7.36%) had developed 60 ADRs, and majority of cases (56.66%) were in the age group of >61 years and most of them were developed in female (80%). The common ADRs observed were cough, hypotension, hyperkalemia, and acute renal failure. In 21.66% cases the dose of the suspected drug was altered and in 78.33% cases the drug was withdrawn. Considering the outcome, 93.33% of cases recovered from ADRs, whereas in 6.66% cases were continuing. Causality assessment showed that majority of ADRs was probable and were found to be moderately severe. **Conclusion:** Our study concludes geriatrics and female patients have higher incidence of ADRs. So early identification and management of ADRs are essential for this population.

Keywords: Adverse drug reactions, Angiotensin-converting enzymes, Cardiovascular drugs

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Introduction

Adverse drug reactions (ADRs) occur frequently with cardiovascular drugs leading to change in therapy, compliance, and increasing morbidity and mortality and inflating the healthcare cost. Angiotensin-converting enzyme (ACE) inhibitors have been increasingly used for the therapeutic management of several conditions, such as hypertension, acute myocardial infarction, left ventricular systolic dysfunction, chronic renal failure, and so on. Large multicentric trials have proved that

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ACE inhibitors not only increase the life expectancy, but also improve the quality of life in high-risk patients suffering from cardiovascular events. ACE inhibitors have specific effect on myocardial and vascular cell growth, also referred to as remodeling, they have a greater protective potential than any other class of antihypertensive drugs.[1,2]

ACE inhibitors have contributed 7.7% of the total ADRs in hospitalized patient.[3,4] Very few studies have conducted to evaluate the occurrence of ADRs due to ACE inhibitors. Reporting of ADRs has become an important component of monitoring and evaluation activities performed in hospitals.[5] Such ADR reporting programs encourage surveillance for ADRs, promote the reporting of ADRs, and stimulate the education of health professionals regarding potential ADRs.[6]

Intensive monitoring study will help in obtaining detailed data on incidence and pattern of ADRs. The

present study was designed to evaluate the incidence and pattern of ADRs due to ACE inhibitors in the cardiology department.

Materials and Methods

A cross-sectional observational study was carried out for the period of 6 months (January–June 2010) in an Indian teaching hospital. The ethical approval was obtained from Institutional ethics committee prior to study initiation (UEC/19/2010). Patients admitted consecutively to the cardiology unit were included in the study. Patients prescribed with ACE inhibitors were only selected for the study. Prescription from each patient during his/her hospitalization in the ward during the study period was included.

Data collection

The information such as demographics, complaints on admission, routine biochemical investigations, were obtained from the patient's clinical records. Details necessary for evaluations regarding previous allergies, concomitant medications, comorbidities, and others were collected. All the prescriptions of the study population were screened for ACEIs-induced ADRs. All drugs were classified with Anatomical Therapeutic Chemical Classification (ATC code – level 1, WHO, 2008). Demographics of the patients were studied to find out the pattern of ADRs. Factors studied were (a) patient characteristics [gender, age (>18 years), comorbidities and length of stay], (b) drug characteristics [number of drugs] and laboratory investigations.

Identification of ADRs were done based on the regular follow of the patients by analyzing the subjective findings like cough, and objective findings like routine monitoring of electrolytes, blood pressure, and serum creatinine. Data on the reported ADRs were evaluated to understand the pattern of the ADRs with respect to patient demographics, nature of the reaction, characteristics of the drugs involved, and outcome of the reactions.

Analysis of ADRs

Causality: In order to assess the likelihood that drugs has caused the reaction, causality assessment was done using Naranjo's ADR probability scale[7] whereby the ADRs were classified into certain, probable, possible, and unlikely to be drug induced depending upon the level of association. Severity: Depending upon the severity, ADRs were classified into mild, moderate, and severe reactions using the criterion developed by Hartwig *et al*. for severity assessment.[5] Preventability: ADRs were categorized into definitely preventable, probably preventable, and not preventable using the criteria of Schumock and Thornton modified.[8] Predisposing

factors: Factors which could have predisposed to the occurrence of ADRs in the individual reports were evaluated. Predisposing factors were generally classified for the purpose of study into age, gender, multiple and intercurrent disease state, and polypharmacy.

Management strategies employed for the management of ADRs were categorized as drug withdrawal, dose reduction, additional treatment for ADR, and no change in regimen with any additional treatment. Further, categorization of the outcome of ADRs was done for response after dechallenge and rechallenge as well as the final outcome of the event.

Statistical analysis

Frequencies with percentage were used to summarize sex, number of drugs dispensed, frequency of ADRs, drugs involved in the ADRs, and severity of ADRs. Mean with 95% confidence interval was used to summarize age and length of stay. The chi-square test was used to find the association between sex, number of drugs, and ADRs. Spearman's correlation was used to find the correlation between numbers of drugs, length of stay with ADRs. A '*P*' value of <0.05 was considered statistically significant. All analysis was performed using SPSS.

Results

Patients, drug characteristics, and ADRs

A total of 692 patients who were prescribed with ACE Inhibitors were analyzed during the study period in cardiology unit and 51 (7.36%) patients had developed 60 ADRs. The significant proportions of patients with ADRs were female 48 (80%) than in male 12 (20%). A total of 35 (58.33%) ADRs were developed mostly in the age group of >61 years, followed by the other age group and the patients who had taken more than 7 drugs developed 54 (90%) ADRs. Patient characteristics and statistical significance of the results were summarized in the Table 1. A total of 37 (61.66%) ADRs were developed with a length of hospital stay of >14 days, followed by 23 (38.33%) with <7 days. The age, sex, and number of drugs taken were identified as the risk factors for developing ADRs (*P*<0.05). Spearman correlation showed that there was an extremely significant linear relationship (r=0.16, 95% CI=2.41–13.44, *P*<0.000) was observed between number of drugs taken and ADRs. Similarly, a significant linear relationship (r=0.08, 95% CI=1.03-3.82, *P*<0.036) between sex and the ADRs in patients and linear relationship (r=0.09, 95% CI=0.30–0.91, *P*<0.022) between age and the ADRs in patients. Ramipril 27 (45%), Enalapril 18 (30.00%), Captopril 11 (18.33%), and Linisopril 4 (6.64%) were the most commonly observed drugs involved and the common

ADRs observed were cough 23 (38.33%), hyperkalemia 19 (31.66%), hypotension 13 (21.66%), and acute renal failure 05 (8.33%). Incidence of individual suspected drugs with their ADRs results are summarized in the Table 2.

Organ system affected by the adverse drug reactions

Present data on ADRs were evaluated for the specific system affected by ADRs. Respiratory system was the most affected organ system class. Respiratory disorders due to cough were 23 (38.33%), followed by metabolic and nutritional disorders due to hyperkalemia 19 (31.66%), which is presented in Table 3.

Causality and severity of ADRs

In majority, 47 (78.33%) of the cases, the suspected drug was withdrawn for the management of the ADRs and a specific treatment for the reaction was instituted in 20 (33.33%). In 56 (93.33%) of the cases, the patient recovered from the reaction at the time of evaluation of the ADR report. An improvement in the adverse reaction was observed in majority (76.8%) of the cases, in which dechallenge or dose reduction was done [Table 4]. Upon causality assessment, majority of the reports were rated as probable 56 (93.33%) followed by possible 4 (06.66%). A total of 13 (21.66%) of reactions were mild and moderate reactions accounted for 47 (78.33%). Predictability and preventability are depicted in Table 4.

Discussion

Our study revealed that the overall incidence of ACEIs-induced ADRs in the study populations were 7.367% which is low, compared to similar studies.[9] A total of 58.33% of ADRs were observed in the age group of more than 61 years and considering the result of the chi-square test for analytical evaluation of the influence of age on occurring ADRs, it appears that older patients are more likely to experience an ADR.[10] Moore *et al.* found an inverse relationship between age and ADRs occurring during hospital stay.[11] Altered physiology in geriatrics could be another reason for higher incidence of ADRs in the population.[12,13] While considering the gender distribution, there was increased number of ADRs present in women than men, which is similar to some earlier reported studies.[14] Several studies have found that risk of developing ADRs was more in females than males.[15,16] Reasons suggested for this include

Table 1: Patient characteristics						
Patient characteristics	Number of ADRs (%)	Chi-square value (χ^2)	Degree of freedom (df)	Confident interval (CI)	r value	*P* value (*P*<0.05)
Gender group						
Male	12 (20)	4.394	1	1.03–3.82	0.08	0.036
Female	48 (80)					
Age (years)						
<40	2 (3.33)	5.283	2	0.30–0.91	0.09	0.022
41−60	23 (38.33)					
>61	35 (58.33)					
No. of drugs taken						
<7	6 (10)	19.588	1	2.41–13.44	0.16	<0.0001
>7	54 (90)					

Table 2: Incidence of individual suspected drugs with their adverse drug reactions					
Suspected drug	No. of cases (*n*=51)	ADRs	Number (%)	No. of controls (*n*=641)	Incidence (%)
Ramipril	22	Hyperkalemia	17 (28.33)	216	9.24
		Hypotension	6 (10.00)		
		Cough	3 (5.00)		
		Acute renal failure	1 (1.66)		
Enalapril	16	Cough	18 (30.00)	180	8.16
Captopril	09	Hypotension	6 (10.00)	159	5.35
		Hyperkalemia	2 (3.33)		
		Acute renal failure	1 (1.66)		
		Cough	1 (1.66)		
Lisinopril	04	Acute renal failure	3 (5.00)	86	4.44
		Cough	1 (1.66)		

Table 3: Organ system affected by the adverse drug reactions

Organ system involved	Preferred term	Number (%)
Respiratory system disorders (1100)	Cough	23 (38.33)
Metabolic and nutritional disorders (800)	Hyperkalemia	19 (31.66)
Cardiovascular disorders (1010)	Hypotension	13 (21.66)
Urinary system disorders (1300)	Acute renal failure	5 (8.33)

Table 4: Management, outcome and analysis of ADRs

Parameters Management	ADRs (%)	Parameters Naranjo's scale	ADRs (%)
Drug withdrawn	47 (78.33)	Define	-
Dose altered	13 (21.66)	Probable	56 (93.33)
No change	-	Possible	4 (6.66)
Treatment given		Unlikely	-
Specific	20 (33.33)	Severity	
Symptomatic	27 (45.00)	Mild	13 (21.66)
Nil	13 (21.66)	Moderate	47 (78.33)
Outcome		Severe	-
After dechallenge		Predictability	
Definite improvement	56 (93.33)	Predictable	60 (100)
No improvement	4 (6.66)	Non predictable	-
Unknown	-	Preventability	
After rechallenge		Definitely preventable	-
Recurrence of symptoms	13 (21.66)	Probably preventable	55 (91.66)
No recurrence of symptoms	41 (68.33)	Not preventable	5 (8.33)
Unknown	6 (10.00)		
Final outcome			
Fatal	-		
Recovery	56 (93.33)		
Continuing	4 (6.66)		
Unknown	-		

differences in perception of ADRs, pharmacology of ADRs, differences in pharmacokinetics such as volume of distribution, polypharmacy, and hormonal differences between men and women.[17,18] The incidence of ADRs was more in the population receiving seven or more medications concurrently, which is supported by previously published studies.[19]

Our results show that drugs like Ramipril 45% and Enalapril 30% had the higher incidence of ADRs and the common ADRs observed were found to be cough 38.33%, hyperkalemia 31.66%, and acute renal failure 8.33% and these results were similar to other studies conducted in various university hospitals.[20-22]

Drug withdrawal or dose reduction is usually the first step to be employed for the management of an ADR. In 78.33% of the cases, the suspected drug was withdrawn and dose reduction was done in 22.2% of cases. Considering the final outcome, 93.33% of patients were recovered from ADRs, whereas 6.66% of patients were continuing and these findings were similar to the one observed by Suh *et al.* in their study patients.[23]

On causality assessment of ADRs, majority of the reactions 93.33% were categorized as probable in nature, followed by possible 6.70%. Considering the severity assessment of the reactions, majority of the reactions were categorized moderate in nature followed by mild and these findings were not comparable with the spontaneous reporting study. Preventability assessment of ADRs showed that 8.33% of the ADRs were not preventable in nature. Definitely preventable ADRs were not present in this study compared to the study conducted on adverse drug reaction to cardiovascular drugs, where 1.9% of ADRs were preventable.[24]

Conclusion

Our study concludes geriatrics and female patients have higher incidence of ADRs. So early identification and management of ADRs are essential for this population. Special attention should be taken to the patients who are in polypharmacy. Drug withdrawal or dose reduction is usually the first step to be employed for the management of ADRs.

Acknowledgment

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