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Prospective cross sectional observational study on prevention of adverse event of drug ACE Inhibitors

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Abstract
Prospective cross sectional study was conducted to prevent the adverse drug reactions of the ACE inhibitors. Total 51 patients were enrolled who are on the ACE inhibitors. Patients were informed about the use of the ACE inhibitors taking the dose the adverse drug reactions to notify to the investigator for the prevention strategies. The study showed adverse reactions of the ACE inhibitors can be prevented in the 15 patients as per the prevention criteria.

Keywords: observational study, drug reactions, ACE inhibitors, prevention criteria

Introduction

Several studies have demonstrated that Adverse Drug Reaction (ADRs) make a major contribution to hospital admissions, although annual incidences of ADR-related admissions vary widely, from 1.83% to 6.5% (Bardou, M, *et al*., 2009) [4]. The safe use of medicines is an important issue for prescribers, pharmacists, nurses, regulatory authorities, the pharmaceutical industry, and the public. Healthcare professionals have a responsibility to their patients, who themselves are increasingly aware of the problems associated with drug therapy (Acharya, D, *et al*., 2006) [1].

It is essential that the practicing pharmacist should have a thorough knowledge about the various adverse effects of the drugs, including its predictability and reversibility, frequency and severity, predisposing factors and recognition, relationship to dosage, and duration of treatment and prevention (Beard, K, *et al*., 2001) [5]. ADRs are a public health problem in older subjects, being responsible for a significant morbidity, disability and mortality. Older subjects are more susceptible to develop ADRs mainly due to polypharmacy, multimorbidity and inappropriate prescribing. Adverse drug events (ADEs) are defined as any injuries resulting from medication use, including physical harm, mental harm, or loss of function (Bates, DW, *et al*., 1995) [6].

Pharmacovigilance is the science and activity relating to detection assessment understanding & prevention of adverse effect or any other possible drug related problem (Meyboom, R, *et al*., 1999) [13]. The prevention of these drug related negative events represents an important aim for physicians treating older patients (Cherubini, *et al*., 2011) [8].

As we know cardiac disease is leading health problem in our country rate of ACE inhibitors (ACEIs) prescribed by physician is 19.28%. The drugs mainly used to treat high blood pressure and heart failure, to prevent repeat heart attacks, to reverse thickening of the heart due to high blood pressure, and to prevent the decline of kidney function in people with high blood pressure and/or diabetes (Bajaj, K, *et al*., 2012) [3].

Angiotensin-converting enzyme inhibitors and angiotensin II receptor subtype 1 antagonists have proven to be effective and well tolerated antihypertensive agents. They also exhibit unique cardio protective and renoprotective properties in patients with co morbid conditions such as congestive heart failure and proteinuria or renal insufficiency.

This benefit is observed most clinical effect than ACE inhibitors in patients with heart failure (Ou, R, *et al*., 1996) [15]. Therapeutic use of ACE inhibitors in hypertension, CHF, MI, Prophylaxis in high cardiovascular risk subject, Diabetic Nephropathy, Scleroderma crisis. These drugs inhibit competitively the activity of ACE (also termed kininase II) to prevent formation of the active octapeptide, angiotensin II, from the inactive decapeptide, angiotensin I. This occurs in blood and tissues including kidney, heart, blood vessels, adrenal gland and brain. Angiotensin II is a potent vasoconstrictor promotes aldosterone release, facilities sympathetic activity and has other potentially harmful effects on the cardiovascular system.

Reduction in blood pressure secondary to vasodilatation following ACE inhibition is greatest when the rennin angiotensin system is stimulated (e.g. following diuretic therapy or in renal artery stenosis) but ACE inhibitors also lower blood pressure when there is normal or low activity of the rennin angiotensin system. Nevertheless, Afro-Caribbeans and elderly individuals, who tend to have low renin hypertension, respond less well to monotherapy with ACE inhibitors. Inhibition of ACE (kininase II) also leads to accumulation of kinins including bradykinin which promotes vasodilator activity and may contribute to the overall effectiveness of ACE inhibitors (Hasford J, 2008) [7].

ADR of ACE inhibitors hypotension at initiation of therapy. Hyperkalemia in patients on Diuretics, B-Blockers and Kidney Diseases. Dry persistent cough is the most common side effect requiring discontinuation of ACE inhibitors. Rashes, urticaria, angioedema, dysgeusia, occur in few cases and are reversible. Headache, dizziness, nausea and bowel upset, granulocytopenia and protein urea may also occur. Acute renal failure is precipitated by ACE inhibitors in patients with bilateral renal artery stenosis due to dilatation. ACE inhibitors cause fetal pulmonary hyperplasia and other fetopathic effects when given in later half of pregnancy (Nancy, R, *et al*., 2002) [14].

Major Drug Interactions of ACE inhibitors includes Lithium levels can increase 3-4X after 2-4 days of ACEI initiation reduce lithium dose and monitor lithium levels Potassium Supplements, Potassium Sparing Diuretics potassium retention, potential severe hyperkalemia Diuretics - Increased risk of first-dose hypotension if hypovolemic sodium and water retention, decreased effect of ACEI, and increased risk of nephrotoxicity.

Contraindications**–**Absolute pregnancy history of angioedema or hypersensitivity to ACEIs bilateral Renal Artery Stenosis (RAS) or RAS of a solitary kidney history of intolerance to ACEIs due to hypotension severe hyperkalemia**.** Relative-hypotension (SBP < 90mm), renal dysfunction, hyperkalemia, cough (Loren, D, *et al*., 1997) [12]. ADRs occur frequently with cardiovascular drugs leading to change in therapy, increasing morbidity, and mortality.

Prevalence rate of cough due ACE inhibitors varied from 0.2-25% (Kam, S, *et al.,* 1995) [11]. Bronchospasm was 5.5% for patients on ACE inhibitors. ACE inhibitors in patients with heart failure, the reported incidence of symptomatic first-dose hypotension ranged from 2 to 33%. (Vitovec, J., *et al*., 2004) [9]. Whereas prevalence of Angioedema, Dysgeusia, due to ACE inhibitors was 0.06,-0.5%.0.5-3% respectively (Tripathi K.D., 2008) [10].

There is need to reduces morbidity & mortality. It can be prevented by early detection of ADR. There are various methods has been developed for prevention of ADR. It can be prevented by using computerized surveillance techniques (Scott, R, *et al*., 1993) [16], also by preventing Administrative error, Medication Errors (Allison, F, *et al*., 2010) [2]. In this study we use the strategy that might be help in prevention of ADR due to ACE inhibitors. Prevention plan for this study is effective communication about safety issue. In past communication documents have been written by that medicine safety specialist responsible for evaluating safety issue.

Methodology

Study was conducted in compliance with the protocol, ICH GCP, Schedule Y guidelines and Indian regulatory requirements. This is observational, retrospective study. This study was carried out in civil hospital, Nasik. Approval from Institutional Ethics Committee was taken prior to initiation of the study. Signed dated written informed consent was taken from all subjects after providing them with patient information sheet and informed consent form before screening. Total 100 subjects and their prescription from medicine department of civil hospital Nasik was collected. Subjects who are on monotherapy of ACE inhibitors for hypertension and also fulfilling inclusion criteria were selected for study. Screening of subject was done according to inclusion and exclusion criteria with help of screening form and after informed consent by subjects they were enrolled in our study.

As per our criteria the patients who was diagnosed as hypertension and who was prescribed with ACE Inhibitors monotherapy by qualified physicians was taken in our study. We were describing them our study and the ADR regarding ACE inhibitors and we were provided them with Safety sheet as per our prevention strategy and then we were record the data in case record form. After seven days from the recruitment day we were contact with our subject on telephone and we collect whether there is any ADR. Also other than listed ADR. We were ask for compliance of patient for dose and dosage schedule for his therapy as prescribed by physician and the other data which was required for our study was noted and then again in same way successive follow ups was taken As per our prevention strategy i.e. Effective communication about safety issue of ADR of ACE inhibitors. The patient should follow the compliance regarding the dosages and dosing schedule. He was informed and contacted to physician as per instructed in safety sheet. After 8 weeks of study the ADR was analyzed as per WHO-UMC and Naranjo's ADR Causality Analysis Scale and their frequency of occurrence was calculated.

Statistical Analysis

The case record forms were analyzed and we get following results.

Result

It is a Prospective Cross Sectional Observational Study on Prevention of Adverse Event of Drug ACE Inhibitors. Study includes Subjects who are on monotherapy of ACE inhibitors for hypertension and also fulfilling inclusion criteria were selected for study. Screening of subject was done according to inclusion and exclusion criteria with help of screening form and after informed consent by subjects they were enrolled in our study. It was evident that the number of males in each study group was more than the females (fig. -1) Their mean (±S.D.) age was 47.09 years; baseline blood pressure (systolic/diastolic), 157.4/101.4 mm Hg; The study drugs were tolerated by the majority, except in five subjects, who presented with adverse events such as hypotension (n = 1), skin rash (n = 2), and chest pain (n = 2), which warranted treatment discontinuation.

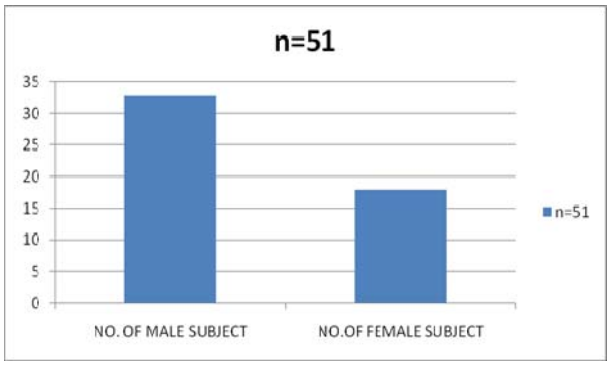

Table 1: Gender distribution of patients receiving ACEI for hypertension

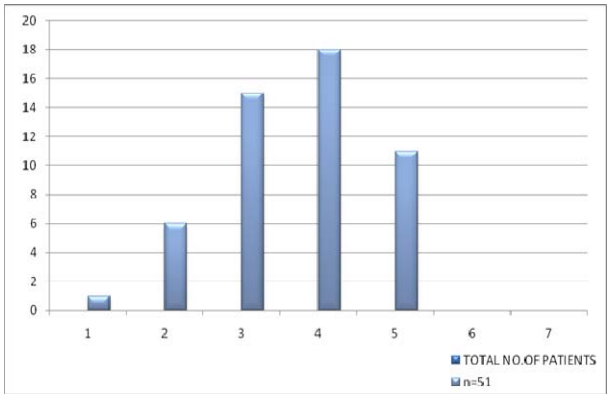

Table 2: Age distribution of study subjects receiving ACEI for hypertension

The various adverse drug reactions observed in the study subjects were dizziness, cough, hypotension, diarrhea, muscle pain, weakness, headache, nausea, and skin rash. we further categorized these reactions according its severity. we found 33% mild reaction, 43% moderate reaction occurred in subject. In 12% subject no adverse reactions were found. We found 12% serious reaction in subject.

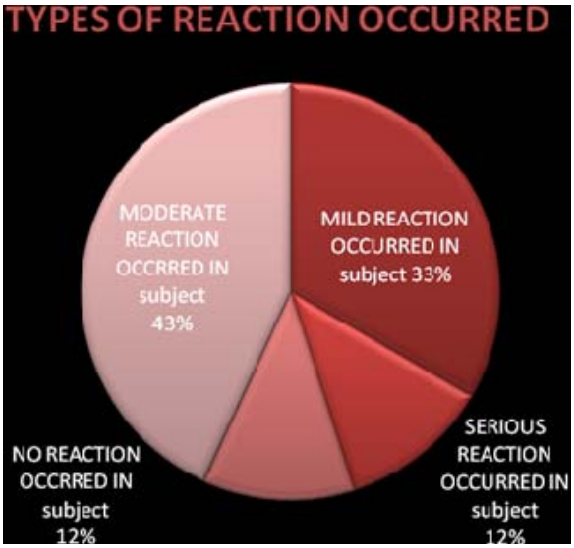

Table 3: Types of Reaction Occurred

We also analyzed patient's compliance with respect of dose and dosage schedule, we found nearly most of subject compliance with their medicine dose and dosing schedule.

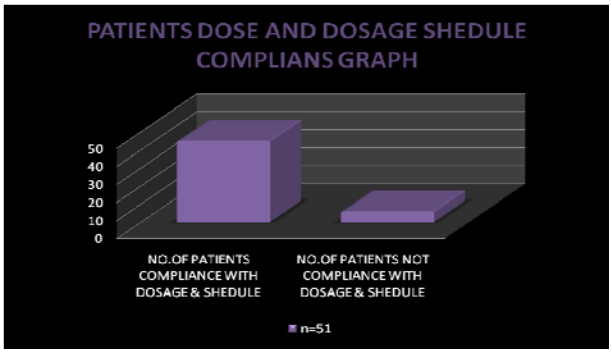

Table 4: Patients Dose and Dosages Schedule Compliance Graph

As per our Aim and objective our prevention strategy i.e. Effective communication about safety issue of ADR of ACE inhibitors. We got the following result ADR prevention graph (Table no.1) shows that from total 51 sample 15 patients are prevented from ADR and 38 patients are not prevented from ADR. In table no. 3 we found that about 88% patients compliance with dose and dosage schedule. In table no 2 we found that moderate reaction occurred in 35% of patients, mild reaction occurred in 25% of patients. No ADR reaction occurred in patients were 29%, serious reaction occurred in 9% patients.

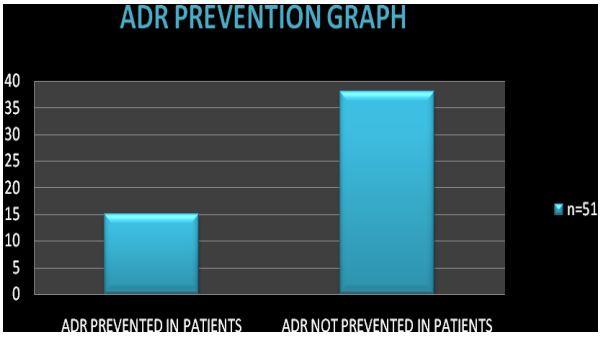

Table 5: ADR Prevention Graph

Discussion

Besides essential hypertension, ACEIs are increasingly used for the management of several other conditions, such as, acute myocardial infarction, left ventricular systolic dysfunction, chronic renal failure, and so on. Large multi-centric trials [Duncan J & Cambell 2003] [17] have proved that ACEIs not only increase the life expectancy, but also improve the quality of life in high-risk patients suffering from cardiovascular events. It appears that by their specific effect on myocardial and vascular cell growth, also referred to as remodeling, they have a greater protective potential than any other class of anti-hypertensive drugs. Our study was designed to monitor the various ADRs seen with the ACEIs and prevent its adverse drug reaction by method of effective communication.

Ever since Captopril (Sulfhydryl group containing ACEI) was introduced as an anti-hypertensive agent in the year 1981, by the USFDA, many adverse effects with its use have been reported. Several other ACEIs followed captopril over the years to come and today we have a surfeit of ACEIs to choose from with more or less a similar ADR profile. Among the ADRs [Table 3] that were encountered with various ACEIs, and we categorized it according to its severity. The incidence of these ADRs was not related to the age group of the study subjects. (Nishant, V, Sangole, *et al*., 2000) [18].

Due to shortage of time we couldn't found adverse drug reaction that encountered in more than week, also we unable to find any laboratory abnormality. We found 33% mild reaction, 43% moderate reaction occurred in subject. In 12% subject no adverse reactions were found. We found 12% serious reaction in subject. In case of serious adverse drug reaction 1st effect of hypotension, chest pain and skin rash were found. Nausea with use of ACEIs is around 1-5% as reported in the literature. [Cooper WD, Sheldon D *et al*. 1987] [19] It is somewhat higher with Lisinopril as compared to Enalapril and Ramipril [Schreiner, M, Berendes, B, *et al*. 1991] [20] and considerably low with Fosinopril.

Result of this study shows that As per our Prevention Strategy we found that we had successful prevent 29% patients ADR in short time but still there are 35% of patients suffered in moderate types of ADR which required either reducing dose or change in therapy. Which shows therapy should be more focus on individual characteristics. Simple Effective communication about safety issue of ADR of ACE inhibitors may be benefited to patients. Strategy may help patients to more aware about their ADR and safety.

Limitations of this study

Time constraints not only restricted the number of subjects recruited in our study, but also the duration of the follow-up period and the number of follow-up. As this study was limited subjects, incorporating more number of subjects will be beneficial. There is a need for an increased number of follow-up visits, over a longer duration, to make this study broad-based and representative of the Indian population.

Conclusion

Effective Communication about safety issue of ADR may be effective.

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