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# Review : To Study Adverse Drug Reactions of Angiotensin Converting Enzyme Inhibitiors as an Antihypertensive Agent

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**Abstract:** *Background : ACE inhibitors are a medication class used to treat and manage hypertension, a significant risk factor for coronary diseases, stroke, heart failure and number of other cardiovascular condition. Due to long therapy ACE inhibitors as an antihypertensive drugs are commonly associated with adverse drug reactions (ADRs). Therefore the study was conducted with the objective to examine the incidence of different types of ADRs in drug treated hypertensive patients.*

*Methods : A prospective cross sectional observational study was conducted in the outpatient of department of general medicine of primary care hospital in Chhatrapati SambhajiNagar. 120 diagnosed hypertensive patients were studied. Questionnaire was asked and their priscription were analysed and follow up was done.*

*Results : In our study total 120 patients were included. Total number of ADR reported was 65. In this study out of 120 patients, 70 (58.33%) were male and 50 (41.66%) were female. Most common ADRs Dry cough ( 10% to 20%), Dizziness ( 12% to 19%), Hypotension ( 7% to 11%) Increased BUN and creatinine ( 2% to 11%), Syncope ( 5% to 7%) and Hyperkalemia ( 2% to 6%) were reported. As per WHO-UMC scale, type of reactions and their percentage are as certain (9.23%), probable/likely (69.23%), possible (15.38%) and unlikely(6.15%). According to Naranjo scale, type of reactions and their percentage are as definite (9.23%), possible (15.38%), probable ( 69.23%) and doubtful (6.15%). Severity assessement is done by Hartwig and Siegel scale. No lethal ADR were reported. 6.15% reactions were severe, 24.61% were moderate category and 64 % were mild reaction.*

*Conclusion : Such type of studies would be useful for the physicians in rational selection of drug therapy for treatment of hypertensive patients . This present data suggest that the ADR monitoring needs to be done in hiopital settings continuously so that unexpected effect caused by different medicines can be identified and documented.*

**Keywords:** Hypertension, ACE inhibitor, Causality assessment, ADR monitoring

## I. INTRODUCTION

Hypertension (HT) is a very common disorder, particularly past middle age. It is an important risk factor for cardiovascular mortality and morbidity, where the systolic BP is more than 140mmHg and diastolic BP is more than 90mmHg. The prevalence of hypertension varies across region and country income groups. The WHO African region has the highest prevalence of hypertension (27%) while the WHO region of the Americas has the lowest prevalence of hypertension (18%). The number of adults with hypertension increased from 595 million in 1975 to 1.14 billion in 2015, with the increase seen largely in low and middle-income countries . This increase is due mainly to a rise in hypertension risk factors in those populations.

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Blood Pressure Categories as per Joint National Committee :
BLOOD PRESSURE CATEGORIES (mmHg = Millimeters in Mercury )

| Adults 18 - years or olders | SYSTOLIC (mmHg) | DIASTOLIC (mmHg) |
|---|---|---|
| Normal | Under 120 | Under 80 |
| Prehypertension | 120 - 139 | or 80 - 89 |
| Stage 1 | 140 - 159 | or 90 – 99 |
| Stage 2 | 160 or over | or 100 or over |

Table 1 : Blood Pressure Categories as per Joint National Committee

**Classification of Antihypertensive Drug :**

| CLASS | SUB-CLASS | DRUGS |
|---|---|---|
| RAAS Inhibitors | ACE inhibitors<br>Angiotensin receptor blocker (ARB)<br>Direct renin inhibitors | Captopril, Enalapril, Lisinopril, Ramipril, Benazepril,<br>Fosinopril, Losartan, Candesartan Irbesartan,<br>Valsartan, Telmisartan, Aliskiren |
| Diuretics | Thiazides<br>Loop diuretics<br>K + Sparing diuretics | Hydrochlorothiazide, Chlorthalidone, Indapamide<br>Furosemide, Bumetanide<br>Spironolactone, Eplerenone, Triamterene, Amiloride |
| Calcium Channel Blockers | Phenylalkylamine<br>Benzothiazepine<br>Dihydropyridine | Verapamil<br>Diltiazem<br>Nifedipine, Felodipine, Amlodipine, Nicardipine |
| Vasodilators | Arterioles<br>Arteriolar + Venous | Hydralazine, Minoxidil, Diazoxide<br>Sodium Nitroprusside |
| Sympathetic Inhibitors | α Adrenergic blockers<br>β Adrenergic blocker<br>α+β blockers<br>Ganglionic blockers<br>Central Sympatholytic | Prazosin, Terazosin, Doxazocin, Phentolamine<br>Propranolol, Metaprolol, Atenolol (others)<br>Labetolol, Carvedilol<br>Trimethaphan<br>Clonidine, Methyldopa |

Table 2: Classification of Antihypertensive drugs

**ANGIOTENSIN CONVERTING ENZYME INHIBITORS :**

The Angiotensin Converting Enzyme inhibitors are a class of drugs that are used in the treatment and management of hypertension, which is a major risk factor for coronary disease, heart failure, stroke, and many other cardiovascular conditions. Most cases are primary and not due to any particular etiology. This activity reviews the indications, contraindications, mechanism of action, adverse events, and other key elements of ACE inhibitor therapy in the clinical setting related to the essential points needed by members of an interprofessional team managing the care of patients with hypertension and its related conditions and sequelae.

**Objective :**

- Identify the mechanism of action of ACE inhibitors.
- Discuss adverse effects of ACE inhibitors.

**Mechanism of Action :**

The angiotensin-converting-enzyme (ACE) is part of the renin-angiotensin-aldosterone system (RAAS; media item 1). It accelerates the process of angiotensin I to angiotensin II. ACE inhibitors, being competitive inhibitors of ACE, prevent angiotensin I from converting into angiotensin II. Angiotensin II works as a potent vasoconstrictor. Its inhibition results in the dilation of vessels and decreases aldosterone secretion.

It is necessary to understand the role of the RAAS hormonal system in depth to appreciate the therapeutic effects of ACE inhibitors and understand why this is a target for hypertensive therapy. Initially, afferent arteriole juxtaglomerular

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cells synthesize prorenin, which is actively cleaved to renin. Angiotensinogen produced from the liver is then cleaved by renin to form angiotensin I. ACE converts the angiotensin I molecule into angiotensin II. Angiotensin II is a molecule with significant actions on many systems. First, angiotensin II causes vasoconstriction, which ultimately increases systemic blood pressure. Angiotensin II stimulates the adrenal cortex to produce aldosterone and the pituitary to produce antidiuretic hormone. Aldosterone causes sodium reabsorption and, in turn, water reabsorption through internal mineralocorticoid receptor activity.

Antidiuretic hormone increases the synthesis of aquaporin-2 channels in the collecting duct, which causes selective reabsorption of water. Actions of angiotensin-II and aldosterone lead to adverse cardiac remodeling. ACE inhibitors prevent adverse cardiac remodeling by reducing the concentrations of angiotensin-II and aldosterone.

**1)** Reducing level of Angiotensin-2 (through inhibition of ACE)

↓

ACE inhibitiors can dilate blood vessels (Primarily Arterioles and to lesser extent the veins)

↓

Reduce blood volume (through effects on the kidney)

↓

Prevent or reverse Angiotensin 2- mediated pathologic changes in the Heart and blood vessels .

**2)** Increasing levels of Bradykinin (through inhibition of kinase 2)

↓

Elevation of Bradykinin levels promotes vasodilation.

↓

Bradykinin promotes vasodilation by stimulating production of prostaglandin and nitric oxide.

**Administration :**

ACE inhibitors are administered most often orally, but they are available intravenously. Drugs most commonly end in the suffix '-pril.' Examples of these include lisinopril, ramipril, and captopril.

All ACE inhibitors are administered orally, except Enalaprilat which is given IV. Except Captopril and Moexipril, all ACE inhibitors can be administered woth food. Except Captopril, all ACE inhibitors have prolonged half-life and can be administered just once or twice a day. Captopeil is administered 2 or 3 times a day. All ACE inhibitors are excreted by kidney. As a result, nearly all can accumulate to dangerous levels in patients with kidney disease, and hence dosage must be reduced in these patients.

| Generic Name | Trade name | Indications | Starting dose | Maintenance dose |
|---|---|---|---|---|
| BENAZEPRIL | Lotensin | Hypertension | 10mg once/day | 20-40mg/day |
| CAPTOPRIL | Capoten | Hypertension<br>Heart failure<br>Diabetic Nephropathy | 25mg bid or tid<br>2.5mg tid<br>25mg tid | 25-50mg bid, tid<br>50-100mg tid<br>25mg tid |
| ENALAPRIL | Vasotec | Hypertension<br>Heart failure<br>Asymptomatic | 5mg once/day<br>2.5mg bid<br>2.5mg bid | 10-40mg/day<br>10-20mg bid<br>10mg bid |
| FOSINOPRIL | Monopril | Hypertension<br>Heart failure | 10mg once/day<br>10mg once/day | 20-40mg/day<br>20-40mg/day |
| ENALAPRILAT | Vasotec I.V | Hypertension | 1.25mg every six hours over a five-minute period | |

Table 3 : Pharmacokinetics of ACE inhibitor drugs

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**ACE Inhibitors are classified into Three Groups According to Chemical Structure**

Sulfhydryl-containing ACE inhibitor: Captopril – Hypertensive drug is 25 mg, which has to be given BID or TID with a maximum of 450 mg. Heart failure drug is 6.25 mg TID to a maximum of 450 mg.

Phosphorus-containing ACE inhibitor: Fosinopril – Dosage for hypertension treatment is 10 mg, and can be increased up to a maximum dose of 80 mg. It can be divided into two equal doses during the day to control blood pressure. Dosage for heart failure treatment is 5 to 10 mg daily up to a maximum dose of 40 mg.

Dicarboxylic-containing ACE inhibitors : Benzapril, Ramipril

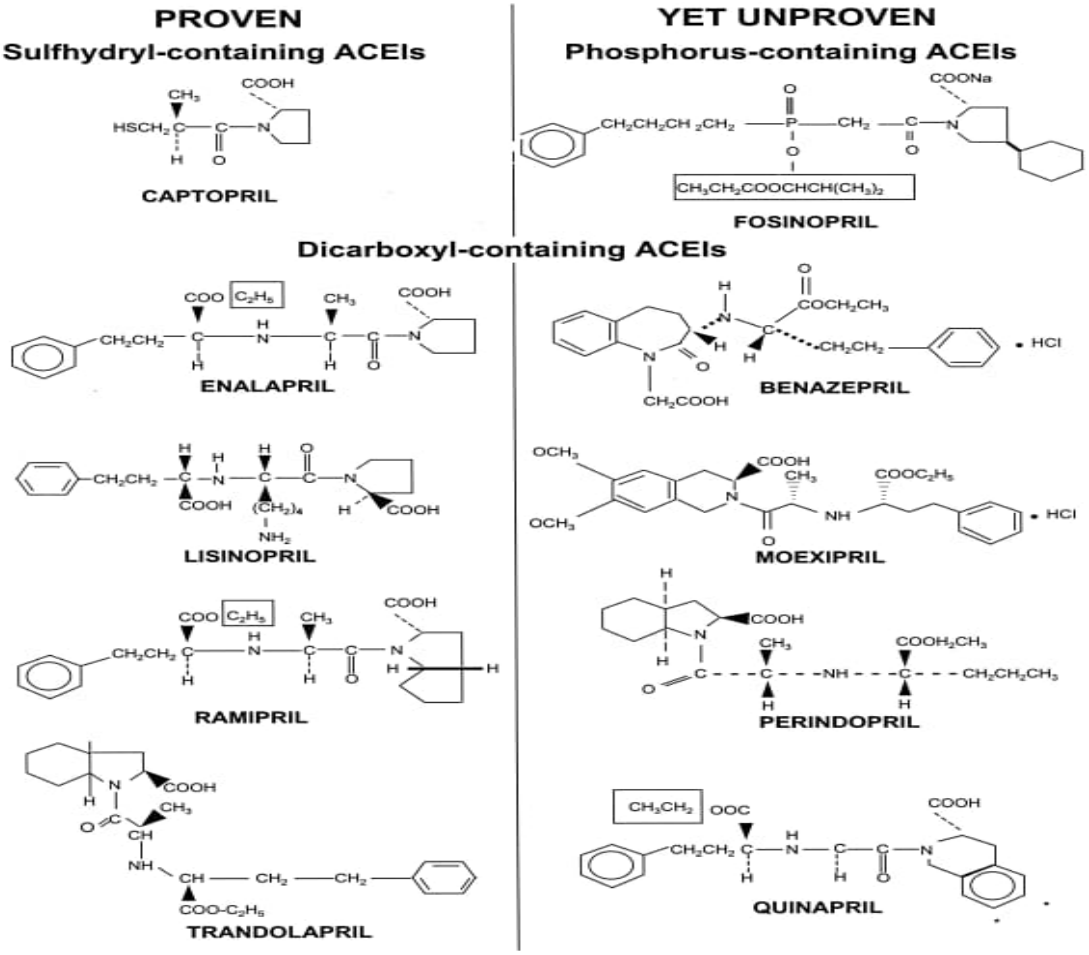


Fig : 1 Chemical structure of ACE inhibitor drugs

**Captopril :**

Captopril, a dipeptide analogue, is the first orally active ACE inhibitior. Introduced in 1977. It does not block AT I or AT II receptors. It is a potent and competitive ACE inhibitior, responsible for conversion of Angiotensin I, → Angiotensin II ( an agent which regulates blood pressure and is a key component of the RAAS ). It is absorbed rapidly from the gut, bioavalability 70%; food interferes absorption – hence should be given 1 hr before meals. It is largely excreted through the kidneys. Side effects → Hypotension, hyperkalemia, cough, urticaria, angioedema, dysgeusia, fetopathic, bowel upset, proteinuria.

**Enalapril :**

It is second drug of this class which is a prodrug, converted into enalaprilat (a tripeptide analogue). This converted form is nit effective orally due to poor absorption, thus is available as injectable preparation. Enalapril is a potent and

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competitive ACE blocker, which is responsible for the conversion of angiotensin I and angiotensin II. Largly excreted via kidney and dose reduction required in renal failure.
Side effects → Unusual tiredness or weakness, chest pain, cough producing mucus diarrhoea, labored breathing, fainting.

**Lisinopril :** It is he lysine derivative of enalaprilat; does not required hydrolysis to become active ACE inhibitor. Its oral absorption is slow and incomplete, but unaffected by food. The duration of action is considerably longer, permitting single daily dose and ensuring uniform hypotensive action round the clock.

**Fosinopril :** This ACE inhibitor is unique in being a phosphinate compound that is glucuronide conjugated and eliminated both by liver and kidney. It is a prodrug suitable for once daily administration. First dose hypotension is more likely.
**Ramipril :** The distinctive feature of this long acting ACE inhibitor is its extensive tissue distribution.
**Benazepril :** Another nonsulfhydryl prodrug ACE inhibitor; has a bioavailability of 37% and is excreted by kidney.

## II. METHODS

**Study design** :
A prospective cross sectional observational study was conducted in the outpatient of department of general medicine of primary care hospital in Chhatrapati SambhajiNagar. The study was initiated after approval from the institutional ethics committee and the hospital authorities.

**Selection criteria :**
The study population consisted of all diagnosed hypertensive patients according to JNC 8 and aged >18 years of either sex. Follow up of at least 3 months was done. Patients who did not receive antihypertensive treatment and patients below 18 years of age were excluded. Patients were diagnosed hypertensive if they had at least 2 visits with diagnosis of hypertension or they had prescription of antihypertensive drug with one recording of elevated BP nor they had elevated BP on two visits. Elevated BP was defined as systolic BP (SBP) >140 mmHg and diastolic BP (DBP) >90 mmHg.
Questionnaire was asked to the patients about their particulars. Drugs received by the patient, dose and duration of treatment, any suspected ADR, onset and duration of ADR, systems involved and any treatment received. The information was also sought from the patient's records wherever necessary. Data of antihypertensive drugs was recorded .
The probability that the adverse event was related to drug therapy was classified as definite, probable, possible, or doubtful. A definite reaction was one that followed a reasonable temporal sequence after a drug or in which a toxic drug level had been established in body fluids or tissues; followed a recognized response to the suspected drug and was confirmed by improvement on withdrawing followed a reasonable temporal sequence after the drug, followed a known response to the suspected drug, was confirmed by withdrawal but not by exposure to the drug and could not be reasonably explained by the known characteristics of the patient's clinical state. A possible reaction followed a temporal sequence after the drug, possibly followed a known pattern to the suspected drug and could be explained by characteristics of the patient's disease. A reaction was defined as doubtful if it was likely related to factors other than a drug. The data obtained was entered in microsoft excel . The tables and figures were used to present the findings in the study patients.

**Monitoring:**
Typical parameters monitored would include renal function, like Blood Urea Nitrogen (BUN), serum creatinine, and electrolytes, such as potassium.
If a patient has collagen vascular disease and/or renal impairment, follow complete blood count with differential periodically to assess kidney erythropoietin production.

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In patients with hypotensive effects within 1 to 3 hours of initial dose or increased dosages or pre-existing hepatic impairment, baseline hepatic function tests are considered.

White and red blood cell counts must be done to assess for rare side effects of anemia, neutropenia, agranulocytosis, and thrombocytopenia.

## III. RESULT

In our study total 120 patients were included. Total number of ADR reported was 65. In this study out of 120 patients, 70 (58.33%) were male and 50 (41.66%) were female.

| Gender | Number of patients (%) |
|---|---|
| Male | 70 (58.33%) |
| Female | 50 (41.66%) |
| Total | 120 (100%) |

Table 4 : Gender wise distribution of study population.

| Total number of patients | Development of No. of ADR's | Percentage (%) |
|---|---|---|
| 120 | 65 | 54.16% |

Table 5: Number of adverse drug reaction recorded

**Adverse Effects :**

- Most Common
- Dry cough ( 10% to 20%)
- Dizziness ( 12% to 19%)
- Hypotension ( 7% to 11%)
- Increased BUN and creatinine ( 2% to 11%)
- Syncope ( 5% to 7%)
- Hyperkalemia ( 2% to 6%)

**Dry Cough:**

Patients on ACE inhibitors have often reported a dry cough between one week after initiation and up to six months. Some say up to one year after initiation. Therapy withdrawal typically resolves the cough within 1 to 4 days after, but it may persist for up to a month. The concern for dry cough when therapy is initiated is that the patient's adherence to medication is decreased. These patients also have a propensity to develop bronchospasm. ACE metabolizes bradykinin and other local molecules. Inhibition of ACE in the lung enhances kinin concentration, that produces bronchial irritation. After stopping ACE inhibitor, an angiotensin receptor blocker (ARB) may be started as alternate treatment. ARB's carry less risk of cough to return than to restart with the ACE inhibitor. However, if cough recurs in patient on ARB treatment then switch to a whole other class of drugs.

**Angioedema**

Angioedema is a rare but potentially life-threatening side effect of ACE inhibitor use. Angioedema is an adverse drug reaction characterized by swelling of the face, lips, and upper airway in an episodic nature. The inflammation creates difficulty in the patient's ability to maintain an airway; therefore, endotracheal intubation is necessary to secure the airway. The mechanism of angioedema is believed to occur through an extensive accumulation of bradykinins in select individuals. Bradykinin causes marked vasodilation and plasma extravasation into the local tissue. Thus, the primary treatment of ACE inhibitor-induced angioedema is the discontinuation of ACE inhibitor therapy. It is also recommended to avoid ACE inhibitor therapy in patients with hereditary angioedema or a history of angioedema episodes. Ghouse J. et al. conducted a genome-wide association study of patients who developed ACE inhibitor-related angioedema. The investigators found variants located near the bradykinin receptor B2 gene.

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**Hyperkalemia:**

Hyperkalemia directly results from the mechanism of action of ACE inhibitors. The blockade of angiotensin II prevents the downstream secretion of aldosterone. Aldosterone causes reabsorption of sodium and subsequently water. Consequently, protons and potassium get secreted into the urine. Without potassium secretion through aldosterone, potassium can easily increase in patients on ACE inhibitor. Co-morbidities that decrease kidney function or medications that cause potassium retention can increase the risk of hyperkalemia.

**Increased BUN and creatinine:**

A mild decrease in GFR is usual at the start of treatment. Patients with heart failure, chronic kidney disease, and bilateral renal artery stenosis with poor renal perfusion may further decrease GFR, necessitating discontinuation of ACE-Inhibitor therapy.

**Hypotension:**

Hypotension may lead to intolerance of therapy and discontinuation in a small population of patients; however, it is more common in the increased baseline renin patients. The repletion of fluids before therapy and discontinuation of diuretic medication will help minimize hypotensive episodes.

**Dizziness:**

Dizziness is one of the most common adverse drug reactions of ACE inhibitor therapy, which can be mitigated by adequate volume status and avoiding concomitant diuretic therapy.

**ADRs WHO causality assessment :**

In the present study, causality assessment between the drug and suspected reaction was determined by using WHO-UMC scale and Naranjo scale .Casuality assessement of ADRs as certain, probable, possible, and unlikely. Table 3 shows that type of reactions and their percentage are as certain (9.23%), probable/likely (69.23%), possible (15.38%) and unlikely(6.15%). According to Naranjo criteria, the ADRs are analyzed on the basis of questionnaire comprising 10 questions in which each question is given a score of +2.+1,0 or -1 dependimg on the analysis. When totaled if the score is >9: labellled as definite ADR,if 5-8: probable ADR, if 1-4: possible ADR, if 0: doubtful ADR. According to Naranjo scale, type of reactions and their percentage are as definite (9.23%), possible (15.38%), probable ( 69.23%) and doubtful (6.15%). Severity assessement is done by Hartwig and Siegel scale. Reactions can be lethal, severe, moderate, and mild. In our study no lethal ADR were reported. 6.15% reactions were severe, 24.61% were moderate category and 64 % were mild reaction.

| Type of Reaction | Number of patients reported ADR (n=65) | Percent |
|---|---|---|
| **WHO causality assessment** | | |
| Certain | 6 | 9.23% |
| Probable/ likely | 45 | 69.23% |
| Possible | 10 | 15.38% |
| Unlikely | 4 | 6.15% |
| Conditional/unclassified | - | - |
| Unassesable?Unclasifiable | - | - |
| **Causality assessment of ADRs by using Naranjo scale** | | |
| Definite | 6 | 9.23% |
| Possible | 10 | 15.38% |
| Probable | 45 | 69.23% |
| Doubtful | 4 | 6.15% |
| **Severity of reported ADRs by modified Hartwig and Sieget scale** | | |
| Lethal | - | - |

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| | | |
|---|---|---|
| Severe | 4 | 6.15% |
| Moderte | 16 | 24.61% |
| Mild | 45 | 69.23% |

Table 6 : WHO causality assessement of ADRs

## IV. DISCUSSION

As per study criteria total 120 cases of hypertensive patients (both sex) male, female were collected. Out of 120 patients, 70 (58.33%) were male and 50 (41.66%) were female. (Table 4).

Total number of ADR reported was 65 (54.16%) (Table 5). Most common ADRs Dry cough (10% to 20%), Dizziness (12% to 19%), Hypotension (7% to 11%) Increased BUN and creatinine (2% to 11%), Syncope (5% to 7%) and Hyperkalemia (2% to 6%) were reported.

As per WHO-UMC scale, type of reactions and their percentage are as certain (9.23%), probable/likely (69.23%), possible (15.38%) and unlikely(6.15%). According to Naranjo scale, type of reactions and their percentage are as definite (9.23%), possible (15.38%), probable (69.23%) and doubtful (6.15%)(Table 6).

Severity assessement is done by Hartwig and Siegel scale. No lethal ADR were reported. 6.15% reactions were severe, 24.61% were moderate category and 64 % were mild reaction(table 6).

## V. CONCLUSION

This prospective observational study was conducted at General Medicine of Primary Care Hospital, Chhatrapati Sambhajinagar, during the period from August 2024 to November 2024 to find out and report of ADR's related to Angiotensin Converting Enzyme class of antihypertensive drugs.

In this study total 120 patients were included and total 65 ADR's were reported. This study found that ACE inhibitors was responsible for most of the ADR's associated with hypertension. Most commom ADR's are dry cough, dizziness, hypotension, syncope, hyperkalemia , angioedema. The results of this study would be useful for the physicians in rational selection of drug therapy for treatment of hypertensive patients. This present data suggest that the ADR monitoring needs to be done in hospital settings continuously so that unexpected effect caused by different medicines can be identified and documented.

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