



DRUG ALERT

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ANGIOTENSIN CONVERTING ENZYME INHIBITORS

Introduction

Angiotensin converting enzyme inhibitors (ACEI) were introduced initially as antihypertensive drugs but now it has become the drug of choice for the treatment of cardiac failure ("ACEI should be used at all costs in CCF"). It has superceded digoxin, beta-blockers and diuretics in the treatment of cardiac failure. When ACEIs are used flipantly, some life threatening adverse effects like precipitation of renal failure and angioedema can occur. This article is to alert the medical practitioners regarding the beneficial effects and adverse effects of ACEI so that a judicious prescription is made.

Mechanism of action:

ACEIs block the conversion of angiotensin I to angiotensin II (AT₂), reduce secretion of aldosterone and vasopressin, decrease sympathetic activity as well as the trophic effects of AT₂. They inhibit kininase II enzyme thereby increasing bradykinin level which in turn stimulates beta 2 receptors leading to the release of nitric oxide and vasoactive prostaglandins and hence vasodilation. Despite marked vasodilatation, there is no reflex tachycardia because of resetting of baroreceptors.

Clinical Pharmacology:

ACEIs are divided into 3 groups based on their chemical structure (Table 1). Class I drugs (having -SH group ligand) are more prone to cause adverse effects like rashes and agranulocytosis. Absorption of ACEIs are variable (25-75%). Presence of food has

either no effect or reduces the rate of absorption but the extent of bioavailability is not changed. They are excreted mainly through kidneys (60-95%) except trandolapril, fosinopril, spirapril and zofenopril which are eliminated by hepatic and renal routes. Some ACEIs are prodrugs and converted into their active form either by hydrolysis in the liver or intestine. Most prodrugs are lipophytic, they have more access to target tissues. Benazepril, captopril, enalapril, enalaprilat, and fosinopril pass into breast milk. In our country, more commonly prescribed ACEIs are enalapril, ramipril, perindopril, lisinopril and captopril

ACEI decrease hypercholesterolemia, hyperuricemia and hyperglycemia. They attenuate hyponatremia and hypokalemia. They have an excellent metabolic profile even when used for long term treatment which is of benefit to cardiac patients.

The most important advantage of ACEI is that they can safely be combined with angiotensin receptor blockers (ARB), beta blockers, calcium channel blockers and diuretics.

Ethnic variability was reported in the response to ACEIs. Blacks show poor response to ACEI monotherapy but when combined with diuretics the effect was commendable in the treatment of systemic hypertension. Genetic polymorphism in the ACE gene was reported. Individuals with DD genotypes tend to respond better with ACEIs.

ACEIs are used in the treatment of congestive heart failure, systemic hypertension, post infarction state, left

Table 1. Classification of ACEIs.

Class 1 (with sulfhydryl group)	Class 2 (with dicarboxyl groups)	Class 3 (with phosphorous groups)
Captopril, alacepril, zofenopril*	Benazepril*, enalapril*, enalaprilat, lisinopril*, perindopril*, quinapril*, ramipril*, spirapril, trandolapril, cilazapril, delapril	Fosinopril*

* prodrug

ventricular dysfunction without overt cardiac failure, nephrotic syndrome, scleroderma renal crisis, diabetic nephropathy, primary pulmonary hypertension and microalbuminuria. The Heart Outcomes Prevention Evaluation (HOPE) trial demonstrated that ramipril, an ACEI, considerably reduced the mortality among myocardial infarction patients. It reduced the number of non fatal strokes, new onset of cardiac failure and diabetes mellitus. Since it improves insulin resistance and prevent microalbuminuria, they are considered as the treatment of choice for diabetic patients with hypertension.

Heart failure and ACEI

In cardiac failure the compensatory events produced by the Renin Angiotensin Aldosterone System (RAAS) form a vicious cycle which compromise cardiac function. There is an increase in afterload, preload, wall stress and remodeling and alteration of the geometry of heart. This vicious cycle is cut-off by ACEI. They improve cardiac output and prevent remodeling and hence they become the mainstay in the treatment of cardiac failure. The mortality is improved in almost all patients with post-infarction left ventricular dysfunction. Various studies (CONSENSUS, SOLVD, AIRE, V-HeFT ii) have proved the protective role of ACEI in heart failure. ACEIs should be given to all patients with cardiac failure due to left ventricular dysfunction unless there is a contraindication.

Hypertension and ACEI

ACEI monotherapy is effective in about 50% of patients with mild to moderate hypertension. Its effectiveness increases to 90% when it is combined with calcium channel blockers or beta blockers or a diuretic. ACEIs are superior to other drugs in the treatment of hypertensive patients with diabetes and in reducing hypertension associated with risks of cardiovascular mortality. They offer advantages over other antihypertensive drugs in that they do not affect cardiovascular reflexes and exercise capacity of the patients. Their heart rate and catecholamine levels were not raised. They do not cause lethargy, weakness, sexual dysfunction but they improve insulin sensitivity and decrease cholesterol levels. Although all ACEIs may be used, captopril is preferred since it has a more favorable effect on quality of life when compared to enalapril.

Adverse effects:

In general, ACEI are well tolerated and the side effects are less common.

Hypotension:

A steep fall in BP can occur following the first dose especially in patients with high plasma renin activity

(e.g., patients with heart failure or salt depletion following high dose of diuretics). It is advisable to start with a low dose of ACEI or withdraw diuretics before initiating ACEI therapy

Dry Cough:

Bradykinin accumulation causes dry cough (5.5% HOPE study). It may disturb the patient and can confuse the treating physician. The dry cough is not dose related, develop between 1 week and 6 months of initiation of therapy, more in females and may require change over or may subside on it's own after 4 months of use. Aspirin and iron supplementation may reduce cough induced by ACEI. Angiotensin receptor blockers (ARB) are a better substitute.

Hyperkalemia:

Aldosterone production is increased which will enhance the retention of potassium. It is more common in congestive cardiac failure, elderly, diabetes mellitus, patients receiving potassium supplements, potassium sparing diuretics, heparin or NSAIDs.

Acute renal failure:

Normally, adequate glomerular filtration is maintained by efferent arteriolar constriction produced by AT2. Administration of ACEI causes efferent arteriolar dilatation in glomeruli, due to prostaglandins production by ACEI, leading to renal failure, especially in patients with low serum sodium (<130meq/l), high serum creatinine, low systolic B.P (<90mm Hg) and in patients above 70yrs. Renal failure also occurs with bilateral renal artery stenosis or renal artery stenosis in solitary kidney. First dose hypotension also may contribute for renal failure.

Pregnancy:

ACEIs are contraindicated in pregnancy. They cause severe teratogenic effects and foetal loss.

Angioedema:

Although this is rare (0.2% in HOPE Study), it can be fatal. It is due to bradykinin accumulation and it occurs more often within first week of therapy or as late as 1 year. Prompt subcutaneous injection of adrenaline helps these patients and some time intubation may be required to save the life. If angioedema occurs the entire group should be withdrawn.

Agranulocytosis:

It is seen with high dose of captopril and those with renal failure and collagen vascular disease like SLE.

Others:

Skin rashes are common with captopril and also in those with underlying collagen vascular disease. ACEI can cause proteinuria and paradoxically they are effective in microalbuminuria of diabetes mellitus.

Table 2: Drug interactions

Drug	Effect
Antacide	Reduce bio-availability
NSAIDs	Reduce the vasodilatory action
Diuretics	Increase the action
Salicylate	Reduce the action?
K+ sparing diuretics or K+ supplements	Exacerbate ACEI induced hyperkalemia

Contra indications:

Bilateral renal artery stenosis, renal artery stenosis in a solitary kidney, serum creatinine > 3mg/dl, history of angioneurotic oedema, pregnancy, aortic stenosis, mitral stenosis, obstructive cardiomyopathy, hypotension.

JIPMER experience:

At our hospital it is a routine practice to prescribe either captopril 6.25 mg or enalapril 2.5 mg in all patients with acute myocardial infarction provided the systolic B.P. is >100mm Hg on day 1 itself. All patients with dilated cardiomyopathy receive either enalapril 2.5 mg or ramipril 2.5 mg daily to start with and the dose is increased to the maximum of 15 mg/day. More over if the echo-cardiography reveals LV dysfunction and the patients do not have overt heart failure, they are put on captopril or enalapril or ramipril. For systemic hypertension they are used along with amlodipine. Many patients with diabetes mellitus and hypertension are started on ACEI. We had come across 2 patients who developed an increase in serum creatinine while using enalapril and the drug was stopped immediately and the creatinine level came down to normal. None of them required dialysis. Many patients (12 hypertensives in the OPD practice) had dry cough after 1 week of therapy with enalapril and they were changed over to ARB. One patient had angioedema and was treated with adrenaline.

Conclusion

ACE inhibitors are a class of drugs which benefit

many cardiac patients and should be prescribed judiciously, keeping in mind its dreaded adverse effects.

Historical perspectives

- 1898 -- Tigerstedt and Bergmann - RENIN
- 1940 -- Braun Menendez - ANGIOTENSIN
- 1950 -- Skeggs and Peart - amino acid sequence of ANGIOTENSIN
- 1957 -- Schwyzer and Bumper - synthesised ANGIOTENSIN
- 1958 -- Gross - effect of RAS on ALDOSTERONE
- 1970 -- ACE inhibitors discovered
- 1990's -- Angiotensin receptor blockers ANGIOTENSIN 3 receptor
- 1990 -- ACE gene identified
- 2001 -- Crackower - identified ACE2

Key points

- ❖ Start low dose, anticipate first dose hypotension & step up every 48 hrs
- ❖ Monitor renal parameters(BUN, serum creatinine) every week
- ❖ Stop therapy if serum creatinine raises more than 3mg/dl
- ❖ Avoid concomitant use of K+ or potassium sparing diuretics
- ❖ Avoid in pregnancy at any cost.
- ❖ Watch for angioedema which may appear late in therapy
- ❖ Remember agranulocytosis though rare may be life threatening
- ❖ Dry haggng cough due to ACEI often mistaken for cardiac failure

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DOES ETHNICITY MAKE PEOPLE SUSCEPTIBLE TO ADRS?

This question is answered to an extent by the article “*Systematic review and meta-analysis of ethnic differences in risks of adverse reactions to drugs used in cardiovascular medicine*” published in BMJ May 2006; 332:1177-1181.

The authors of this study have tried to look for evidence of ethnic differences in susceptibility to adverse drug reactions (ADRs) to cardiovascular drugs. To achieve this they have searched Medline and Embase databases along with hand search for

necessary articles. For including a study into this meta analysis, it should have reported at least two ethnic groups and one or more ADRs. From the initial 3602 studies retrieved, a final figure of 24 studies was chosen for analysis after they fulfilled the inclusion and exclusion criteria.

The drug wise analysis showed that **ACE inhibitors** are more likely to produce angio-oedema in black patients than non-blacks with a relative risk of 3.0 (95% CI 2.5 to 3.7). The other interesting finding of ACE inhibitors was the high incidence of cough in East Asians (Chinese, Korean or Japanese) than in whites with a relative risk of 2.7 (95% CI 1.6 to 4.5). The incidence of intracranial hemorrhage with **thrombolytic therapy** was higher in blacks compared to non-black patients, relative risk 1.5 (95% CI 1.2 to 1.9). East Asian patients reported more ADRs (26%) to **antihypertensive** drugs than the white patients (13%). Blacks were found to have increased risk to **digitalis** associated ADR requiring hospital admission than white patients.

Many factors influence the susceptibility to ADRs

like age, sex, disease state etc. and one such factor is genetic. The authors further state that genetic basis of this ethnic difference in ADRs could be due to inter ethnic differences in the frequencies of polymorphisms in drug metabolizing enzyme cytochrome P450.

The authors themselves point out that interpretation of the results of the present analysis should be done cautiously as there is a possibility of publication bias, lack of data on confounding factors in some studies.

Efficacy as well as toxicity of a drug is influenced by many factors including genetic and environmental. These factors vary from one geographic region to another and even among different ethnic groups with in a particular geographic region. This article has brought out the importance of ethnic differences in susceptibility to ADR and also the significance of compiling data on ADR in each population.

For an effective and safe drug treatment (rational drug treatment), it is necessary to have data on ADR in our population as ethnicity does matter in determining patients' susceptibility to harmful effects of drugs.

GUIDELINES FOR REPORTING ADVERSE DRUG REACTIONS

Regional Pharmacovigilance Centre, JIPMER, Pondicherry invites reports of all suspected adverse reactions to drugs and other medicinal substances, including herbals, traditional and complementary medicines, blood products, medical devices and vaccines.

REPORT EVEN IF:

- The drug is an established one and the adverse drug reaction is well known
- You are not certain the product caused adverse event
- You don't have all the details

WHO CAN REPORT:

Any health care professional (doctors including interns, residents, dentists, nurses and pharmacists)

WHERE TO REPORT: You can report online at www.jipmer.edu or send your reports to:

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Note: *If you are at JIPMER you can also use the yellow forms provided in wards.*