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Original Articles

Study of the Efficacy of Enalapril in the Treatment of Pakistani Patients with Heart Failure

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SUMMARY

A randomized, prospective, open-ended study of 20 Pakistani patients with moderate-to-severe heart failure (NYHA class II and III) was carried out. Patients had to have global left ventricular (LV) dysfunction with ejection fraction (LVEF) < 35%.

The patients were randomized into two groups, C and E. Group C patients (N=9) were optimized on conventional therapy i.e. diuretics, digoxin and nitrates whereas group E patients (N=11) had enalapril added to this therapy & increased gradually. The subjects were followed for a period of 12 to 120 weeks with a mean of 58 weeks. Serial tests were done at 12 weekly intervals. These included echocardiography, exercise stress test, urea, creatinine, sodium & potassium.

Results showed a significant improvement in NYHA class in group E. 10 of the 11 patients in this group improved by one class while only 1 out of 9 patients improved by one class in group C. There was a highly significant ($p < 0.001$) increase in exercise time in group E from 417 secs to 730 secs while there was an insignificant increase in group C. Hemodynamic measurements showed a significant fall in heart rate in group E from 90 bpm to 83 bpm ($p=0.01$) but an insignificant fall in group C from 94 bpm to 86 bpm. Systolic and diastolic blood pressure (BP) fell in both groups (121/81 vs 108/74 in group C and 117/77 vs 110/72 in group E) but only the fall in systolic BP in group E was significant ($p=0.05$). Echocardiography showed significant improvement in left ventricular systolic ($p=0.001$) and diastolic ($p<0.05$) dimensions & LVEF ($p<0.001$) in group E while there was no significant change in group C. In addition, digoxin usage fell significantly in group C.

Although cough was more prevalent in group E, this did not reach significance levels. Other side effects were not significantly different between the two groups and serial blood tests also did not show any significant difference.

In conclusion, the addition of enalapril to conventional therapy in Pakistani patients of moderate-to-severe heart failure significantly improved NYHA class, exercise capacity, LV dimensions & LVEF. In addition, it also reduced the need for other anti-heart failure medications and was generally well tolerated.

INTRODUCTION

The renin-angiotensin system (RAS) is intimately involved in the control of blood pressure and electrolyte homeostatis[1]. Angiotensin II contributes to congestive heart failure by directly stimulating the adrenals to release aldosterone thereby exacerbating sodium and water retention[1]. Consequently, pulmonary and systemic venous congestion develop, contributing to increased vascular stiffness[1]. Angiotensin converting enzyme (ACE) inhibitors, in addition to their blood pressure-lowering effects, have been shown to reduce vascular hypertrophy, attenuate atherosclerosis and influence coronary ischemia & reperfusion injury[2]. In patients with moderate-to-

severe heart failure, ACE inhibitors combined with diuretics and/or digoxin have been shown to improve clinical signs and symptoms,exercise tolerance and New York Heart Association (NYHA) functional class[2,3].

Heart failure is a progressive and debilitating condition affecting approximately 4 million patients in the United States annually[4]. ACE inhibitors have significantly reduced mortality & morbidity in patients with left ventricular dysfunction in several clinical trials worldwide[5-13]. However, no long term clinical trials have been published in Pakistan on ACE inhibitors.

This study was designed to assess the efficacy of enalapril in the treatment of Pakistani patients with heart failure with particular emphasis on affect on NYHA class, echocardiographic parameters and exercise time. Also, tolerability as regards dosage and side effects was to be assessed.

PATIENTS AND METHODS

This was a randomized, prospective, open-ended study of patients of moderate-to-severe heart failure in which a group of patients on conventional treatment i.e. diuretics, digitalis & nitrates, was compared with another group of similar patients in whom enalapril was added to the conventional treatment regimen. The former was labelled as group C while the latter was called group E.

The patients were recruited from the cardiology department of Shaikh Zayed Hospital, Lahore, if they fulfilled the following inclusion criteria:

1. Patients with moderate-to-severe heart failure, NYHA class II & III.
2. Patients with ejection fraction 35% or less and global dysfunction.
3. Patients with age 18 years or above.
4. Ambulatory patients.
5. Patients who had not used any angiotensin converting enzyme (ACE) inhibitors or vasodilators during the last 6 weeks.
6. Patients with heart failure maintained only on diuretics and/or digitalis and/or nitrates.

The patients were excluded if they had any of the following:

1. Patients less than 18 years of age.
2. Pregnant women and lactating mothers.
3. Hospitalized patients.
4. Patients with a concomitant heart problem which required additional cardiovascular drugs.
5. Patients with serum creatinine level more than 3 mg/dl.
6. Patients hypersensitive to enalapril.

There was a washout period of 2 weeks, in which baseline tests were also done, before randomization. The target was to recruit 20 patients & follow them for 36 weeks or longer but to include all those who completed a minimum of 12 weeks in the study. Evaluation visits were scheduled at weeks 0,2,4,8 and then every 4 weeks till the end of the trial. At each visit, the patient underwent a full physical examination and was questioned about symptoms and side effects.

Baseline tests were performed at week 0. These included a complete blood count, urea, creatinine, sodium, potassium, random blood sugar, total cholesterol, liver function tests and routine urine examination. These were repeated every 12 weeks.

A standard 12 lead electrocardiogram was done at baseline and at the end of the study.

A chest X-ray was done at baseline and repeated only if indicated.

An echocardiogram was performed at baseline using a Toshiba Sonolayer SSH-40 A machine. Left ventricular measurements were taken in the left lateral position in the parasternal long axis view. These included left ventricular internal dimension in diastole (LVIDd) and left ventricular internal dimension in systole (LVIDs). Left ventricular ejection fraction (LVEF) was then calculated by the POMBO method. The echocardiogram was repeated every 12 weeks.

A symptom-limited exercise tolerance test was done on a treadmill. The protocol used was Naughton's (Table 1). This was repeated at 12 weekly intervals.

On randomization, enalapril was begun in group E in an initial dose of 2.5mg/day in addition to the conventional treatment. It was increased gradually in subsequent visits as per requirement & toleration of the patient. The maximum upper limit was 40mg/day. In addition, diuretics and digitalis were gradually tapered off in group E, if possible.

Table 1: Naughton's treadmill protocol used in the study

Study	*Speed*	*Grade*	*Duration*	*Mets*
I	2.0 (MPH)	00	3 MIN	2
II	2.0	3.5	3 MIN	3
III	2.0	7.0	3 MIN	4
IV	2.0	10.5	3 MIN	5
V	2.0	14.0	3 MIN.	6
VI	2.0	17.5	3 MIN	7
VII	2.0	21.0	3 MIN	8
VIII	2.0	24.5	3 MIN	9

In group C, the dosage of diuretics and digitalis was adjusted according to the patient's requirements. If any patient in this group deteriorated, crossover was permitted to the enalapril group.

Statistics

Standard statistical methods were applied & p values calculated. P value of less than 0.05 was taken as significant. The statistics were carried out on the two groups on an intention-to-treat basis and crossovers were regarded to be in the group in which they started.

RESULTS

A total of 26 patients were randomized, 13 in each group (Table 2). However, four patients died before 12 weeks. These included two in each group (details are given later). One patient in group C was lost to follow up before 12 weeks while another patient in the same group had an amputation of the leg and thus had to be excluded from the trial. Therefore, 9 patients were left in group C and 11 in group E making a total of 20 patients.

Table 2: Results

Patients randomized	26
Lost to follow up before 12 weeks	01
Died before 12 weeks	04
Excluded (amputation at week 6)	01
Total patients in trial	20

These twenty patients were followed for a minimum of 12 weeks with a mean of 58 weeks (Table 3). Results were calculated for the first 60 weeks only as after that, only one patient was left in the conventional group (Table 3).

Table 3: Follow up period

	Conventional (n=9)	*Enalapril (n=11)*
12 weeks	2	1
36 weeks	-	1
40 weeks	1	1
48 weeks	3	1
60 weeks	1	-
68 weeks	-	1
72 weeks	1	4
90 weeks	1	-
108 weeks	-	1
120 weeks	-	1

Mean follow up = 58 weeks

Table 4 gives the baseline characteristics of the two groups. The conventional group was somewhat older (55 yrs vs 45 yrs) but not significantly and had less females (45% vs 73%) and more males (55% vs 27%) but again this was not statistically significant. However, the two groups were very similar regarding heart rate, systolic and diastolic blood pressure, serum sodium, potassium and creatinine. There were more conduction defects in group C (66% vs 27%, statistically not significant) but exercise duration and ejection fraction were similar in the two groups (440 secs vs 417 secs and 29.3% vs 29.8%) respectively.

During the trial period, heart rate (HR) in group C reduced gradually from a mean of 94.4 to a mean of 86.0 at 60 weeks. This was not significant. A decline in HR was also seen in group E from 90.3 to 83.2, but this was statistically significant. The HR values between the two groups were not statistically different at any stage.

The systolic blood pressure (SBP) fell initially in the enalapril group and was lower than in group C from 12 to 36 weeks but was then similar in both

groups (Table 5). The change in SBP between the two groups was not significant while the fall in SBP in group E from baseline (117.3mm) to week 60 (110mm) was significant ($p=0.05$).

Table 4: Baseline demographic and clinical characteristics of patients in the two treatment groups

	Conventional (n=9)	*Enalapril (n=11)*	*p value*
Age (Years)	55 (28-70)	45 (18-58)	ns
Weight (Kg)	54	60	ns
Height (cm)	158	155	ns
BSA (M2)	1.56	1.59	ns
Blood Pressure Sitting (mmHg)			
Systolic	118	117	ns
Diastolic	80	75	ns
Heart rate (bpm)	95	90	ns
Serum sodium (mmol/L)	138	141	ns
Serum potassium (mmol/L)	4.1	4.1	ns
Serum creatinine (mg%)	1.1	1.2	ns
Blood urea (mg%)	43	31	ns
Sex			
Male	55% (5)	27% (3)	ns
Female	45% (4)	73% (8)	ns
E.C.G.			
Sinus rhythm	89% (8)	100% (11)	ns
Atrial fibrillation	11% (1)	-	ns
Conduction defects	66% (6)	27% (3)	ns
Exercise duration	440 secs	417 secs	ns
Ejection fraction	29.3%	29.8%	ns
Etiologic Factors			
Coronary artery disease	33% (3)	54% (6)	ns
Cardiomyopathy (Idiopathic)	55% (5)	45% (5)	ns
Hypertension	33% (3)	36% (4)	ns
Diabetes mellitus	33% (3)	27% (3)	ns
Hypothyroidism	-	9% (1)	ns
Others	22% (2)	27% (3)	ns
Drug Therapy			
Digitalis	55% (5)	64% (7)	ns
Diuretics	100% (9)	91% (10)	ns
Nitrates	33% (3)	27% (3)	ns

Diastolic blood pressure (DBP) also showed a similar response as SBP but less marked (Table 5). In this case there was neither a significant difference between the groups nor within the group when baseline values were compared with the values at week 60.

The mean exercise time improved gradually in group E from 417 secs to 730 secs at 60 weeks (Table 6). This was highly significant ($p<0.001$). In contrast, it fell in group C from 440 secs at baseline to 319 secs at 12 weeks, improved to 425 secs at 36 weeks and was 407 secs at 48 weeks. At week 60, it increased to 563 secs, but did not achieve significance levels. There was no statistically significant difference between the two groups at any stage.

The echocardiographic measurements showed a mild decrease in LVIDd in group C from 65.7mm at baseline to 62.3mm at week 60 which was not significant (Table 7). This was paralleled in group E with a decline from 64.7mm at the start to 60.5mm at 60 weeks which was significant ($p<0.05$).

The LVIDs also decreased mildly in group C from 58.5mm at the start to 54.3mm at week 60 which was also not significant (Table 7). There was a more marked reduction in group E from 57.7mm to 50.0mm which was highly significant ($p=0.001$). However, there was no statistically significant difference between the two groups in terms of both LVIDd or LVIDs at any stage.

LVEF improved in group C from 29.3% at baseline to 34.3% at 60 weeks but this was not significant (Table 7). However, in group E, it increased from 29.8% at the start to 44.1% at 60 weeks which was highly significant ($p<0.001$). There was also a significant difference in LVEF between the two groups from week 36 onwards ($p=0.008$ at week 36, $p=0.05$ at week 48 & $p=0.01$ at week 60).

All the patients in group C were in NYHA class III at the start and only one patient improved to class II. In contrast, 10 out of the 11 patients in groups E improved by one class (Table 8). This improvement in NYHA class in the enalapril group was highly significant ($p<0.001$).

The mean daily dose of furosemide rose from 75mg to 90mg at week 12 in group C but ended at 73.3mg (Table 9). However, in group E it dropped steadily from 74mg at the start to 50mg at week 60. The changes in furosemide dosage, however, did not achieve significance levels either between the

Table 5: Haemodynamic measurements (mean)

	Baseline C=9 E=11	*12 Weeks* C=9 E=11	*24 Weeks* C=7 E=10	*36 Weeks* C=7 E=10	*48 Weeks* C=6 E=9	*60 Weeks* C=3 E=7	*p value (between weeks 0 and 60)*
HR (bpm)							
C	94.4	93.7	91.7	94.7	92.5	86.0	ns
E	90.3	88.6	86.2	88.4	87.0	83.2	0.01
p value (between C and E)	ns	ns	ns	ns	ns	ns	
SBP (mm)							
C	121.7	118.2	119.7	120.5	113.3	108.0	ns
E	117.3	104.5	111.0	111.6	114.4	110.0	0.005
p value (between C and E)	ns	ns	ns	ns	ns	ns	
DBP (mm)							
C	81.1	78.7	79.7	79.4	78.0	74.0	ns
E	77.2	71.6	73.6	72.8	74.2	72.0	ns
p value (between C and E)	ns	ns	ns	ns	ns	ns	

Table 6: Exercise tolerance: Naughton's protocol - Total time in seconds (mean)

	Baseline C=9 E=11	*12 Weeks* C=9 E=11	*24 Weeks* C=7 E=10	*36 Weeks* C=7 E=10	*48 Weeks* C=6 E=9	*60 Weeks* C=3 E=7	*p value (between weeks 0 and 60)*
C	440	319	388	435	407	563	ns
E	417	478	574	636	645	730	< 0.001
p value (between C and E)	ns	ns	ns	ns	ns		

groups or within each group. The mean weekly dose of digoxin remained at 1.5mg throughout the trial in group C but dropped in group E from 1.3mg initially to 0.6mg at 60 weeks (Table 9). This was highly significant ($p < 0.001$). The difference between the two groups in terms of the weekly digoxin dosage became significant ($p < 0.005$) at week 12 & then remained significant till week 60.

The mean daily enalapril dose was 6.4mg at week 12 in group E and increased gradually to 9.2mg at week 60 (Table 9). The mean daily dosage of isosorbide dinitrate was 37.5mg in group C at the start & 30mg at week 60 whereas in group E, it was 30mg initially & 40mg at 60 weeks. The changes were not significant either within the individual groups or between the two groups.

Table 10 shows the laboratory profile of the trial patients. The mean serum urea remained almost steady in group C (41.5mg at week 0 vs 39.3mg at week 60) but showed a mild rise in group E (32.8mg/dl initially vs 45.2mg/dl at 60 weeks). Similarly, mean serum creatinine values also remained constant in group C (1.0mg/dl at the start vs 0.9mg/dl at week 60) but increased mildly in group E (1.1mg/dl at week 0 vs 1.3mg/dl at week 60). Mean serum sodium levels remained almost constant in both groups (138.1mmol/L in group C & 141.2 in group E initially vs 142.0 in group C & 141.1 in group E at 60 weeks). However, the mean serum potassium levels fell slightly in group C from 4.0mmol/L to 3.8mmol/L but increased slightly in group E from 4.1mmol/L to 4.3mmol/L. None of

Table 7: Echocardiographic measurements

	Baseline C=9 E=11	*12 Weeks* C=9 E=11	*24 Weeks* C=7 E=10	*36 Weeks* C=7 E=10	*48 Weeks* C=6 E=9	*60 Weeks* C=3 E=7	*p value (between weeks 0 and 60)*
LVIDd (mm)							
C	65.7	65.1	64.4	62.5	62.8	62.3	ns
E	64.7	63.7	63.2	60.2	60.5	60.5	0.047
p value (between C and E)	ns	ns	ns	ns	ns	ns	
LVIDs (mm)							
C	58.5	57.0	56.0	53.8	53.6	54.3	ns
E	57.7	55.2	54.8	50.2	50.5	50.0	0.001
p value (between C and E)	ns	ns	ns	ns	ns	ns	
LVEF (%)							
C	29.3	32.8	34.1	35.8	37.6	34.3	ns
E	29.8	35.0	35.1	42.6	42.0	44.1	< 0.001
p value (between C and E)	ns	ns	ns	0.008	0.05	0.01	

the changes in the laboratory parameters was significant, neither when compared within the individual group from baseline to week 60 nor when a comparison was made between the two groups at the 12 weekly testing intervals.

Table 8: New York Heart Association Class

Class	*Conventional (n=9)*		*Enalapril (n=11)*	
	At start	*At end*	*At start*	*At end*
1.	-	-	-	9.1%
2.	-	11.1%	9.1%	81.8%
3.	100%	88.9%	90.9%	9.1%
4.	-	-	-	-

The improvement in NYHA class was highly significant ($p<0.001$)

The side effect profile was not significantly different between the two groups (Table 11). Hypotension was predictably encountered more often in group E (27.3% vs 11.1%) but this was not significant. Similarly, hyperkalemia was more common in group E (18.2% vs 0%) but this did not reach significance levels. As expected, cough was more common in group E (6 patients) than in group C (2 patients). However, it was mostly transient and only one patient in group E had persistent, dry cough. Even in this patient, enalapril was not stopped as the cough was not severe enough to be intolerable.

A total of 5 patients died while in the trial, 3 in group C and 2 in group E (Table 12). 4 of them died before completing 12 weeks & were thus not included in the analysis. One patient died during sleep around week 70. Of the patients who died before week 12, two had sudden death (one in each group). One patient in group C died around 11 weeks following a stroke and pulmonary oedema. Interestingly, one patient in group E died around week 9 due to a road traffic accident.

Three patients deteriorated clinically despite optimal conventional therapy in group C and had to be put on enalapril at weeks 12,12 and 16 (Table 12). However, for analysis purposes, they were regarded as being in the conventional therapy group

DISCUSSION

ACE inhibitors have been shown to be extremely valuable in the management of heart failure. These drugs relieve symptoms and improve exercise capacity & hemodynamic function while reducing hospitalization rates and mortality[7,14,15].

Table 9: Heart failure drug therapy (mean)

	Baseline C=9 E=11	*12 Weeks* C=9 E=11	*24 Weeks* C=7 E=10	*36 Weeks* C=7 E=10	*48 Weeks* C=6 E=9	*60 Weeks* C=3 E=7	*p value (between weeks 0 and 60)*
Furosemide (mg/day)							
C	75.0	90.0	85.7	82.8	80.0	73.3	ns
E	74.0	64.0	57.7	55.5	55.0	50.0	ns
p value (between C and E)	ns	ns	ns	ns	ns	ns	
Digitalis (mg/wk)							
C	1.5	1.5	1.5	1.5	1.5	1.5	ns
E	1.3	1.0	0.8	0.7	0.6	0.6	< 0.001
p value (between C and E)	ns	0.005	0.005	0.005	0.05	0.05	
Enalapril (mg/day)							
C	-	-	-	-	-	-	-
E	-	6.3	7.9	8.5	9.1	9.2	-
Isosorbide dinitrate (mg/day)							
C	37.5	52.5	30.0	30.0	30.0	30.0	ns
E	30.0	34.2	42.8	38.5	38.5	40.0	ns
p value (between C and E)	ns	ns	ns	ns	ns	ns	

Table 10: Laboratory profile of patients during treatment (mean)

	Baseline C=9 E=11	*12 Weeks* C=9 E=11	*24 Weeks* C=7 E=10	*36 Weeks* C=7 E=10	*48 Weeks* C=6 E=9	*60 Weeks* C=3 E=7	*p value (between weeks 0 and 60)*
Urea (mg/dl)							
C	41.5	35.1	38.4	40.1	41.6	39.3	ns
E	32.8	33.4	39.9	42.0	42.2	45.2	ns
p value (between C and E)	ns	ns	ns	ns	ns	ns	
Creatinine (mg/dl)							
C	1.0	1.0	1.0	1.0	1.0	0.9	ns
E	1.1	1.0	1.1	1.2	1.3	1.3	ns
p value (between C and E)	ns	ns	ns	ns	ns	ns	
Sodium (mmol/L)							
C	138.1	141.7	139.8	140.7	140.5	142.0	ns
E	141.2	141.0	141.1	141.0	140.7	141.1	ns
p value (between C and E)	ns	ns	ns	ns	ns	ns	
Potassium (mmol/L)							
C	4.0	4.2	4.0	4.0	3.8	3.8	ns
E	4.1	4.3	4.3	4.5	4.3	4.3	ns
p value (between C and E)	ns	ns	ns	ns	ns	ns	

Table 11: Side effects

Symptom	*Conventional (n=9)*	*Enalapril (n=11)*	*p value*
Dizziness	11.1% (1)	9.1% (1)	ns
Hypotension	11.1% (1)	27.3% (3)	ns
Gastro-intestinal	22.2% (2)	18.2% (2)	ns
Cough			
- Transient	22.2% (2)	45.4% (5)	ns
- Persistent	-	9.1% (1)	ns
Muscle cramps	11.1% (1)	-	ns
Hyperkalemia	-	18.2% (2)	ns

Table 12: Crossovers.

	Mortality		
	Conventional	*Enalapril*	*Mode of death*
1.	Week 1+	-	Sudden
2.	-	Week 9 +	Road traffic accident
3.	-	Week 9 +	Sudden
4.	Week 11 +	-	Pulmonary oedema & stroke
5.	Week 70 +	-	During sleep

03 patients had to be crossed over to the enalapril group due to clinical deterioration. This was done at weeks 12, 12 and 16

This study was not large enough to consider hospitalization or mortality as end-points but in other parameters, its results paralleled the findings of sestern studies.

The two groups in this study were fairly well matched. Although the conventional group patients were somewhat older and this group had relatively more females, the differences were not statistically significant. The patients were followed up for a minimum of 12 weeks & maximum of 120 weeks. The 12 week follow-up appears to be rather short but in actual fact, this happened in only a few patients. 50% of the trial patients were followed for at least 60 weeks while the mean follow-up came to 58 weeks.

The hemodynamic parameters showed a small but significant fall in the resting heart rate in the enalapril group probably secondary to the improvement in LVEF. Also this group showed a significant fall in SBP due to the direct vasodilating effect of enalapril.

There was a significant improvement in the mean exercise time in the enalapril group from 417 sec. to 478 secs at 12 weeks and 730 secs at 60 weeks. This was similar to that seen in a study on cilazapril[16] in a matching group of patients. In this study, the mean exercise time improved from 402 secs to 462 secs at 12 weeks. In another study on benazepril[17] in a similar group of patients, the mean exercise time increased from 485 secs to 585 secs at 12 weeks.

The conventional group showed a fall in the mean exercise time from 440 secs to 310 secs at 12 weeks but then increased to 563 secs at 60 weeks. This appears to be paradoxical but has a valid explanation. Firstly, the three patients left in the conventional group at 60 weeks had a mean exercise time of 453 at baseline. And secondly, in the cilazapril study by Dossegger et al[16], it was found that in the placebo group, patients able to exercise for more than 360 secs. at baseline showed an increase in exercise time at week 12 while those able to do less than 360 secs. at baseline showed a decrease. This is very similar to what occurred in our study.

There was significant reduction in left ventricular size, both diastolic & systolic dimensions, and increase in LVEF in our study. This matches that seen in multiple other studies[6,18,19]. In the study by Naganuma et. al[19], LVEF improved from 42% to 48% after 3 months' treatment with enalapril while both end-diastolic and end-systolic volumes were significantly reduced.

Improvement in Killip Class was seen in 10 out of the 11 patients in the enalapril group whereas only one patient improved his Killip Class in the conventional group. In contrast, in the CONSENSUS study[6], 42% of the patients showed improvement in Killip classification. The better response in our trial may have been due to the fact that our patients were better at baseline (class II & III) whereas the CONSENSUS patients all started in class IV.

As seen in the CONSENSUS trial[6], in our study also, it was possible to reduce the use of

digoxin significantly in the enalapril group while the diuretic dosage was also reduced but did not achieve significance levels. The maximum enalapril dose achieved on average was 9.2mg/day which is considerably less than the 18.4mg/day achieved in the CONSENSUS trial[6] or the 16.7mg/day in the SOLVD studies[7,8]. This may reflect a racial sensitivity to enalapril in the Pakistani population about which there is a lot of anecdotal evidence.

The laboratory profiles showed a mild rise in serum urea, creatinine and potassium in the enalapril group as would be expected but none of these changes were significant.

The incidence of side effects was generally low & none of these was intolerable. As expected, hypotension was seen more in the enalapril group. This was corrected by reducing the dose of enalapril. The incidence of transient cough was 45.5% in the enalapril group and 22.2% in the conventional group. This compares with 35.0% and 30.2% seen in the CONSENSUS trial in the two groups respectively. However, only one patient in our trial had persistent cough & even in this patient, enalapril was not withdrawn as the symptom was not disabling.

Three patients from the conventional group had to be crossed over to enalapril group during the trial due to clinical deterioration. This was done at weeks 12, 12 and 16. However, as statistical analysis was done on an intention-to-treat basis, these patients were continued to be considered as conventional group patients.

Five patients died during the follow-up period, 2 in the conventional group and 2 in the enalapril group. In the former group, two died suddenly while one had pulmonary oedema and stroke. In the latter group, one died suddenly while the other one died in a road traffic accident, the victim of a rash minibus driver. The trial was too small in numbers to get meaningful data on mortality & therefore, this was not considered as a statistical end-point.

The drawbacks of this trial are the small number of patients, lack of blinding and placebo-control and the variation in the follow-up period. However, as for as replication of results achieved in much larger trials of enalapril world wide are concerned, it achieved its objectives. The main difference found was that Pakistani patients tolerated only about half the dose of enalapril used in western trials. This confirms the experience of physicians in Pakistan not only with reference to enalapril but also with other ACE inhibitors as well as other drugs like beta-blockers and diuretics etc.

In conclusion, the addition of enalapril to conventional therapy in Pakistani patients of moderate-to-severe heart failure significantly improved NYHA class, exercise capacity, LV dimensions and LVEF. In addition, it reduced the need for other anti-heart failure medications & was generally well tolerated though in a much lesser mean daily dose as compared with the western population.

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