Cross-sectional study of heart failure therapy with angiotensin converting enzyme inhibitors and digoxin

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ABSTRACT

Objective: The aim of the present study is to show a better short-term (2 weeks) clinical improvement in patients with heart failure (HF) who are receiving angiotensin converting enzyme inhibitors (ACEIs) (with or without digoxin) when compared to the standard therapy excluding ACEIs.

Methods: The study was conducted in Al-Gamhuria Teaching Hospital, Aden, Yemen, from January to July 2003. In this study, 78 patients with HF were enrolled into 3 therapeutic groups (ACEIs alone, ACEI and digoxin and digoxin alone) and their responses within 2 weeks were recorded. Exclusion criteria were as follows: thyroid disorders, gastrointestinal disturbances (diarrhea, malabsorption), electrolyte unbalanced (unless corrected) and insufficient data. Serum creatinine was measured at the beginning and after 10 days. In addition, the patients' body weight and age were recorded. Criteria for a complete improvement within 2 weeks were the occurrence of the following: 1) The relief of pulmonary congestion, 2) Decrement in heart rate to less than 74 ± 5, 3) Disappearance of the lower limb edema, and 5) Recorded positive electroencephalogram change. Partial amelioration was recognized if only 2 or 3 of the preceding criteria were observed.

Results: Nine patients received digoxin alone, while 40 patients were treated with ACEIs and digoxin. Treatment with ACEIs without digoxin was observed in 29 patients. The discrepancy between the number of patients was necessitated by the need of patients with HF. This last category of treatment regimen produced better clinical improvement (complete with 10.1%, partial with 24.3%) compared to the digoxin group without ACEI (complete 2.5% or partial 5.1%). Nevertheless, the addition of digoxin to an ACEI increased this ratio (17.8% for complete and 28.2% for partial improvement). A 49.3% increase in serum creatinine was observed after 10 days in 25 HF patients, who were randomly selected and followed up (the baseline concentration was 99.75 ± 9.9 µmol/L, while the level after 10 days was 148.97 ± 19.8 µmol/L, p=0.005).

Conclusions: We confirmed that short-term use of ACEI regimens has a superior effect on the therapy of HF (34.4% complete and partial response) as compared to the therapy of not using ACEI (7.6% had a complete and partial response). The combination of ACEI and digoxin has resulted in the best outcome (46% had a complete and partial response). However, we also noticed a significant rise in serum creatinine by 49% concomitant with the use of ACEI (the baseline concentration was 99.75 ± 9.9 µm/L, while the level after 10 days was 148.97 ± 19.8 µmol/L, p=0.005).

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The therapy of patients with heart failure (HF) has changed in the last 10 years in parallel with a better understanding of the pathological, biochemical and biological factors. Before 1990, treatment regimens promoted the use of diuretics and digoxin. Even while improving symptoms, this

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had a little effect on mortality.[1] In well-designed trials, digoxin has shown to increase the left ventricular ejection fraction (EF) and the exercise tolerance in patients with chronic congestive heart failure (CHF), but did not affect the mortality.[2,3] Digoxin is now recommended for severe HF, and for mild or moderate failure if additional symptomatic relief is needed, after angiotensin converting enzyme inhibitor (ACEI) and diuretic therapy is maximized. Congestive cardiac failure (CCF), once sets in, runs a malignant progression with a very high morbidity and mortality. Pharmacotherapy can blunt this malignant progression and is useful in both the prevention as well as the treatment of HF. Over the past few years, several large, prospective, randomized, placebo-controlled clinical studies have examined the usefulness of ACEIs in patients with varying degrees of HF.[5-11] They established the role of ACEIs as an effective treatment for lowering mortality or preventing adverse events. The results of these studies strongly indicated that inhibition of ACE in patients with systolic dysfunction prevents or delays the progression of HF, decreases the incidence of sudden death and myocardial infarction,[12] decreases hospitalization and improved quality of life and increase survival rate of 30%. The more severe the ventricular dysfunction the greater is the benefit from ACEI. **Table 1** summarizes the main clinical trials on the group related benefits of ACEIs. When captopril, for example, is added to the standard therapy before and after acute myocardial infarction (MI) it would attenuates left ventricular remodeling (structural changes and enlargement), which occurs after MI, that could lead to left ventricular dysfunction (LVD) and it increases risk of death.[13] Angiotensin converting enzyme inhibitors improve cardiac hemodynamics by decreasing the peripheral vascular resistance and subsequently the load on the heart. Their cardioprotective actions may also be related to neurohormonal effects that limit ventricular remodeling and improve endothelial function. The various modulators of neurohormonal activation are 1) norepinephrine, 2) angiotensin II, 3) aldosterone, 4) endothelin, 5) oxygen radicals, 6) cytokines and 7) growth factors.[4] In particular, ACE inhibitors inhibit production of angiotensin II and increase nitric oxide production. The results are decreasing vascular and smooth muscle proliferation and migration, diminished oxidative stress, decreased activation of monocytes, macrophages and platelets and a reduction in the inflammatory milieu that predisposes to coronary events.[25] These neurohormonal effects also play a role in limiting the maladaptive ventricular dilatation and remodeling process that occurs in weeks and months after an MI. Arterial inflammation plays a key role in the pathogenesis of coronary artery disease. The addition of ACE inhibitors and beta blockers to aspirin and a statin, a hypolipidemic drug, may slow this process and help preserve the vascular endothelial function. The use of ACEIs nowadays, overwhelm digoxin[26,27] due to the above mentioned multifunctional effects and benefits, although some of their mechanisms are not completely understood yet.[22] Undoubtedly, some contribution to the positive outcome derived from the inhibition of the effects of angiotensin II at a cellular level, which include intimal and vascular smooth muscle cell proliferation and plaque stability.[22] Notwithstanding, there is a considerable variation in the plasma concentrations of ACEIs in patients with comparable renal function even if it is equally dosed.[28] The aim of the present study is to gather and show data supporting the better clinical improvement in HF patients within a short period (2 weeks) under conventional therapy with ACEIs and the combination of ACEIs plus digoxin, in relationship to the standard therapy excluding ACEIs.

Methods. The study was conducted in Al-Gamhuria Teaching Hospital, Aden, Yemen from January 2003 to July 2003. One hundred and seventeen patients were admitted to the hospital with HF being the principle cause for admission. They were given oral digoxin (0.250 mg/day) or one of the ACEIs. Captopril was used in 65 patients. Patients were randomly distributed in digoxin (mean age 49 ± 9), ACEIs and digoxin (mean age 47 ± 15) and ACEIs groups with the mean age of 45 ± 19. Exclusion criteria were: thyroid disorders, gastrointestinal disturbances (diarrhea, malabsorption), electrolyte imbalance (unless corrected), and insufficient data. Accordingly, only 87 patients were found suitable for inclusion in the study. The patients' body weight, age, and serum creatinine levels were recorded according to a pre designed protocol. All patients included in the study presented with dyspnea, shortness of breath and at least 3 of the following clinical features: raised heart rate, inspiratory crepitation, edema (pulmonary or lower limb), abnormal electroencephalogram (ECG) and x-ray, fatigue and poor effort tolerance, oliguria, high jugular venous pressure and hepatic congestion. Criteria for a complete improvement within 2 weeks were: the relief of pulmonary congestion, a decrement in heart rate to less than 74 ± 5, the disappearance of the lower limb edema and a registered positive ECG change. Partial amelioration was recognized if only 2 or 3 of the preceding criteria were observed. In case of improvement of only one of them this was

recognized as no change. Serum creatinine measurements were performed according to the mentioned procedure in references.[29] The plasma level of digoxin was indirectly calculated by the equation according to the previous study.[30]

Statistical analysis. Data are presented as a mean values and percentages. Comparison of data was performed with the help of t-test in computerized statistical package of social sciences (SPSS) program.

Results. ***Short term clinical improvement of heart failure patients with digoxin and ACEIS.*** Nine of the 87 patients included in the trial died. There were 3 from each of the 3 groups. The remaining 78 patients were distributed into 3 groups. **Table 2** shows the total number of patients with 2-week clinical responses to digoxin, to ACEI and the combination of both drugs. **Figure 1** illustrates the percentage of clinical outcomes (complete, partial or none according to the criteria described above). Digoxin group showed the lowest results (2.5% complete and 5.1% partial improvement). The group treated with digoxin and ACEI had a higher percentage as complete improvement compared to that of ACEI alone (10.1%).

Comparison between improvement and plasma digoxin concentration. Twenty-five of 49 patients receiving digoxin were studied. Eighteen of these were treated with a combination of digoxin and an ACEI. Of these 18 patients, 13 had an acceptable PDCs (normal range was 0.8-2 microg/L = 0.8-2 ng/ml) but 5 had a high values (patients 2, 8-11 in **Table 3**). These patients had a higher levels than the normal, and partially improved. Two patients (**Table 3**) did not improved as they suffered nausea, vomiting, extrasystole and diarrhea. Subsequently their digoxin dose was reduced to 0.125 mg (half a tablet) per day. An increase in serum creatinine (SCR) concentration during the study period was observed. The baseline concentration of SCR of 25 HF patients was 99.75 ± 9.9 μmol/L, while the level after 10 days was 148.97 ± 19.8 μmol/L (p=0.005). The increase of 49.3% was statistically significant.

Discussion. The results showed different clinical improvement of patients with HF under appropriate treatment including an ACEI and digoxin as a classical drug. According to the inclusion criteria, 87 patients were enrolled, but 9 of them died. **Table 2** shows that 11.5% received digoxin while 37.2% were treated with ACEIs, which reflects the tendency of an updated therapy changes. It also shows that the treatment with ACEI alone (without digoxin) produced better clinical improvement (complete or partial) within 2 weeks than using digoxin alone. This improvement became more evident when an ACEI was combined with digoxin (0.250 mg/day) (**Figure 1**).

The most commonly used ACE inhibitor was captopril, starting with 6.25 mg twice a day until full recommended for daily dose (150 mg/day). Enalapril and lisinopril were also used. The higher percentage of patient improvement in the ACEI plus digoxin group in relation to the other 2 groups is in agreement with reported comparative studies.[27] These trials showed the short and long term use of such drugs with comparable improvement.

Additional digoxin, which produces additional relief of symptoms and increases the ejection fraction[2,3] to an ACEI, which reduces ventricular remodeling effectively, hospitalization and mortality, exerts multifunctional effect to accelerate the improvement. This may explain the higher results of complete improvement and patients' improvement in this group. It can be concluded that the association of an ACEI plus digoxin, in the present of a diuretic, which enhances the effect of ACEI, seems to be the most appropriate in this condition, and the observed results support the current recognized regimens for HF therapy. The use of furosemide with ACEIs did not significantly change the serum electrolyte concentrations in this study (data not shown). Fluctuations in serum potassium concentrations were not also evident. Once an ACEI has been initiated, it should be continued indefinitely, probably for life, if tolerated.[28] Their main contraindications to the use of ACEIs are hypersensitivity, such as a history of angioedema to these drugs (hypersensitivity reaction), and pregnancy. The risk of renal dysfunction with ACEI is reported. But the exact frequency of glomerular filtration rate (GFR) decline during ACEI therapy is not known. However, significant deterioration of renal function seems to be limited and, in most instances, temporary. A decline in renal function with the use of ACEI can occur in patients with renal artery stenosis, either bilateral or unilateral in a solitary functioning kidney. Nevertheless, it is in these patients that ACEI are considered the medical treatment of choice.[31] The overall frequency of worsening renal function reported in the literature is 5-20%. Common side effects, such as hyperkalemia, hypotension and renal dysfunction are usually dose related and can be prevented with low initial doses, gradual monitoring and carefully titration. It is interesting to remark that the benefits of ACEIs in patients with HF cannot be completely explained by the degree to which blood pressure is reduced.[22]

In this study, 25 patients were followed up prospectively. All of them, except 5, had an acceptable digoxin serum level between 0.95-1.96 (normal, 0.8-2 microg/L). These 5 patients (patient

Table 1 - Comparative clinical studies of the benefits of angiotensin converting enzyme inhibitors in heart failure.

Investigators	Reference	Subset of patients	Finding
CARMEN trial 3	14	Asymptomatic with LVD	Enalapril. Improvement of ventricular remodeling. Delay progression to CCF. Decrement of mortality.
SOLVD prevention trial 4	15,16	Asymptomatic with LVD	Enalapril. 8% decrement in CV and overall death.
SAVE 5 and TRACE 6 trial	17, 18	Post MI-LVD	Enalapril. Same benefits.
ISIS-4 trial	13	High-and low risk patients post MI	Captopril. Attenuates LV remodeling post MI.
CONSENSUS-17 and SOLVD treatment 8	19, 20, 21	CCF	Enalapril, captopril. Symptoms improvement. Blunting progression. Decrement of mortality.
SOLVD 4, 8 and SAVE 5	22	High risk patients without LVD	Captopril. Highly efficacious
HOPE trial 10	23	High risk patients without LVD	Ramipril (10 mg/day) Decrease in CV events and stroke by 20%
PEACE trial 11	24	Patient with CAD	Trandolapril In progress to assess prevention of MI and CV events in patients with CAD.

CARMEN - Carvedilol Angiotensin Converting Enzyme Inhibitors Remodelling Mild Heart Failure Evaluation.
SOLVD - Studies of Left Ventricular Dysfunction, SAVE - Survival and Ventricular Enlargement trial,
TRACE - Trandolapril Cardiac Evaluation trial, ISIS-4 - Fourth International Study of Infarct Survival,
CONSENSUS - Cooperative North Scandinavian Enalapril Survival Study, HOPE - Heart Outcomes Prevention Evaluation,
PEACE - Prevention of Events with Angiotensin-Converting Enzyme Inhibition Trial, LVD - left ventricular dysfunction, CV - cardiovascular,
CAD - coronary artery diseases, CCF - congestive cardiac failure, LV - left ventricle, MI - myocardial infarction

Table 2 - Clinical improvement score (78).

Item	Digoxin (%)	ACEI %	Digoxin (%) - ACEI
Complete improvement	2 (2.5)	8 (10.1)	14 (17.8)
Partial improvement	4 (5.1)	19 (24.3)	22 (28.2)
No change	3 (3.8)	2 (2.5)	4 (5.7)
Total	**9 (11.5)**	**29 (37.2)**	**40 (51.3)**

ACEI - Angiotensin converting enzyme inhibitor

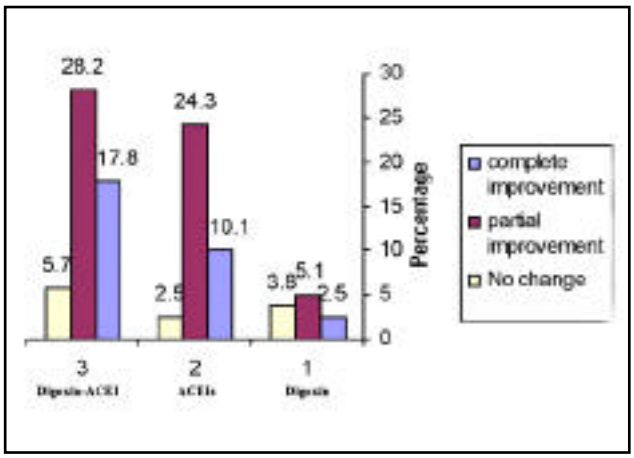

Figure 1 - Clinical improvement score. ACEI - Angiotensin converting enzyme inhibitor

number 2, 8-11 in **Table 3**) presented high steady state serum levels of digoxin although different pictures of improvement were shown. Two patients tolerated well the high level (patient no. 9 and 11 in **Table 3**) but the others experienced signs of toxicity, nausea, vomiting, extrasystole and diarrhea. Consequently, their dose was reduced to 0.125 mg/day. This high level can be partially explained by concurrent use of an ACEI, which probably increases the digoxin level,[32] patient's condition (hyperglycemia), obstructive cholestasis, which reduces its elimination and increases plasma level,[33] intermittent variation[30] and impaired renal function (remote explanation). The finding of higher incidence of partial improvement within the patients can be accounted to the slow response of ACEIs including the effect on the renal hemodynamic function.[34] The possible fluctuations in the bioavailability of digoxin due to different pharmaceutical manufacture[30,35] should be excluded as most of the patients used the same preparation (Egypt manufacture).

It was suggested that the use of an ACEI should be monitored within the first week[36,37] of treatment for creatinine and potassium change. Such parameters were likely to increase initially, though they return to the previous levels after prolonged use. In that case, nevertheless, a modification of the dosage regime of digoxin might be necessary in a number of patients. This finding need further study. Some other clinical conditions leading to modification of potassium level in plasma were exclusion criteria for patients enrolled in the present study, which lessen the risk of confusion and misunderstanding.

Table 3 - Digoxin clearance and serum concentration at steady state (C^{ss}_{pdig}).

Subject	Cl_{cr}	Digoxin clearance L/hour	C^{ss}_{pdig} microg/L	Comments
1	40.73	3.48	1.94	PI
2	24.60	2.12	3.19	NC
3	44.06	3.86	1.75	PI
4	40.15	3.45	1.96	PI
5	104.23	7.11	0.95	PI
6	76.61	4.82	1.40	CI
7	87.40	6.04	1.12	CI
8	33.09	3.07	2.20	PI
9	27.14	2.53	2.67	PI
10	13.91	1.74	3.89	PI
11	39.17	3.10	2.18	PI
12	42.13	3.46	1.95	CI
13	43.23	3.72	1.81	PI
14	46.92	3.91	1.73	NC
15	46.32	3.98	1.70	NC
16	84.77	5.36	1.26	CI
17	105.39	6.97	0.97	CI
18	53.60	4.18	1.61	PI

PI - partial improvement, NC - no change, CI - complete improvement, Cl_{cr} - creatinine clearance ml/min, C^{ss}_{pdig} - digoxin plasma concentration at steady state microg/L.

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