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A three year clinical review of the impact of angiotensin converting enzyme inhibitors on the intra hospital mortality of congestive heart failure in Nigerians

AD ADEWOLE, RT IKEM, AQ ADIGUN, AO AKINTOMIDE, MO BALOGUN, *AA AJAYI

Angiotensin converting enzymes inhibitors are now regarded as the cornerstone of congestive heart failure therapy owing to established reduction in mortality and the symptomatic amelioration following their use. Although the response to converting enzyme inhabitor therapy may be influenced by race, we have reported a trend to reduce intra hospital mortality, the correction of hyponatremia and shortened hospitalization in Nigerians treated with converting enzyme inhibitors.

We have now conducted an extended retrospective study, to evaluate the trends in the use of enalapril or captopril and its impact on prognosis in Nigerian patients with heart failure alone, admitted between January 1992 to December 1994. The proportion of heart failure treated with (captopril or enalapril) increased from 37pc in 1992, to 50pc in 1993, to 65pc in 1994. The demographic variables and cause of heart disease were similar in patients treated with converting enzyme inhibitors (n=55) and those treated conventionally (n=36).

The cumulative mortality among converting enzyme inhibitors treated patients, was (8/55, 14pc) compared to patients not treated (17/36, 48pc) x^2 =12,4;p<0,0001. There was no sex predilection in mortality (M=25pc, F=28pc, mean 27pc). However, initial serum Na+,125mmol was significantly (x^2=11,1; p<0,001) more common in the dead patients, 25pc compared to the survivors discharged home 7,5pc.

The median hospital stay was 17 days in captopril treated survivors (range two to 44 days) and 19 days (range four to 67 days) in conventionally treated patients. Thus converting enzyme inhibitor therapy may reduce intra hospital mortality in Black Africans hospitalized for congestive heart failure and shorten hospital stay, despite the epidemiologically low plasma renin in Blacks. Hyponatremia may be a poor prognostic index in heart failure in our patients, and its reversal by converting enzyme inhibitors may reflect neurohormonal inhibitor.

Earlier and more wide spread use of angiotensin converting enzyme inhibitors in Nigerian and Black Africans with chronic heart failure is now clearly indicated.

Introduction

The reduction in mortality in congestive heart failure and amellioration of symptoms and diminished frequency of hospitalization by converting enzyme inhibitors have been established in several large multicentre trials[1-5]. While there are established interracial differences in the plasma renin activity[6], which is a determinant of response to converting enzyme inhibition[7,8], these large multicentre trials did not address the issue of the impact of converting enzyme inhibitors on prognosis, on Black people who epidemiologically have low plasma renin activity[6] and who may be poorly responsive to converting enzyme inhibitor monotherapy of essential hypertension[9,10].

The presence of heart failure, however, is associated with compensatory neuro-endocrine and renin-angiotensin system activation[11]. We have previously reported the beneficial effects of enalapril on hyponatremia, exercise, tolerance and symptoms[1] in Nigerians with congestive heart failure[12,13] as well as preliminary evidence for a trend to a reduction of intra hospital mortality, and shortened hospital stay[14]. We have now conducted an extended three year retrospective study of the trends in the use of converting enzyme inhibitors (captopril and enalapril) in our setting, as well as their impact on intra hospital mortality in chronic congestive heart failure in Nigerians.

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Materials and Methods

A retrospective study was carried out. The decision to undertake the review was taken in December 1994, by one of us who was away and did not partake in the management of the patients during the period of the study. The case jackets and nursing records of all medical admissions for congestive heart failure between 1 January, 1992 and 31 December, 1994 were obtained. The exact clinical diagnosis, aetiology of heart disease, demography, admission and discharge dates (or death), and eventual patient outcome (survival or death), the use or not of converting enzyme inhibitors in treatment, the choice of the converting enzyme (captopril or enalapril) and the dose employed were all noted and extracted into a standard protocol work sheet[14].

All patients were treated conventionally with Digoxin (0,125 to 0,25 mg/day) diuretics, (frusemide 40 to 160 mg/day) other

drugs including antihypertensives and methyldopa or antirrhythmics. Patients with chronic renal failure, chronic obstructive airways disease with cor/pulmode were excluded. A total of 91 patients' records were then available for analysis over the three year period. The patients were of all grades of heart failure severity. Fifty five of these received captopril (25 to 50 mg/day) and 10 enalapril (2,5 to 5 mg/day). Thirty six patients received only digoxin and diuretics, and received no converting enzyme inhibitors because of the relatively high cost of therapy; initial low blood pressure; physician preference. Contra-indications to converting enzyme hypertension were the commonest cause of heart failure in all the patients, 59pc, followed by dilated cardiomyopathy (36pc) and then rheumatic heart disease.

The demographic and clinical data of the patients who received converting enzyme inhibitor therapy and those who did not are shown in Table I. These two groups were apparently well matched in the aetiology, sex distribution, and baseline characteristics.

Table I: Baseline characteristics of patients.

Conventional therapy + angiotensin converting enzyme inhibitor treated.	Conventional therapy + no converting enzyme inhibition
n=55	n=36
Aetiology of heart failure	
Hypertension (pc) 59	59pc
Cardiomyopathy (pc) 37	40
Valvar (pc) 7	1
Others —	1
M.F. ratio	
Drugs 1:1	1:1
Enalapril (pc) 10 (19pc)	—
Captopril (n) 45 (81pc)	—
Digoxin (n) 55 (100pc)	36 (100pc)
Frusemide (n) 55 (100pc)	36 (100pc)

Results

General: The proportion of CHF patients treated with converting enzyme inhibitor increased from 37pc in 1992 to 50pc in 1993 to 65pc in 1994.

Impact converting enzyme inhibitor therapy on three year mortality: These results are shown in Table II. The cumulative mortality rate over the three year period was significantly lower, (8/55, 14pc) in patients treated with converting enzyme inhibitors during hospitalization, in comparison to patients not treated with converting enzyme inhibitors (17/36, 48pc) $x^2=12,4;p<0,001$. The overal pooled mean mortality rate was 27pc in both groups. There was no sex prediction in mortality rate (male = wepc, female =28pc).

Six out ofthe eight mortality cases in the converting enzyme inhibitor treated group had hypertensive heart failure, while two had dilated cardiomyopathy. Hypertensive heart failure, followed by cardiomyopathy were also leading causes of mortality in the convertionally treated group.

Peak mortality (from all causes) tended to occur in the first week of admission, with about 30pc dying within three days of hospitalization. No distinction was made between cardiac death due to progressive pump failure or sudden (arrhythmic) death in the case records.

Table II: Threee year (1992 to 1994) mortality in Nigerian patients with congestive heart failure. The impact of converting enzyme inhibitor therapy.

	Dead	Alive	Total	pc Mortality
Angiotensin converting enzyme inhibitor treated	8*	47	55	14
No converting enzyme inbibitors	17	19	36	48
Total	25	66	91	27

*$p<0,001 x^2=12,1$.

Impact of baseline (initial) serum Na^+ on mortality: An initial serum sodium concentration of 125 was found to be a poor prognostic index for mortality. Hyponatremia patients (125 mmol Na^+/l) had a (7/10) 70pc mortality rate compared to 17/54 (29pc) mortality rate in those values/125mmol/L. This represents an odds ratio for mortality of 2,3 in severe hyponatremia compared to those with the values 125mmol/L Na^+ (see Table III), ($x^2=11,1$; $p<0,001$). In the dead patients, 298 had hyponatremia (125 mmol/L compared to only 7,5pc survivors (see Table III). In dead patients, who received prior converting enzyme inhibitor therapy the serum sodium concentration ranged from 122 to 156 mmol/L (median) 131 mmol/L.

Table III: Influence of serum sodium and hyponatremia on intra hospital mortality (n=64).

Serum Na=	Dead	Alive	Total	pc Mortality
125 mmol/L	7*	3	10	70
7/125 mmol/L	17	37	34	30
Total	24	40	64	37

*$p<0,001 x^2$-11,1.

Duration of hospitalization: Median hospitalization duration was 17 days in converting enzyme inhibitor treated survivors (range two to 44 days) and it was 19 days (range four to 67 days) in conventionally treated patients not receiving either enalapril or captopril.

Discussion

The result of the present study indicates that the converting enzyme inhibitor treatment of Nigerian patients with congestive heart failure, during hospitalization is associated with a significant (0,001) reduction in intra hospital mortality compared to patients not so treated. This finding confirms and extends our preliminary observation[14], and is consistent with the findings of our large scale, prospective multicentre studies[1-5]. Owing to material or managerial constraints, prospective controlled large scale studies of the impact of converting enzyme inhibitors on heart failure mortality may not be feasible on a world wide scale. However, in this retrospective analysis, patients receiving converting enzyme inhibitors, and those who did not, appear well matched in baseline clinical characteristics. The choice of enalapril or captopril in treatment was dictated by economic factors, initial blood pressure (contra indicated by hypotension),

and physician preference. It is, however, unclear whether these factors may have confounded the direct impact of the converting enzyme inhibitors on survival, as shown in the study.

The three year mortality rate of 48pc, in patients not treated with converting enzyme inhibitors is similar to values reported in the placebo arm of other studies[1-5]. Another interesting observation in this study is the demonstration of the poor prognostic value of hyponatremia in congestive heart failure. This study is concordant with established experience[15] and may reflect the stimulation of arginine-vasopressin in severe heart failure by angiotensin II, with consequent dilutional hyponatremia[16]. Since converting enzyme inhibitors, including enalapril may correct hyponatremia in Nigerians[13] with heart failure, putatively via an inhibition of neurohormonal activation, it may be mechanistically relevant in the reduction in mortality[15].

The median duration of hospitalization was 19 days in patients not receiving converting enzyme inhibitors, and is similar to the figures reported in some studies[17]. There was a slight reduction in the converting enzyme inhibitor treated group to a median of 17 days. The prolonging of longevity by captopril or enalapril may itself exert a paradoxical effect to prolong hospital stay in patients, who otherwise might have died in hospital, had they nor received converting enzyme inhibitor treatment. This might have mitigated a discernible effect on the duration of hospitalization in this study, due to converting enzyme inhibitors.

The beneficial effect of enalapril and captopril on mortality in Nigerian heart failure patients was attained at relatively low daily doses; 2,5 to 5 mg/day and 25 to 50 mg/day respectively, in order to minimize cost. Although a formal cost effectiveness analysis of angiotensin converting enzyme inhibition in heart failure in Nigerians is required, we have already noted a reduction in the frequency of repeat hospitalizations and the admission rate of ambulatory patients treated with these drugs (Ajayi AA 1995, unpublished observations).

In conclusion, treatment of Nigerian heart failure patients with converting enzyme inhibitors, enalapril or captopril, was associated with a significant reduction in intra hospital mortality compared to patients receiving only digoxin and diuretics. This beneficial effect on prognosis is seen despite the epidemiologically low renin profile of Nigerians without heat failure. Earlier and widespread use of converting enzyme inhibitors in Nigerians with heart failure is now clearly indicated.

Additionally, retrospective analyses and comparison with historical controls may be a useful way to examine the impact of converting enzyme inhibitors on mortality in heart failure world wide, both because of the ethical dilema of further placebo controlled studies, and the prohibitive cost of formal prospective clinical trials in less developed countries.

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