Clinical Studies of Enalapril Treatment for Patients with Severe Congestive Heart Failure

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The clinical efficacy of enalapril was investigated in 21 patients with severe heart failure. For each subject, the following parameters were compared before and one month after enalapril maintenance treatment. NYHA functional class, Killip's class, cardiothoracic ratio (CTR), left ventricular (LV) function estimated by echocardiography and gated equilibrium radionuclide angiography, Holter ECG recordings, serum digoxin concentration (SDC), plasma renin activity, plasma aldosterone concentration, plasma norepinephrine concentration (PNE), etc. Short- and long-term hemodynamic responses to enalapril were also studied, with simultaneous measurement of enalapril concentration by radioimmunoassay. After maintenance therapy, patients showed a significant improvement as judged by NYHA functional class, Killip's class, and CTR. The LV fractional shortening and the ejection fraction significantly increased. The frequency of ventricular tachycardia showed a significant tendency to decrease after the therapy. The SDCs were unchanged, which indicates no pharmacokinetic drug interaction between digoxin and enalapril. Hemodynamic assessment showed a reduction in systemic vascular resistance, a reduction in mean blood pressure, and an increase in the cardiac index. No major side effects were observed during the study period. According to a multivariate analysis, the coefficient of determination of PNE was the highest for the final global improvement rating. This may reflect the neurohormonal improvement of congestive heart failure by enalapril therapy. In conclusion, enalapril is recommended for treating patients with severe CHF.

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IT is well-known that reducing mortality from congestive heart failure (CHF) mainly relates to left ventricular dysfunction and ventricular tachyarrhythmia. Both are amenable to pharmacological intervention, so the potential exists for reducing mortality from CHF. For the past two decades there has been a search for new positive inotropic agents that can stimulate the depressed myocardium, since the benefits of digitalis in

the treatment of severe CHF are limited. New, potent antiarrhythmic drugs have also been sought. However so far all efforts have failed. Many new cardiotonic drugs have appeared, but it is reported that they may further depress sick myocardial cells and promote underlying cardiac disease¹. It is also reported that antiarrhythmic drugs are not effective in treating ventricular tachyarrhythmias in severe CHF². Indeed, they may even have proarrhythmic effects³.

The treatment of CHF has evolved rapidly since the advent of vasodilator therapy, especially orally administered angiotensin

Key words:

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TABLE I CLINICAL CONDITIONS OF PATIENTS AT BASELINE

No.	Age	NYHA class	Killip's class	CTR (%)	LVEF (%)		Cl (l/min/m ²)	Forrester's class	Combined drugs			Enalapril dose (mg/day)
					UCG	Radio-nuclide			Digitalis	Catecholamine	Nitrates	
1	64	IV	III	65.8	31	22.1	1.48	IV	○	○	○	2.5
2	57	II	I	56.8	27	20.0	2.44	I	○			5.0
3	55	II	I	53.9	24	25.5	2.48	I				5.0
4	60	II	I	67.3	18	8.5	1.26	IV	○			5.0
5	49	II	I	61.2	23	22.0	2.59	I	○			2.5
6	54	II	I	59.8	26	14.0	1.62	IV	○			2.5
7	65	II	I	64.6	16	14.0	1.81	IV	○			2.5
8	15	IV	II	79.2	16	13.0	2.38	II	○	○	○	5.0
9	31	III	II	62.0	21	9.5	1.70	IV	○		○	5.0
10	47	IV	III	59.3	24	10.5	2.08	IV	○		○	5.0
11	64	II	II	63.0	32	19.0	1.78	IV	○		○	5.0
12	36	IV	I	72.7	24	2.0	1.38	III	○	○	○	5.0
13	43	II	I	67.8	17	7.5	1.85	IV	○		○	5.0
14	64	II	I	72.1	16	8.0	1.67	IV	○		○	5.0
15	59	II	I	71.0	28	19.5	1.37	IV				5.0
16	80	III	II	58.0	24	18.5	2.08	IV	○	○	○	5.0
17	75	III	III	61.3	(-)	(-)	1.68	IV	○	○	○	5.0
18	84	IV	II	67.5	37	36.0	2.89	II	○		○	2.5
19	68	II	I	52.4	28	17.7	(-)	(-)	○		○	2.5
20	77	II	I	72.0	22	30.1	(-)	(-)	○			5.0
21	49	IV	III	70.0	48	52.3	(-)	(-)	○		○	5.0
Mean	56.9	2.7	1.6	64.6	25.1	18.4	1.91	3.2				

1~16: DCM, 17~19: IHD, 20: Valvular heart disease, 21: Renal arteriovenous fistula

Fig.1. Changes in NYHA functional class, Killip's class, CTR, and left ventricular function before and after enalapril therapy

converting enzyme (ACE) inhibitors such as captopril and enalapril. Recently, the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) trial⁴ has reported that adding enalapril to conventional therapy with digitalis and diuretics in patients with severe CHF can reduce mortality and improve clinical symptoms; the beneficial effect on mortality is due to a reduction in death from the progression of CHF. However, it remains to be determined whether there is a pharmacokinetic digitalis-enalapril drug interaction like the digitalis-captopril interaction reported already⁵; and whether enalapril is effective for life-threatening ventricular tachyarrhythmias in patients with severe CHF.

To clarify these problems in clinical settings, we conducted clinical studies of enalapril treatment for patients with severe CHF.

SUBJECTS AND METHODS

The subjects were 21 hospitalized patients with severe CHF, 17 males and 4 females. The mean age was 56.9 years ranging from 15 to 84 years. The underlying heart dis-

eases were dilated cardiomyopathy (DCM) in 16 patients, ischemic heart disease (IHD) in 3 patients, valvular heart disease in 1 patient and renal arteriovenous fistula in 1 patient. All patients had clinical signs and symptoms of CHF despite intensive treatment with furosemide and the other combined drugs.

The daily dosage of enalapril was 2.5 to 5 mg. The following tests and examinations were carried out before and 1 month after the therapy started: New York Heart Association functional class (NYHA class), chest X-ray, left ventricular ejection fraction (LVEF) by echocardiography and radionuclide angiography, Holter ECG recording, plasma renin activity (PRA), plasma aldosterone concentration (PAC), serum digoxin concentration (SDC), and routine laboratory tests. Both short-term and long-term hemodynamic responses to enalapril were also studied using Swan-Ganz catheters. At the same time, the serum enalapril concentration was measured by radioimmunoassay (RIA).

Table I summarizes the clinical conditions in the patients at baseline before the administration of enalapril. All patients were in NYHA classes II to IV and in Killip's classes I to III. The mean cardio-thoracic ratio (CTR) was 64.6%, the radionuclide LVEF was 18.4% and the cardiac index (CI) was 1.91 L/min/m². By Forrester's classification, 12 patients were in class IV. All patients had severe resting left ventricular dysfunction.

Three patients were not treated with digitalis because they were extremely sensitive to it. Digitalis and diuretics were continued before and during enalapril therapy, but they were withheld for at least 24 h before and 1 month after the therapy began, to measure hemodynamic parameters.

During enalapril therapy, digitalis was continued at constant dosages, but diuretics, catecholamine and nitrates were adjusted as needed.

RESULTS

1. Changes in NYHA class, Killip's class, CTR, and left ventricular function before and after enalapril therapy

After enalapril therapy, the NYHA class improved in all but 5 of the patients, as

Fig.2. Hemodynamic responses to long-term enalapril therapy

shown in Fig. 1. Killip's class improved in 9 patients. The two changes were statistically significant. After enalapril treatment, the CTR decreased from 64.6 to 60.5%. In echocardiographic evaluation, the left ventricular fractional shortening (FS) increased from 11.9 to 14.7%, and the LVEF increased from 23.6 to 28.0%. These changes were statistically significant. The LVEF determined by radionuclide angiography increased, though not significantly, from 15.4 to 17.8%.

2. Hemodynamic responses to enalapril therapy

Figure 2 shows the hemodynamic responses before and 1 month after treatment with enalapril. The mean blood pressure (mBP) fell from 89.0 to 84.2 mmHg. The

mean pulmonary capillary wedge pressure (PCWP) changed from 22.0 to 16.2 mmHg and the mean systemic vascular resistance (SVR) was reduced from 3,600 to 3,061 dyne/sec/cm⁻⁵, while the mean CI rose from 1.93 to 2.13 L/min/m². These changes were all statistically significant.

Figure 3 shows the time course of changes in mBP, PCWP, SVR and CI in both short-term and long-term treatments with enalapril. These changes in hemodynamic effects were statistically significant with in at least 3h after the administration of enalapril in both treatments, except PCWP which did not change with the long-term treatment.

Figure 4 illustrates the differences in hemodynamic response to enalapril in 3 patient groups classified according to baseline PRA (less than 4 ng/ml/h, 4~10 ng/ml/h,

Fig.3. Time course of hemodynamic effect of enalapril

more than 10 ng/ml/h). The mean change in the SVR of group 2 was significantly higher than that of group 1; the other changes were not statistically significant. Thus, the action of enalapril does not depend on baseline PRA only.

3. Changes in PRA, PAC, plasma norepinephrine concentration (PNE), and urinary norepinephrine per day (UNE), and the data of routine laboratory tests before and after long-term enalapril therapy

Figure 5 shows the changes in PRA, PAC, PNE and UNE. The mean PRA increased from 6.7 to 11.3 ng/ml/hr and the mean PAC decreased from 22.1 to 13.5 ng/ml. These changes were statistically significant. The persistent increase in PRA and the decrease

in PAC indicate a long-term inhibition of the converting enzyme.

The mean PNE and UNE tended to decrease after the therapy. The former changed from 0.66 to 0.43 ng/ml and the latter decreased from 170 to 80 μ g/day. During the therapy, sympathetic activity decreased, presumably in response to improved left ventricular function.

Enalapril did not produce any abnormalities in the blood count or blood chemistry after the long-term therapy. Liver function tests, such as total bilirubin, aspartate transaminase, alanin transaminase, lactate dehydrogenase and alkaline phosphatase improved after enalapril treatment. Also, serum creatinine decreased significantly. These changes may reflect an improvement in both

Fig.4. Hemodynamic response to enalapril in three patient groups classified according to PRA

hepatic and renal circulation secondary to the alleviation of severe CHF. The mean serum potassium concentration increased from 4.3 to 4.4 mEq/l after enalapril treatment, but this change was not statistically significant.

4. Combined drugs and side effects during enalapril therapy

After enalapril treatment, the dosage of the combined drugs was less than before enalapril. The doses of diuretics were decreased in 7 patients out of 21, furosemide in 4, and spironolactone in 3. Catecholamine was decreased in 3 patients out of 5 and nitrate was withdrawn from 1 patient out

of 13.

No side effects were observed during the study period. Although 2 patients developed skin rash and leukopenia during captopril therapy, they had no side effects with enalapril in this study.

5. Serum enalapril concentration and its pharmacokinetic parameters

Figure 6 shows the time-curves of the mean serum enalapril concentration measured by RIA in 12 patients out of all subjects, and the pharmacokinetic parameters of the active metabolite (MK-422) and the total drug. The mean peak concentration of the active metabolite occurred 4.7 h after

Fig.5. Changes in PRA, PAC, PNE and UNE before and after long-term enalapril therapy

enalapril therapy started.

The time-curves for our patients with CHF were similar to those reported by others for healthy volunteers. This indicates good absorption of this drug even in patients with CHF.

6. Frequency of premature ventricular complexes (VPC) and the Lown grading system on 24 h Holter electrocardiogram

Figure 7 illustrates the changes in the frequency of VPC and the Lown grading system before and after the long-term therapy. After 1 month of treatment with enalapril, the frequency of VPC and ventricular couplets decreased. However, these changes were not statistically significant. The frequency of ventricular tachycardia (VT) defined as 3 or more VPC in succession had a significant tendency to decrease after the therapy. However, the Lown grading system was

unchanged.

7. SDC and ECG before and after enalapril therapy

SDC was measured by RIA as serum minimum digoxin concentration in steady-state. Fig. 8 shows that the SDCs were unchanged before and 1 month after enalapril therapy. The ventricular rates decreased (Table II), but the changes in PQ and QTc on ECG recordings were not statistically significant. These data indicate that there is no pharmacokinetic digitalis-enalapril drug interaction.

8. A multiple linear regression analysis of final global improvement rating

At first, 22 independent variables in 21 patients were chosen by a hierarchical clustering method from changes in 57 clinical data before and 1 month after enalapril therapy.

Pharmacokinetic parameters

	Cmax (ng/ml)	Tmax (hr)	t _{1/2} (hr)	AUC (ng·hr/ml)
MK-422	26.14 ± 11.13	4.7 ± 1.0	8.0 ± 2.3	379.7 ± 145.4
Total drug	55.25 ± 17.16	2.0 ± 0.0	6.6 ± 1.5	472.5 ± 149.2

Fig. 6. Mean serum enalapril concentration time curves (during maintenance therapy, n=12)

Next, 8 independent variables were determined by stepwise regression from these 22 variables. They were PNE, Na, K, Lown's grade, Killip's class, total VPC and PAC.

A multiple linear regression with the final global improvement rating as the dependent variable was analyzed on an IBM electronic computer using the VARCLUS procedure and the STEPWISE procedure (SAS Institute Inc.). The multiple regression equation and multiple correlation coefficient (R) obtained were: final global improvement rating = $2.97 + 0.608$ (PNE) $- 0.161$ (Na) $+ 1.52$ (K) $+ 0.178$ (CTR) $- 0.541$ (Lown's grade) $+ 0.665$ (Killip's class) $+ 0.0000303$ (total VPC) $- 0.0291$ (PAC), $R = 0.957$. The coefficients of determination of these 8 variables and individual one were: 0.9161, PNE: 0.3460, Na: 0.2019, K: 0.1049, CTR: 0.1381, Lown's grade: 0.0330, Killip's class: 0.0407, total VPC: 0.0267, PAC: 0.0246. The coefficient of determination of PNE was the high-

est of the eight. These results may reflect the improvement of CHF neurohormonally by enalapril therapy.

DISCUSSION

An appreciation of the important role played by enhanced peripheral vasoconstriction in the pathophysiology of CHF has led to the use of various vasodilators as treatment for patients with CHF. At present, vasodilators are the third-line drugs, following diuretics and digitalis, in the treatment of CHF. However, it was not until the advent of orally administered ACE inhibitors such as captopril and enalapril that vasodilator therapy became widespread in clinical settings.⁶ It has been pointed out that their more favorable effects than those of other vasodilators in long-term therapy for patients with CHF may depend on a reduction in sympathetic activity.^{7,8} There are many pa-

Fig.7. Frequency of VPC and Lown's grade on 24h Holter electrocardiogram

Fig.8. SDC, K, serum creatinine (Cr) before and after enalapril therapy

pers from experimental and clinical viewpoints reporting that ACE inhibitors are beneficial in the treatment of CHF^{4,6-15} Furthermore, they may reduce the fre-

quency of ventricular tachyarrhythmias in patients with severe CHF¹⁶ although it was reported that conventional antiarrhythmic drugs exacerbated these arrhythmias³ The

TABLE II ECG FINDINGS BEFORE AND AFTER ENALAPRIL THERAPY

	Before	After	Paired <i>t</i> -test
*PQ (sec.)	0.207±0.007	0.200±0.007	NS
ventricular rate (beats/min)	87.5±4.1	82.7±4.8	<i>p</i> <0.1
QRS (sec.)	0.166±0.005	0.114±0.005	NS
QT (sec.)	0.415±0.012	0.422±0.014	NS
*QTc (sec.)	0.480±0.007	0.475±0.006	NS

**n*=14 (3 cases with Af excluded), Mean±SEM, NS: No significant difference

precise mechanism for the improvements is not known. It is possible that some of their beneficial effects may be mediated through actions on myocardial sympathetic stimulation.

ACE inhibitors are often used with digitalis in the treatment of CHF, and pharmacokinetic digoxin-captopril interaction has been reported.⁵ Captopril increases serum digoxin concentration by reducing renal clearance of the drug. It has been reported that there is no pharmacokinetic drug interaction between digoxin and enalapril,¹⁷ but we can find no detailed report referring to ECG findings. Therefore, we analyzed the clinical application of enalapril treatment in patients with severe CHF. Our results confirmed that enalapril is very useful for treating patients with severe CHF, as already reported. In summary, 1 month after maintenance therapy with enalapril, patients who had been resistant to the other drugs improved significantly as judged by subjective patient impression and physical findings. Hemodynamically, the PCWP and SVR were significantly reduced, and the CI and LVEF were significantly increased. The PAC decreased significantly while the PRA increased. Plasma and urinary norepinephrine were decreased. The mean serum enalapril concentration time-curves for our patients were similar to those for healthy volunteers reported by others. The mean Tmax of the active metabolite (MK-422) was 4.7 h. No major side effects were observed during the study period. In addition, the frequency of VT using 24 h Holter electrocardiogram showed a significant tendency to decrease after the therapy. Unlike captopril, there is no pharmacokinetic digitalis-enalapril drug interaction. According to the results of a multivariate analysis, the coefficient of deter-

mination of PNE was the highest for the final global improvement rating. This is in accord with the data reported by Cohn and his colleagues.¹⁸

In conclusion, enalapril is recommended for treating patients with severe CHF.

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