EFFECT OF CAPTOPRIL ON CONGESTIVE HEART FAILURE

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- 1) Captopril was orally administered in a dose of 12.5 mg to 12 patients with congestive heart failure to follow changes in its blood concentration and determine changes in clinical test values.
- 2) The blood concentration of captopril reached its peak in 2 h after medication, the mean value being 274 ng/ml and the half-life 3.16h. The T_{max} and $T^{1/2}$ were found to be extended as compared with those of normal humans and hypertensive patients that had been reported. No significant differences were noted between Group I of mild cases and Group II of serious cases.
- 3) Following administration of captopril, a rise in angiotensin I and renin activity and a reduction in aldosterone were noted. These were found to be correlated or inversely correlated with the changes in the blood concentration of captopril. Greater changes were noted in Group II than in Group I. All clinical test values in each group tended to return to the control value 6h after the administration.

CAPTOPRIL (Captopril®)¹ was developed originally as a therapeutic agent for essential hypertension which acts on the renin-angiotensin-aldosterone system (RAA system)²⁻⁶. Its mechanism of action is considered to consist of inhibiting the angiotensin I converting enzyme⁷, suppressing formation of angiotensin II, which is a physiologically hypertensive substance, and exhibiting a hypotensive effect by reducing systemic vascular resistance⁸. It has a tendency to increase the flow of blood in the brain and kidneys without causing any reduction in the flow of blood in other principal organs. It has been shown to act by causing the moderate excretion of sodium due to reduction in secretion of aldosterone caused by suppression of formation of angiotensin II⁹.

Captopril has been shown in a number of

recent reports¹⁰⁻¹⁷ to be effective for congestive heart failure in the chronic as well as acute stage. However, captopril is considered to be absorbed and excreted in patients with congestive heart failure more slowly than in normal humans. In the present study, with a view to (1) looking into the *in vivo* pharmacokinetics of captopril and its association with humoral factors and (2) making a comparative study of its pharmacokinetics in normal humans and hypertensive patients with that in patients with congestive heart failure, we orally administered a single dose of captopril to patients with moderate to serious congestive heart failure and followed the changes made with time. A report on this study is presented.

1. Study Subjects

We studied 12 consecutive patients with congestive heart failure (eight male patients and four female patients, mean age: 60 years) who were hospitalized at Department of Cardiovascular Medicine, Hokkaido Uni-

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versity and Sapporo Kosei Hospital (Table I). The etiology of their heart failure was mitral regurgitation in 9 cases, dilated cardiomyopathy in 2 cases, mitral regurgitation and aortic regurgitation in 1 case, New York Heart Association (NYHA) functional class II in 7 cases, class III in 3 cases and class IV in 2 cases. Left ventricular dysfunction was

TABLE I CLINICAL PROFILE OF STUDY POPULATION

Case No.	Age	Sex	Diagnosis	NYHA
1	50	M	DCM	II
2	61	M	MR	II
3	45	F	MR	II
4	43	F	MR	II
5	51	F	MR	II
6	70	M	MR	II
7	72	M	DCM	II
8	56	F	MR	III
9	66	M	MR	III
10	66	M	MR	III
11	61	M	MR	IV
12	79	M	MR/AR	IV

DCM=Idiopathic Dilated Cardiomyopathy

MR=Mitral Regurgitation

AR=Aortic Regurgitation

confirmed in all cases by cardiac catheterization, echocardiography and radionuclide studies. All the patients had already been administered diuretics, digitalis or vasodilators but no angiotensin converting enzyme inhibitors, and they had been kept in a stable condition for at least one week. The test subjects were classified according to the New York Heart Association into two groups, Group I comprising cases of NYHA class II and Group II cases of NYHA class III and IV.

2. Method

After all vasodilators, diuretics and positive inotropic agents had been discontinued 24 hours before commencement of the test, captopril was orally administered in a single dose of 12.5 mg on a fasting state at rest. Blood was collected before medication and 30, 60, 90 min, 2, 4 and 6 h after its administration and centrifuged in a chilled state at 4°C. The plasma thus obtained was kept frozen at -20°C. Each sample of blood was 15 ml.

3. Determination of Blood Concentration of Captopril

Concentrations of captopril were determined by the HPLC method using MDCM

TABLE II METHOD OF DETERMINATION OF CLINICAL TEST VALUES

Test item	Method	Standard value
Renin activity	RIA solid phase method	0.3-4.0 ng/ml/h
Adrenaline	HPLC (THI method)	<120 pg/ml
Noradrenaline	HPLC (THI method)	40-350 pg/ml
Angiotensin I	RIA, DCC method	<220 pg/ml
Angiotensin II	RIA, DCC method	<60 pg/ml
Aldosterone	RIA, PEG method	4-18 ng/ml

TABLE III CLINICAL TEST VALUES OBTAINED BEFORE ADMINISTRATION OF CAPTOPRIL

Test item	Group I	Group II	Mean
Renin activity (ng/ml/h)	0.9±1.1	8.0±11.4	3.5±7.2
Adrenaline (pg/ml)	46.6±61.7	57.8±42.6	50.6±53.5
Noradrenaline (pg/ml)	257±155	467±284	334±223
Angiotensin I (pg/ml)	47±22	283±331	133±218
Angiotensin II (pg/ml)	30±15	124±164	64±102
Aldosterone (ng/ml)	16.1±14.1	21.8±20.0	18.2±15.7

Fig. 1. Serum Concentration of captopril in Patients with Congestive Heart Failure (Oral administration of 12.5 mg).

[N- (6,7-methylenedioxy-4-methyl-3-coumarinyl) maleimide] as color reagent. Details of this method are as follows:

Column: μ -Bondapack C18

Mobile phase: Acetonitrile : water : acetic acid = 37 : 6 : 1

Detection: 355 nm for excitation, 435 nm for determination. The limit of determination was 2 ng/ml.

4. Determination Clinical Test Values

The methods of determination of clinical test values and standard values are shown in Table II.

5. Statistical Tests

All values were expressed as mean $\pm$ standard deviation. Paired Student's t-test was applied to compare the results and p values less than of 5% were considered significant.

RESULTS

The clinical test values obtained before administration of captopril are shown in Table III. Blood concentrations of captopril

and clinical test values were compared in terms of their mean values of Groups I and II and the entirety.

1. Blood Concentration of Captopril

The changes in the blood concentration of captopril are shown in Fig. 1. The concentration of captopril reached its peak 2 h after administration of the drug, mean values of which were 281 ± 116 ng/ml in Group I, 261 ± 151 ng/ml in Group II and 274 ± 122 ng/ml in the entirety. Thereafter these values declined with time, and no significant difference was noted between Groups I and II. $T^{1/2}$ was calculated on the basis of the values obtained 2 h following medication, mean values of which were 2.79 h in Group I, 4.00 h in Group II and 3.16 h in the entirety. The time of decline in serious cases tended to be greater.

2. Humoral Factors

The changes in the blood concentration of angiotensin I and II are shown in Fig. 2-a and b. The blood concentration of angiotensin I reached its peak 2 h after medication and then declined. This tenden-

Fig. 2. Changes of each humoral factors with group I (■), group II (▲) and mean (●).

cy was found to be correlated with the blood concentration of captopril. The changes were greater in Group II than in Group I. Practically no change was noted in the blood concentration of angiotensin II up to 6 h after medication. The plasma renin activity (PRA) attained its peak value 90 min to 2 h after medication and then decreased with time (Fig. 2-c). This tendency also paralleled the changes in the blood concentration of captopril. Comparison of Group I with Group II showed greater changes in Group II. The hourly changes in the plasma concentration of adrenaline and noradrenaline are shown in Fig. 2-d and e, where no significant changes due to administration of

captopril were noted. The plasma concentration of aldosterone fell to a minimum 2 h after medication but rose thereafter as shown in Fig. 2-f.

DISCUSSION

It is well known that vasodilator therapy is an effective treatment of congestive heart failure. Majid et al¹⁹ were the first to try vasodilators to treat serious heart failure and achieved remarkably beneficial effects from the use of phentolamine, an α blocker. Thereafter various kinds of vasodilators have been used for patients with congestive heart failure and their usefulness has been

documented^{20,21} Since captopril, which is an angiotensin converting enzyme inhibitor (ACE inhibitor), also has a vasodilating action in arteries as well as veins and works against aldosterone, it has been reported to have been used for the treatment of hypertension and congestive heart failure with beneficial effect^{22,23}

We administered orally 12.5 mg of captopril to patients with congestive heart failure and determined changes in the blood concentration of captopril and various humoral factors up to 6 h after medication. The blood concentration of captopril reached its peak 2 h after medication and then declined with time. As compared to the T_{max} in the case of normal humans, which is 0.93 h²⁴ that in the case of congestive heart failure was found to be greater. While it has been reported that in the case of hypertensive patients T_{max} was 0.98 h and $T^{1/2}$ 0.66 h²⁵ these parameters in the case of patients with congestive heart failure were found longer than those of hypertensive patients. Therefore, in serious case of congestive heart failure with long term administration the concentration of captopril in the blood was found to be much greater. It is thus important to consider the patient's background. Whether this was associated with the reduction in the renal blood flow was not investigated in the present study.

Robertson et al^{26,27} reported that two hours after administration of captopril in hypertension, a reduction in aldosterone and angiotensin II and a rise in PRA and angiotensin I occurred. They also reported that five weeks after captopril was administered in serious heart failure, PRA rose and angiotensin II, aldosterone and noradrenaline fell. In our determination in the present study, a rise in angiotensin I and PRA and reduction in aldosterone were also noted. These tendencies were found to be correlated or inversely correlated with the blood concentration of captopril. The RAA system may be said to respond to rises in the blood concentration of captopril in real time. However, in our study noradrenaline did not show any definite tendency.

It has been reported²⁸ that a single dose of captopril fell short of producing any significant correlation between improvement of kinetics of blood circulation and the rate of

change in the concentration of noradrenaline. This may be accounted for by acute impairment of the nervous and humoral responses in the case of serious heart failure.

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