Original Article

Long-Term Plasma Levels and Dose Modulation of Alacepril in Patients with Chronic Renal Failure

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Because most angiotensin-converting enzyme inhibitors are excreted into urine, any decrease in renal function increases the plasma levels of these drugs. This study was designed to investigate the appropriate doses of alacepril in patients with chronic renal failure. The total plasma concentration of captopril, an active metabolite of alacepril, was measured in 47 patients with chronic renal failure or normal renal function. Fifteen patients on chronic hemodialysis were also enrolled in this study. In patients treated with 12.5, 25 and 50 mg alacepril, the plasma concentration of captopril was linearly correlated with serum creatinine and creatinine clearance (Ccr). There was an approximately 40% decrease of the plasma captopril concentration after 4 h of hemodialysis. Among patients treated with 25 or 50 mg alacepril for 4.5 years, the plasma concentration of captopril gradually increased along with an increase in serum creatinine (from 2.0 to 5.8, and from 1.9 to 7.1 mg/dL, respectively). Although the plasma concentration of captopril was higher in the 50 mg group, the increase in serum creatinine during this period was not different between the two groups. The plasma aldosterone concentration did not increase during this period. These data suggest that alacepril should be reduced from 50 to 25 and 12.5 mg/day in patients with a serum creatinine level of greater than 2–3 and 4–6 mg/dL, respectively, in order to maintain a plasma level equivalent to that in subjects with normal renal function receiving 50 mg/day alacepril. For patients on chronic hemodialysis, 12.5 mg alacepril is the appropriate dose. (*Hypertens Res* 2008; 31: 29–36)

***Key Words*: angiotensin-converting enzyme inhibitor, chronic renal failure, dose modulation, hypertension**

Introduction

Angiotensin-converting enzyme (ACE) inhibitors exert renoprotective effects mainly by decreasing intraglomerular pressure and, subsequently, proteinuria (*1*, *2*). The widespread use of ACE inhibitors has revolutionized the treatment of patients with chronic kidney disease (CKD) (*3–6*). Proteinuria and blood pressure are the main determinants of the progression of CKD, and thus the appropriate doses of ACE inhibitors are determined by the effects on proteinuria and blood pressure, by safety (*i.e.*, lack of side effects), and by cost (*7–10*). Most of the ACE inhibitors are excreted into urine, and their doses have to be titrated depending upon the renal function. ACE inhibitors suppress the synthesis of angiotensin II and aldosterone, which can sometimes induce hyperkalemia in patients with reduced renal function (*11*). Therefore, it is generally recommended that the doses be reduced under certain circum-

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stances, especially in patients with a serum creatinine level of more than 2.5 mg/dL, to avoid excess doses and the resultant hyperkalemia (*12*).

However, it is very difficult to use ACE inhibitors in patients with moderate to severe renal failure. The decrease in serum ACE activity by the administration of ACE does not correspond to the renoprotective effect of ACE inhibitors but is known to be a marker of drug regimen compliance (*13*). Plasma levels of ACE inhibitors have been examined to determine the appropriate concentrations of ACE inhibitors (*14–17*). However, the plasma concentration of ACE inhibitors has been studied mainly after short-term administration. It is not known whether the plasma concentration of ACE inhibitors is stable after long-term administration, especially in patients with chronic renal failure.

ACE inhibitors are divided into two groups according to the presence of sulfhydryl groups in the compound. Alacepril and captopril belong to the sulfhydryl-containing group. Alacepril (DU-1219) is desacetylated to form desacetylalacepril (DU-1227) and is then converted to captopril (*18–20*), an active metabolite of alacepril. However, DU-1227 is readily transferred to the vascular wall and also has a direct effect on sympathetic nerve activity, such that alacepril has a 1.5 to 2 times longer antihypertensive effect than captopril (*18*).

The initial aim of the present study was to investigate whether the plasma concentration of captopril is stable after long-term administration of alacepril in patients with CKD, and to determine whether the decline of renal function over time affects the plasma concentration of captopril. The ultimate goal of our investigation was to determine the appropriate doses of alacepril in patients with chronic renal failure. To accomplish these goals, we examined the plasma concentration of captopril in CKD patients taking alacepril for more than 1 year.

Methods

Patients

The study group included 47 patients (25 males and 22 females) with CKD who had been treated with alacepril for more than 1 year. All patients were diagnosed as having hypertension (hypertension without proteinuria: 4 patients) or chronic glomerulonephritis (immunoglobulin A [IgA] and other primary nephropathy, 22 patients; diabetic nephropathy, 11 patients; hypertensive nephrosclerosis, 7 patients; amyloidosis, 3 patients). The percentage of patients with hypertensive nephrosclerosis in our study was lower than the estimated percentage of such individuals in the general population in the United States (*21*). All of our patients had a normal or reduced renal function. In some patients, long-term follow-up was performed to examine the relationship between the gradual decrease in renal function and the increase in plasma level of captopril. Additionally, 15 patients on chronic hemodialysis were enrolled. These patients were on 4-h hemodialysis three times per week. The dialyzers used were polysulfon and polyacrylonitrile membranes with a surface area of 1.2–1.4 m^2. Blood flow was 180–220 mL/min and dialysate flow was 500 mL/min.

Table 1. Baseline Characteristics of the Patients

	Start	End
No. of patients (male/female)	47 (25/22)	
Age (years old)	55±2	
Height (cm)	158±1	
Weight (kg)	55±1	
Period (months)	25.0±1.7	
Serum creatinine (mg/dL)	2.1±0.1	3.6±0.3
Creatinine clearance (mL/min/1.73 m^2)	42.5±4.9	31.9±4.2
Serum potassium (mEq/L)	4.7±0.1	5.0±0.1
Systolic blood pressure (mmHg)	147±2	143±3
Diastolic blood pressure (mmHg)	78±2	75±2
Diagnosis		
Hypertension without proteinuria	4	
Hypertensive nephrosclerosis	7	
Chronic glomerulonephritis	22	
Diabetic nephropathy	11	
Amyloidosis	3	

Data are expressed as mean±SEM. Start: start of administration of alacepril; End: end of administration of alacepril.

Alacepril Dosing and Laboratory Measurements

Since a decline of renal function causes an increase in the plasma levels of ACE inhibitors, the doses of alacepril were reduced according to the reduction in renal function. The usual doses of alacepril were 50 mg/day in patients with a serum creatinine level of less than 2 mg/dL, 25 mg/day in patients with a serum creatinine level of 2–5 mg/dL, and 12.5 mg/day in patients with a serum creatinine level greater than 5 mg/dL. However, the doses of alacepril were further adjusted according to blood pressure response.

Serum levels of creatinine, urea nitrogen (BUN), sodium, potassium, chloride, calcium, and phosphorus were measured using an automatic analyzer (Hitachi, Tokyo, Japan). Renal function was measured by serum creatinine and creatinine clearance (Ccr). Ccr was calculated using the Cockcroft-Gault formula (*22*), with 0.85 used as a multiplier in the female patients:

$$Ccr = (140 - Age) \times BW/(72 \times S\text{-}Cr)$$

Age, years old; BW, body weight (kg); S-Cr, serum creatinine (mg/dL).

The plasma aldosterone and angiotensin II concentrations (PAC and AT2, respectively) were repeatedly measured in certain patients to check for the aldosterone escape phenomenon. PAC and AT2 were measured by radioimmunoassay (SRL, Tokyo, Japan). Serum ACE activity was also mea-

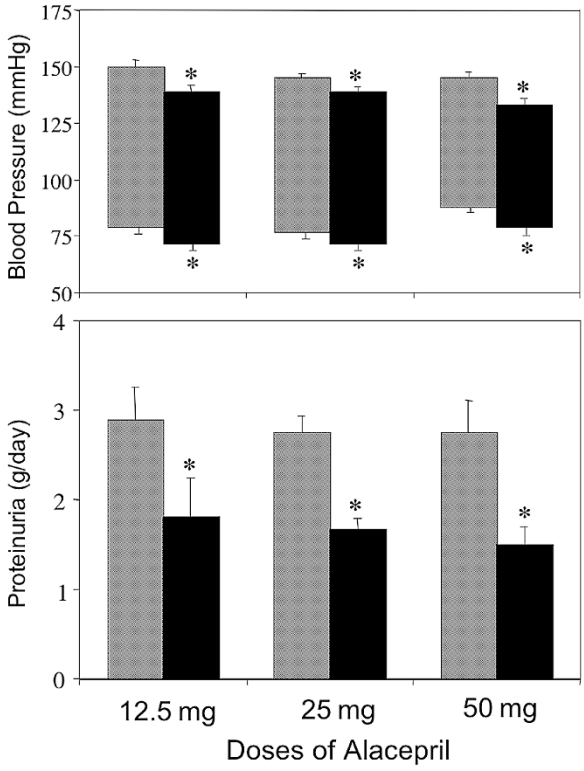

Fig. 1. *Effects of alacepril on blood pressure and proteinuria. Alacepril decreased both systolic and diastolic blood pressure (SBP and DBP; upper panel). Effects of 50 mg alacepril were greater than those of 12.5 and 25 mg. Alacepril also reduced proteinuria (lower panel). 12.5, 25 and 50 mg alacepril decreased proteinuria by 37.3%, 39.3% and 45.8%, respectively. The gray and black bars represent pre- and post-administration of alacepril, respectively. *p < 0.05 vs. pre-administration.*

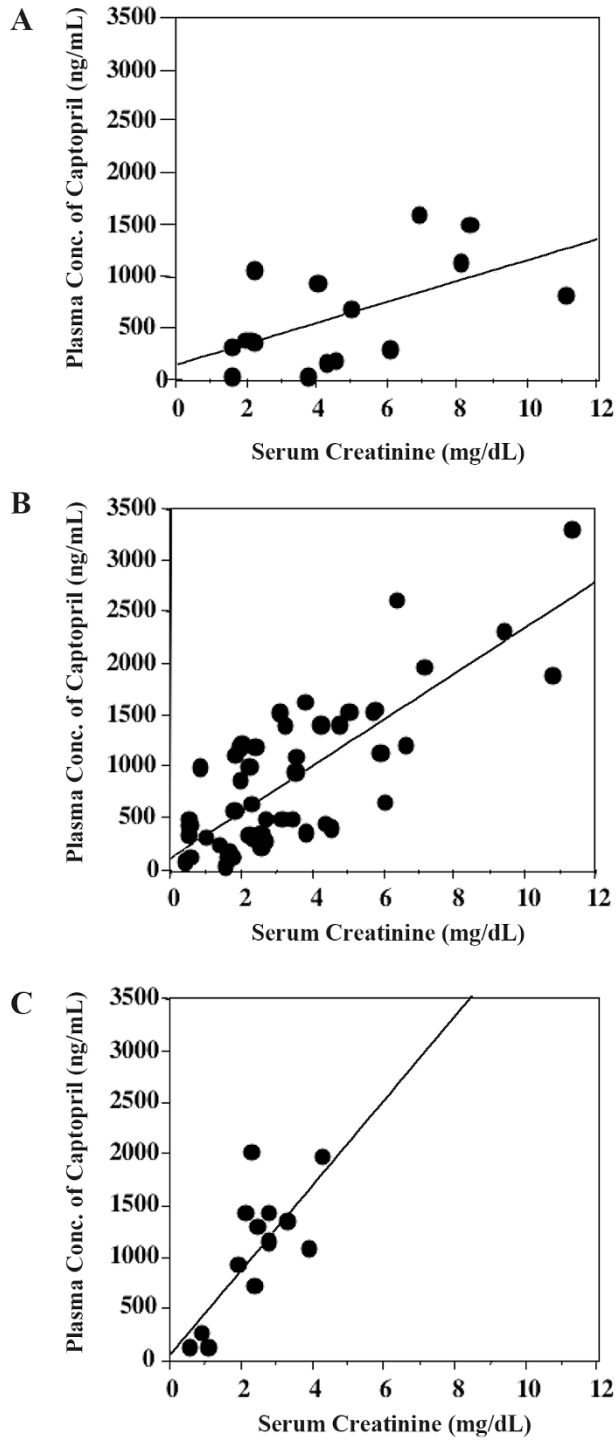

Fig. 2. *Relationship between the plasma concentration of captopril (y) and serum creatinine (x) with different doses of alacepril (A: 12.5; B: 25; and C: 50 mg). In patients treated with alacepril, the plasma concentration of captopril increased with the increase in serum creatinine. The slope was larger at higher doses of alacepril. A: $y = 101x + 146$, $r^2 = 0.32$, $p < 0.01$; B: $y = 224x + 112$, $r^2 = 0.61$, $p < 0.001$; C: $y = 427x + 55$, $r^2 = 0.56$, $p < 0.001$.*

sured. Since insertion/deletion (I/D) polymorphism of the ACE gene affects the renoprotective effects of ACE inhibitors, ACE gene polymorphism was examined as described previously (*23*, *24*).

Alacepril is metabolized to desacetylalacepril and then to captopril, which is the active form of alacepril (*18–20*). Therefore, the plasma concentration of captopril was measured. Captopril exists in both free and protein-combined forms. We measured the total (free plus protein-combined forms) concentration of captopril by high-performance liquid chromatography (*25*). Plasma levels of captopril were measured 2 h after taking alacepril in the morning. The assay of the plasma concentration of captopril was performed at the Teijin Laboratories (Tokyo, Japan). The protocol of this study was reviewed and approved by the Committee on Ethics of the Kumamoto University Graduate School of Medical Sciences (# 650). The details of the examination were explained to and informed consent was obtained from all patients.

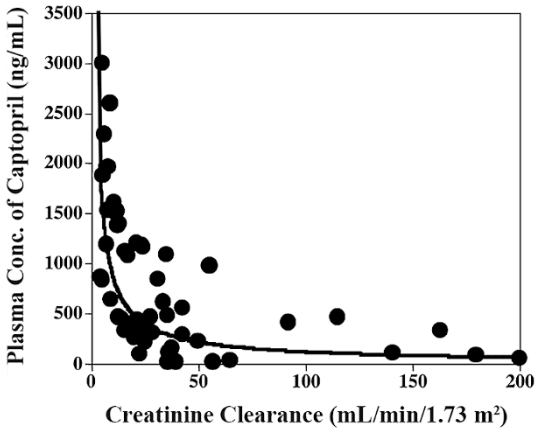

Fig. 3. *Relationship between the plasma concentration of captopril and creatinine clearance in patients treated with 25 mg alacepril. Creatinine clearance was calculated by the Cockcroft-Gault formula as described in the text. There was a close relationship between the plasma concentration of captopril (y) and creatinine clearance (x): $y = exp\ (8.735) \times x^{-0.856}$, $r^2 = 0.41$.*

Statistics

Data are expressed as the means±SD or SEM as appropriate. Results were analyzed using *t*-test or analysis of variance (ANOVA) and Dunnett's test for multiple comparisons. Data were analyzed using Dr. SPSS II software (SPSS, Tokyo, Japan). Values of $p<0.05$ were considered to indicate statistical significance.

Results

The patient baseline characteristics are summarized in Table 1. The mean age of the patients was 55±16 (mean±SD) years and the mean body weight was 55±10 kg. The mean period of alacepril treatment was 25.0±11.7 months. The mean serum potassium level was changed from 4.7±0.6 to 5.0±0.7 mEq/L, while the serum creatinine level was increased from 2.1±0.7 to 3.6±1.9 mg/dL by the administration of alacepril. Hyperkalemia of more than 5.6 mEq/L appeared in 6.7% and 9.7% of the patients administered 50 and 25 mg alacepril, respectively. It is not clear whether the changes in serum potassium concentration were due to the decline of renal function or to the administration of alacepril. However, the observed increase in serum potassium was approximately that expected in a patient with compromised renal function. None of the patients had dry cough that necessitated withdrawal of alacepril.

The effects of alacepril on blood pressure and proteinuria were examined. Alacepril significantly decreased both systolic and diastolic blood pressure (SBP and DBP) and urinary protein excretion. The effects of 50 mg alacepril on blood pressure and proteinuria were greater than those of 25 and 12.5 mg alacepril (Fig. 1).

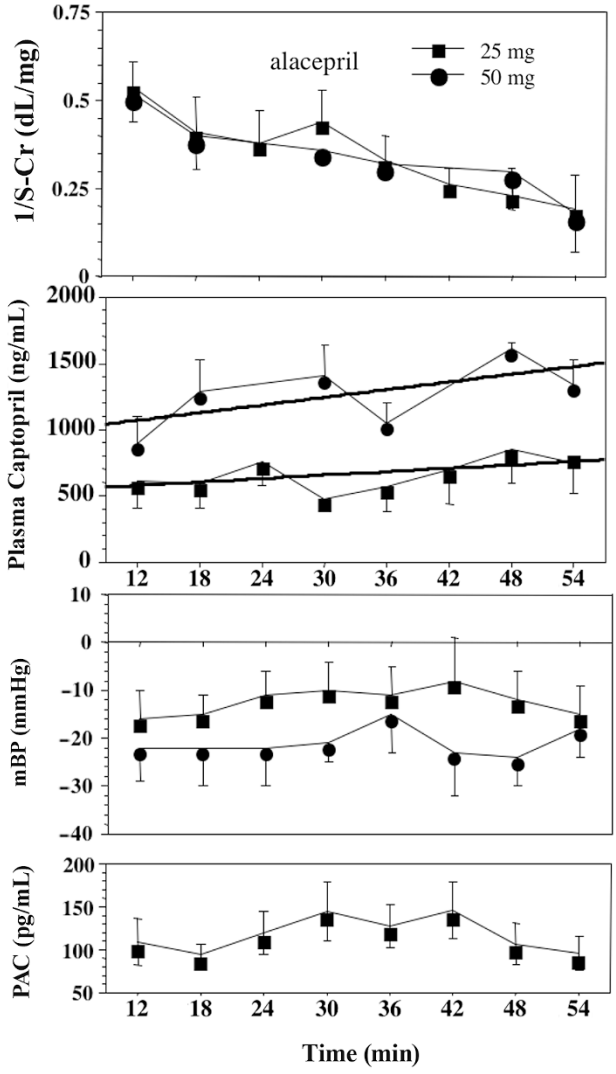

Fig. 4. *Long-term changes in the plasma concentration of captopril and plasma concentration of aldosterone with a decrease in renal function in patients treated with 25 or 50 mg alacepril. The decrease in the reciprocal of serum creatinine with time was almost the same with 25 and 50 mg alacepril (7 and 5 patients, respectively, upper panel). The increase in the plasma concentration of captopril with time was also the same between 25 and 50 mg alacepril (upper middle panel). The decrease in mean blood pressure (mBP) was larger by 50 mg than by 25 mg alacepril (lower middle panel). The plasma concentration of aldosterone (PAC) in patients treated with 25 mg alacepril did not increase with time, suggesting the lack of aldosterone escape in these patients (lower panel).*

At a dose of 25 mg/day alacepril, the plasma concentration of captopril ranged from 123 to 3,010 mg/dL, while the serum

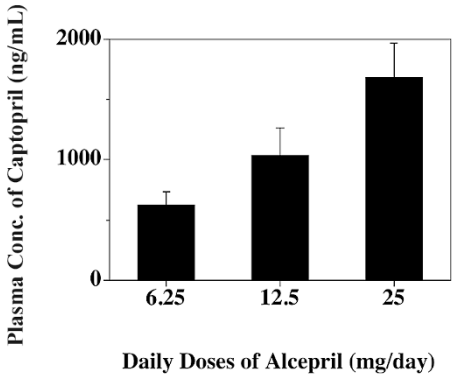

Fig. 5. *Plasma concentration of captopril in patients with Ccr of less than 10 mL/min treated with alacepril. Patients with severe renal failure but without hemodialysis were treated with different doses of alacepril. The plasma concentration of captopril increased with the increase in doses of alacepril.*

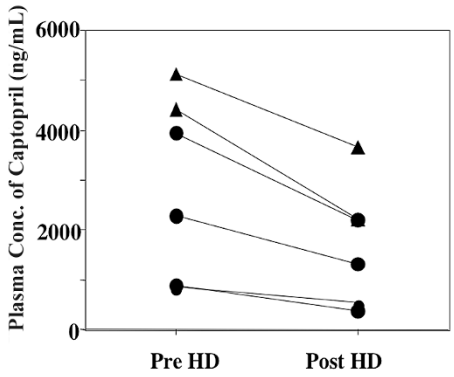

Fig. 6. *The changes in plasma concentration of captopril in chronic hemodialysis patients treated with alacepril. The plasma concentration of captopril was decreased by 40% after 4-h hemodialysis. Triangles and circles indicate patients receiving 50 and 25 mg/day alacepril, respectively. HD, hemodialysis.*

creatinine levels ranged from 0.4 to 11.3 mg/dL. There was a linear relationship between the serum creatinine levels and plasma concentration of captopril (r^2=0.61, p<0.001; Fig. 2). The same linear relationship was observed for 12.5 mg/day and 50 mg/day alacepril treatment (r^2=0.32, p<0.01 and r^2=0.56, p<0.001, respectively; Fig. 2). The increase in the plasma levels of captopril was largely in proportion to the doses of alacepril. At a dose of 50 mg/day, the plasma concentration of captopril in subjects with normal renal function was 623 mg/dL (*26*). To maintain an equivalent plasma concentration of captopril in patients with renal failure, the dose of alacepril has to be reduced to 25 mg/day at a serum creatinine level of 2–3 mg/dL. The plasma concentration of captopril also exhibited a close relationship with the calculated Ccr (r^2=0.41, p<0.001, alacepril 25 mg; Fig. 3). Serum creatinine of 2–3 mg/dL was calculated to correspond to Ccr of 30–20 mL/min by the Cockcroft-Gault formula ($Ccr = 62.0 \times Cr^{-1.10}$, r^2=0.911, p<0.001). To maintain a roughly equivalent plasma concentration of captopril in patients with severe renal failure, alacepril should be reduced to 12.5 mg at a serum creatinine level of 4–6 mg/dL (Ccr: 15–10 mL/min).

Next, long-term changes in the plasma concentration of captopril were examined in 12 patients who had taken alacepril (25 mg in 7 patients and 50 mg in 5 patients). Although the plasma concentration of captopril differed according to the serum creatinine levels, a gradual increase in serum creatinine from 2.0 to 5.8 mg/dL over 54 months caused an increase in the plasma concentration of captopril from 608 to 744 ng/mL in seven patients receiving 25 mg/day alacepril (Fig. 4). Although the plasma concentration of captopril was two-fold higher in patients receiving 50 mg alacepril than in those administered 25 mg alacepril, 25 and 50 mg alacepril resulted in almost the same decrease in renal function in patients with a mean serum creatinine greater than 2 mg/dL (Fig. 4). PAC was not increased in these patients, suggesting an absence of the aldosterone escape phenomenon (Fig. 4).

In patients with a Ccr of less than 10 mL/min who were administered 6.25, 12.5 or 25 mg/day alacepril, the plasma concentrations of captopril were 621±99 (mean±SEM), 1,055±190, and 1,679±275 ng/mL, respectively (Fig. 5). At a dose of 25 mg/day alacepril, the mean plasma concentration of captopril was 1,993±725 ng/mL in patients on chronic hemodialysis, and it decreased to 1,115±415 ng/mL after 4 h of hemodialysis (Fig. 6). The plasma concentration of captopril in patients on chronic hemodialysis increased with the increase in the daily dose (Fig. 7).

The relationship between the renin-angiotensin-aldosterone system and ACE gene polymorphism during alacepril treatment was examined in 29 patients who had been treated with 25 mg alacepril. PAC, AT2 and serum ACE activity were examined as markers of the renin-angiotensin-aldosterone system. During 25 mg alacepril treatment, PAC and AT2 were lowest in patients of the DD genotype and highest in patients of the II genotype (Fig. 8). In contrast, serum ACE activity was highest in the DD and lowest in the II genotype (Fig. 8). There was an inverse relationship between ACE activity and the PAC in all three ACE genotypes.

Discussion

ACE inhibitors and angiotensin II receptor blockers are the most powerful renoprotective agents in patients with CKD (*3–6*, *27*). The results of the present study demonstrate the safety of long-term administration of the ACE inhibitor alacepril in patients with end-stage CKD. The appropriate dose for patients with chronic renal failure differs depending on their renal function. In order to maintain a plasma level of captopril equivalent to that in subjects with normal renal function

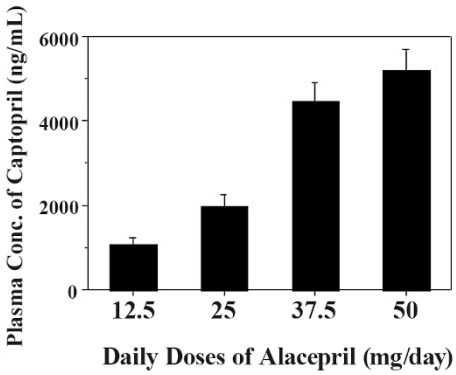

Fig. 7. *Plasma concentration of captopril in hemodialysis patients treated with alacepril. Increases in the daily dose of alacepril were associated with an increase in the plasma levels of captopril in patients on chronic hemodialysis. The numbers of patients treated with 12.5, 25, 37.5 and 50 mg alacepril were 3, 8, 2, and 2, respectively.*

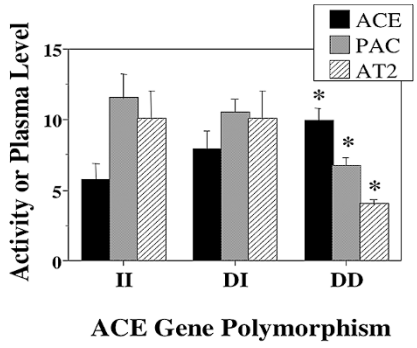

Fig. 8. *Serum ACE activity (IU/L/37°C), plasma aldosterone (pg/mL) and angiotensin II (pg/mL) concentration during 25 mg alacepril treatment in patients with the II, DI and DD ACE genotypes. 29 patients who had been treated with 25 mg alacepril were enrolled in this study (II: 10 patients; DI: 13 patients; DD: 6 patients). Although serum ACE activity was highest in patients with the DD genotype, the plasma aldosterone and angiotensin II concentration was lowest in patients with the DD genotype. The plasma aldosterone concentration is expressed as 1/10. Serum ACE activity in patients with the DD genotype was significantly higher than that in patients with the II genotype (*$p < 0.05$). The plasma aldosterone and angiotensin II concentrations in patients with the DD genotype were significantly lower than those in patients with the II and DI genotypes (*$p < 0.05$). PAC, plasma aldosterone level; AT2, plasma angiotensin II concentration.*

receiving 50 mg/day alacepril, the dose of alacepril should be reduced from 50 to 25 and 12.5 mg/day at a serum creatinine level of 2–3 and 4–6 mg/dL, respectively (Ccr of 30–20 and 15–10 mL/min, respectively). A dose of 12.5 mg alacepril after hemodialysis is sufficient in patients on chronic hemodialysis.

Full-dose administration of ACE inhibitors is recommended for adequate renoprotection. An appropriate dose of alacepril for achieving satisfactory renoprotective effects is 50–100 mg/day in subjects with normal renal function. Alacepril (DU-1219) is converted to desacetylalacepril (DU-1227) and then to captopril (*18–20*). Since captopril is an active metabolite of alacepril, we measured total captopril concentration in plasma. The peak plasma concentration of captopril after the administration of 50 mg alacepril is 623 ng/mL and occurs at 1 h in healthy subjects (*26*). In 9 patients with chronic renal failure and a mean serum creatinine of 4.4 mg/dL, the peak plasma concentration of captopril after the administration of 50 mg alacepril was 1,310 ng/mL (*28*). Since alacepril is excreted into urine after the conversion to captopril, the plasma concentration of captopril increases in accord with the decrease in renal function. Patients with reduced renal function may need a greater inhibition of the renin-angiotensin-aldosterone system than patients with normal renal function. Nevertheless, a reduction in renal function usually requires a reduction of the dose of ACE inhibitors. The mean plasma level of captopril in patients treated with 25 mg alacepril and with a serum creatinine level of 2 mg/dL was 612 ng/mL in our study (Fig. 2B), which is almost the same level seen in healthy subjects administered 50 mg alacepril (*26*). Taken together, these findings indicate that the dose of alacepril should be reduced to 25 mg/day in patients with serum creatinine levels greater than 2–3 mg/dL (Ccr of 30–20 mL/min) to safely maintain a plasma concentration of captopril equivalent to that in subjects with normal renal function taking 50 mg/day alacepril.

In patients with a Ccr of less than 10 mL/min, administration of 6.25, 12.5 and 25 mg alacepril resulted in mean plasma levels of captopril of 621, 1,055, and 1,679 ng/mL, respectively. This means that only 1/8 of the dose of alacepril used for patients with normal renal function is required to maintain an equivalent plasma level in patients with a Ccr of less than 10 mL/min. Even with sustained administration of 25 mg/day or 50 mg/day alacepril in patients with reduced renal function, the reduction of renal function did not differ much between the two doses in our study (Fig. 4). To receive larger renoprotective effects with larger doses of alacepril, long-term therapy may be required. If the progression of decline in renal function is rapid, the chance to receive such a larger renoprotective effect would be small. The progression speed is one of the key points in choosing an appropriate dose of alacepril. Since the differences of the effects of 50 and 25 mg alacepril on blood pressure and proteinuria were small (Fig. 1), the reduction of doses of alacepril in patients with reduced renal function would be safe. Considering the plasma concentration of alacepril (captopril), these data suggest that 25 and 12.5 mg alacepril may be sufficient and appropriate for patients with serum creatinine levels of greater than 2–3 and 4–6 mg/dL, respectively.

Severe side effects were not observed in the current study. Since alacepril suppresses the renin-angiotensin-aldosterone system, some subjects may develop metabolic acidosis and subsequent hyperkalemia and require careful follow-up (*11*). Only a few subjects developed hyperkalemia in our study. Mean serum potassium increased from 4.7 to 5.0 mEq/L following alacepril administration. However, this increase was attributed to the decrease in renal function rather than to the direct effect of alacepril itself. Even with a slight increase in the plasma potassium concentration, the improvement of metabolic acidosis by sodium bicarbonate would decrease the plasma potassium concentration. However, sodium bicarbonate was not administered to our patients.

The PAC differed according to ACE gene polymorphism. Although the serum ACE level was highest in the patients with the DD genotype, the PAC was lowest in these patients (Fig. 8). The AT2 was also lowest in the DD patients (Fig. 8). Although the precise mechanisms by which the DD genotype results in low AT2 and PAC are still unclear, it may be that low sodium intake, angiotensin-converting enzyme 2 (ACE2), or some other mechanism blunts the renin-angiotensin-aldosterone system (*29*, *30*). Considering the small renoprotective effects of ACE inhibitors observed in DD patients, the PAC cannot be considered a good marker of the efficacy of ACE inhibitor therapy. The aldosterone escape phenomenon has been identified as the reason for the decline in the renoprotective effects of the ACE inhibitors after several years' administration (*21*, *31*). In a 4.5-year follow-up of our patients, the plasma concentration of captopril increased with increases in the plasma creatinine level from 2 to 6 mg/dL (Fig. 4). PAC did not increase during this period, suggesting the absence of aldosterone escape in our patients. Although reduction of alacepril may be necessary in patients with a serum creatinine level of greater than 2 mg/dL, a further reduction may not be necessary to avoid aldosterone escape. Further long-term study to determine the relationship between aldosterone escape and plasma levels of captopril may be required.

Since the plasma concentration of captopril was decreased by 40% with 4-h hemodialysis (Fig. 6), 12.5 mg alacepril can be administered after hemodialysis to maintain the plasma captopril concentration in patients on chronic hemodialysis.

In summary, the present data show that the alacepril dose can be reduced from 50 to 25 and 12.5 mg/day in patients with serum creatinine levels of greater than 2–3 and 4–6 mg/dL (Ccr of 30–20 and 15–10 mL/min), respectively, in order to maintain a plasma level equivalent to that in subjects with normal renal function receiving 50 mg/day alacepril. For patients on chronic hemodialysis, 12.5 mg alacepril would be appropriate dose.

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