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# Comparison of Imidapril and Alacepril for the Effects of Lowering Blood Pressure in Hypertensive Patients

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We compared blood pressure lowering effects between imidapril of 5 mg and alacepril of 25 mg. The subjects were 11 hypertensive Japanese patients (6 males and 5 females) aged 51-87 years with the mean±standard deviation of 73±10 years, and their blood pressure had been controlled well by anti-hypertensive agents including imidapril of 5 mg. After we changed the administration of imidapril of 5 mg once a day to that of alacepril of 25 mg once a day, without any changes of other anti-hypertensive agents, the systolic blood pressure (mean±stan dard deviation) in patients significantly increased from 130±7.5 mmHg to 140±11 mmHg ($p$<0.0005). The present study suggests that imidapril of 5 mg is stronger than alacepril of 25 mg for lowering blood pressure in patients with hypertension.

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**Keywords:** Angiotensin converting enzyme inhibitor; Dose; Hypertension

## Introduction

The role of angiotensin-converting enzyme (ACE) inhibitors for the treatment of hypertension has been well established, and ACE inhibitors are widely used in the management of hypertension. There are more than ten ACE inhibitors, but the difference in their effects is not clear.

Both imidapril and alacepril are ACE inhibitors made in Japan. However, there is no report about the difference in blood pressure lowering effect of these agents based on the direct comparison study. We compared the blood pressure (BP) lowering effects between imidapril of 5 mg and alacepril of 25 mg in the same patients.

## Materials and Methods

The subjects were 11 hypertensive Japanese patients (6 males and 5 females) aged 51-87 years with the mean±standard deviation of 73±10 years. The profiles of these patients are summarized in Table 1. Complications other than hypertension were as follows: old cerebral infarction in 3 patients; old myocardial infarction without heart failure in 1; gout in 1; and hypercholesterolemia in 1 (Table 1). Their blood pressures had been controlled for more than 1 year by imidapril of 5 mg alone or imidapril of 5 mg with other anti-hypertensive agents including calcium channel blocker, a-blocker, and diuretics (Table 2). In these patients, only imidapril of 5 mg once a day was changed to alacepril of 25 mg once a day. Blood pressure was measured at supine position after at least 30-minute rest at outpatient clinic. In these patients, BP, physical data, and blood test data measured before and 4 weeks after the change of

**Table 1.** Patients' profiles

| Age (years) | Sex | Diagnosis[a] | Medicine other than anti-hypertensive drugs |
|---|---|---|---|
| 51 | Female | HT | — |
| 60 | Male | HT | — |
| 65 | Male | HT | — |
| 68 | Female | HT, CVD | Aspirin 100 mg/day |
| 71 | Female | HT | — |
| 76 | Female | HT, HL | Atorvastatin 10 mg/day |
| 80 | Male | HT, CVD | Aspirin 100 mg/day |
| 80 | Male | HT, Gout | Allopurinol 100 mg/day |
| 81 | Male | HT, IHD | Isosorbide 40 mg/day |
| 81 | Female | HT | — |
| 87 | Male | HT, CVD | Aspirim 100mg/day |

[a]HT=Hypertension; CVD=Cerebrovascular disease; HL=Hyperlipidemia; IHD=Ischemic heart disease.

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**Table 2.** Anti-hypertensive agents administered to patients

| Medication | Number of patients |
|---|---|
| Calcium antagonist | 9 (82%) |
| Amiodipine (5 mg/day, 2.5 mg/day) | 7 (6, 1) |
| Benidipine 8 mg/day | 1 |
| Nifedipine CR (20 mg/day) | 1 |
| Alpha-blocker | 2 (18%) |
| Doxazocine (4 mg/day, 2 mg/day) | 2 (1, 1) |
| Diuretics | 2 (18%) |
| Trichlomethiazide 1 mg/day | 1 |
| Furosemide 20 mg/day | 1 |
| Combination | 9 (82%) |

these agents were compared.

Data were summarized by mean±standard deviation, and the effects of the change were evaluated by paired *t*-test.

## Results

There was no significant difference in blood test data and physical data measured before and after the change of agents in these patients (Table 3). The systolic BP significantly increased from 130±7.5 mmHg to 140±11 mmHg after the change of imidapril of 5 mg /day to alacepril of 25 mg/day ($p$=0.0004), while the change in diastolic BP was not significant (from 77±5.6 mmHg to 80±8.3 mmHg, $p$=0.283) (Figure 1). In 4 of these patients, the dose of alacepril was increased from 25 to 50 mg/day, and their systolic BP was returned from 149±6.7 mmHg to 128±5.9 mmHg, which was close to the control level of systolic BP with imidapril 5 mg /day (132±6.2) (Figure 2).

In one of these 11 patients, alacepril was changed to losartan, an angiotensin II receptor antagonist, because of dry cough which is one of the side effects of ACE inhibitors; she had not had dry cough with imidapril.

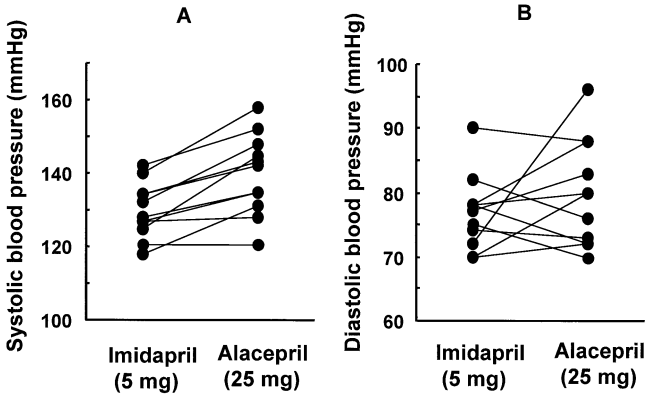


**Figure 1.** Comparison of blood pressure before and after the change of imidapril to alacepril. The systolic blood pressure significantly ($p$=0.0004) increased after the change of imidapril of 5 mg to alacepril 25 mg (A), while the diastolic blood pressure did not change significantly ($p$=0.283) (B).

**Table 3.** Change in blood test data and physical data of patients after the change of agents

| Parameter[a] | Imidapril of 5 mg | Increase after the change to alacepril of 25 mg | *p*-value |
|---|---|---|---|
| BMI (kg/m$^2$) | 22.7±1.8 | 0.12±0.71 | 0.71 |
| Heart rate (/min) | 65±5 | 0.50±1.37 | 0.70 |
| WBC (/mm$^3$) | 4457±1102 | 142±506 | 0.62 |
| Hb (g/dL) | 13.4±1.4 | 0.21±0.30 | 0.20 |
| PLT (/mm$^3$) | 19.3±5.7 | 0.57±1.80 | 0.59 |
| AST (IU/L) | 20.7±2.5 | 0.14±2.10 | 0.88 |
| ALT (IU/L) | 15.7±3.2 | 0.11±1.81 | 0.88 |
| LDH (IU/L) | 225±37 | 2.43±8.96 | 0.56 |
| TP (g/dL) | 7.6±0.4 | 0.07±0.43 | 0.51 |
| Glu (mg/dL) | 101±19 | 0.72±5.58 | 0.81 |
| TC (mg/dL) | 202±19 | 2.71±9.91 | 0.56 |
| TG (mg/dL) | 108±29 | -4.43±17.3 | 0.55 |
| HDL-C (mg/dL) | 58±12 | 0.43±3.3 | 0.74 |
| Na (mEq/L) | 141±1.1 | -1.00±2.19 | 0.29 |
| K (mEq/L) | 4.3±0.2 | 0.13±0.22 | 0.26 |
| Cl (mEq/L) | 103±1.3 | -0.29±2.14 | 0.75 |
| BUN (mg/dL) | 16.8±3.5 | -0.03±1.32 | 0.95 |
| Cr (mg/dL) | 1.1±0.2 | -0.03±2.07 | 0.46 |

[a]BMI=Body mass index; WBC=White blood cell count; Hb=Hemoglubin; PLT=Platelet; AST=Aspartate aminotransferase; ALT=Alanine aminotransferase; LDH=Lactate dehydrogenase; TP=Total protein; Glu=Glucose; TC=Total cholesterol; TG=Triglyceride; HDL-C=High density lipoprotein-cholesterol; BUN=Blood urea nitrogen; Cr=Creatinine; UA=Uric acid.

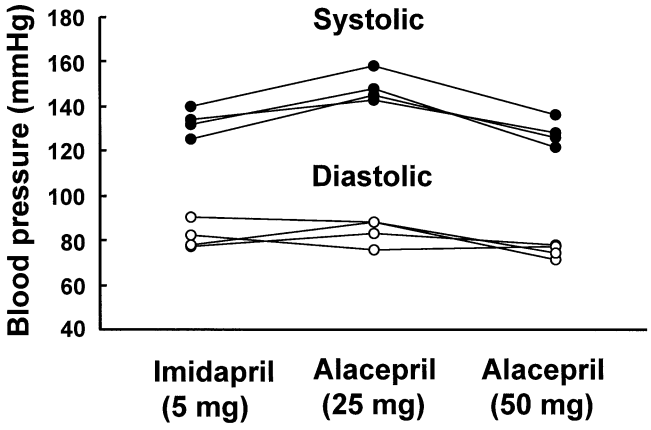


**Figure 2.** Change in blood pressure after increasing the dose of alacepril. A dose of alacepril was increased from 25 to 50 mg in 4 patients whose systolic blood pressure significantly increased ($p$=0.007) after the change of imidapril of 5 mg to alacepril of 25 mg. Their systolic blood pressure significantly decreased ($p$=0.003) to return to control level of systolic blood pressure with imidapril of 5 mg; no significant difference was observed in systolic blood pressure between imidapril of 5 mg and alacepril of 50 mg ($p$=0.129). Their diastolic blood pressure did not significantly change either by the change of imidapril of 5 mg to alacepril of 25 mg ($p$=0.622) or by increasing the dose of alacepril from 25 mg to 50 mg ($p$=0.124).

## Discussion

Imidapril contains no sulfhydryl groups in its chemical structure, and is a pro-drug which becomes active as it is hydrolyzed and converted to a diacid metabolite (imidaprilat). With respect to lowering blood pressure in human, the potency of imidaprilat is about twice that of enalaprilat (the active metabolite of enalapril) and about 10 times that of captopril.[1] The previous study demonstrated that imidapril showed excellent clinical efficacy and safety.[2-5] Vandenburg et al[5] suggested that imidapril of 10 mg achieved maximal ACE inhibition and was maximal dose for lowering BP in most patients, that the 2.5 mg dose showed no significant effect, and that the 5 mg dose gave an intermediate effect.

The characteristics of the effect exerted by alacepril are considered to be derived from its unique pharmacodynamic and pharmacokinetic profile as a pro-drug of captopril via des-acetyl alacepril.[6] Alacepril has a slower onset and a longer duration in antihypertensive action as compared with captopril,[7] and is a more effective antihypertensive agent than captopril in hypertensions.[8] The previous studies demonstrated that a single dose of 25 to 50 mg of alacedpril had excellent clinical efficacy in essential hypertension.[9,10]

A dose of imidapril for hypertention treatment is 5 to 10 mg/day. On the other hand, a dose of alecepril is 25 to 75 mg/day and the maximum dose for severe hypertension is 100 mg/day. There was no report which compared imidapirl and alacepril of usual initial dose for the effects of BP lowering. The present study suggests that imidapril of 5 mg/day is stronger than alacepril of 25 mg/day to lower blood pressure in patients with hypertension, and that imidapril of 5mg/day and alacepril of 50 mg/day are almost equivalent in the BP lowering effect.

ACE inhibitors have been proven to be effective for left ventricular systolic dysfunction, post-myocardial infarction, renal failure, and diabetic nephropathy as well as hypertension.[11] ACE inhibitors are used in different ways depending on their effectiveness. Thus, we propose that imidapril may be used to lower BP strictly as well as to inhibit organ damage in hypertensive patients, while alacepril may be used for organ protective effect in patients with mild hypertension.

Cough is one of the most important side effects of ACE inhibitors. The previous studies demonstrated that incidence of cough was significantly less under the treatment by imidapril than by enalapril, while there was no difference between the two ACE inhibitors in the antihypertensive effects.[2-4] In the present study, only one patient had a cough after imidapril was changed to alacepril.

These agents differ in the price as well; alacepril of 25 mg is cheaper than imidapril of 5 mg. Recently, imidapril has been replaced by alacepril as ACE inhibitor in some hospitals because of cost. However, there is no difference between imidapril and alacepril in the cost-effectiveness for lowering blood pressure since alacepril of 50 mg and imidapril of 5mg cost almost the same.

In conclusion, we have to consider the difference in BP lowering effect between imidapril of 5 mg and alacepril of 25 mg in the treatment of patients with hypertension.

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