—Short Communication—

Effects of Candesartan Cilexetil Compared with Amlodipine on Serum Asymmetric Dimethylarginine Levels in the Chronic Stage of Cerebral Infarction: A Preliminary Study

Eiko Sunami[1–3], Koichi Nomura[1,2], Yutaka Nishiyama[1,2] and Yasuo Katayama[2,4]

[1]Department of Neurology, Shioda Hospital, Chiba, Japan
[2]Department of Internal Medicine, Division of Neurology, Nippon Medical School, Tokyo, Japan
[3]Department of Rehabilitation Medicine, Nippon Medical School, Tokyo, Japan
[4]Department of Neurology, Tokyo General Hospital, Tokyo, Japan

Objective: Asymmetric dimethylarginine (ADMA) is an endogenous nitric oxide synthase inhibitor and a marker of vascular endothelial damage. Angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker (ARB) are reported to reduce the serum ADMA level. Our group administered either ARB or calcium antagonist to patients after cerebral infarction and discussed the ADMA changes observed.

Methods: Hypertensives in the chronic stage of cerebral infarction were enrolled. These subjects included patients of atherothrombotic cerebral infarction or lacunar infarction. The patients received candesartan cilexetil (candesartan group) or amlodipine (amlodipine group). The blood pressure and serum ADMA concentration were measured and compared before the treatment commenced and at 1–3 months after the treatment commenced.

Results: Seven subjects received candesartan and six received amlodipine. There was no difference between the groups in the change of blood pressure before and after the drug treatment. The ADMA level (nmol/mL) fell significantly from 0.57 ± 0.10 (before administration) to 0.52 ± 0.09 (after administration) in the candesartan group ($P<0.05$). The ADMA level did not change between before and after administration in the amlodipine group.

Conclusion: Treatment with candesartan cilexetil reduced the level of ADMA in hypertensive patients in the chronic stage of cerebral infarction. Candesartan cilexetil may be useful in hypertensive patients at the chronic stage of cerebral infarction with expected anti-atherosclerotic effect.

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Key words: asymmetric dimethylarginine, cerebral infarction, hypertension, candesartan cilexetil, angiotensin II receptor blocker

Introduction

Endothelium-derived nitric oxide (NO) is a potent vasodilator and endogenous anti-atherosclerotic molecule. NO is synthesized from L-arginine by NO synthase (NOS) in endothelium.

Asymmetric dimethylarginine (ADMA) is an endogenous NOS inhibitor. The serum ADMA level is reportedly higher in diseases known to promote vascular endothelial dysfunction such as hypertension, dyslipidemia and diabetes mellitus. The ADMA level is also associated with cerebral infarction[1].

Hypertension is the strongest risk factor for cerebral infarction. However, no specific antihypertensive is confirmed to be significantly effective in preventing relapses of cerebral infarction. We find in the literature that angiotensin II receptor blocker (ARB) is significantly more effective than calcium antagonist in suppressing cerebral infarction relapse[2].

Correspondence to Eiko Sunami, Department of Rehabilitation Medicine, Nippon Medical School, 1–1–5 Sendagi, Bunkyo-ku, Tokyo 113–8602, Japan
E-mail: s2047@nms.ac.jp
Journal Website (http://www.nms.ac.jp/jnms/)

Angiotensin-converting enzyme (ACE) inhibitor and ARB are reported to be effective in reducing ADMA[3–6]. There is no report, however, confirming reduced ADMA levels in response to ARB treatment in hypertensive patients with cerebral infarction in the chronic stage.

In this study we administered candesartan cilexetil (ARB) or amlodipine (calcium antagonist) to hypertensive patients in the chronic stage of cerebral infarction and investigated the effect of the agents on serum ADMA levels.

Materials and Methods

The subjects were hypertensive patients in the chronic stage of cerebral infarction who received inpatient or outpatient treatment at Shioda Hospital over the period from February 2011 and September 2013. Subjects included patients of atherothrombotic cerebral infarction or lacunar infarction with the time line of more than 1 month following onset of ischemic stroke or patients of asymptomatic lacunar infarction. Hypertension was diagnosed based on a systolic blood pressure of 140 mmHg or more or a diastolic blood pressure 90 mmHg or more without oral antihypertensive therapy.

Patients receiving cilostazol were excluded because of its potential effects on the serum ADMA level.

The patients were divided into two groups at random. One group used candesartan 2 mg or 4 mg (candesartan group) and the other group used amlodipine 2.5 mg (amlodipine group). The blood pressure and serum ADMA concentration were measured once before the treatment commenced and once at 1–3 months after the treatment commenced. The serum ADMA level was measured by high-performance liquid chromatography (SRL, Tokyo, Japan) using blood extracted from a vein.

This study was approved by the ethics committee of Shioda Hospital. Informed consent was obtained from all of the subjects prior to their participation in the study.

The statistical analysis was performed with Stat View 5.0 software (SAS Institute Inc., USA). Differences between groups at baseline were tested by Fisher's exact test and the unpaired T-test. Differences between groups in blood pressure changes before and after treatment were tested by the unpaired T-test. Changes in ADMA levels were tested by the paired T-test. Data are shown as averages ± standard deviation. A P value of less than 0.05 was considered significant.

Results

The **Table** shows the characteristics of the patients at baseline. The candesartan group consisted of 7 patients and the amlodipine group consisted of 6 patients. The clinical characteristics of the two groups were that no statistically significant differences were shown except the usage of Clopidogrel.

The blood pressure change between before and after drug treatment was 30 ± 21/13 ± 18 mmHg in the candesartan group versus 21 ± 22/17 ± 17 mmHg in the amlodipine group (see **Fig. 1**). There was no significant difference between the groups in the change of systolic blood pressure (P=0.500) or diastolic blood pressure (P= 0.770).

Figure 2-a and **Figure 2-b** respectively show the changes in ADMA levels in the candesartan group and the amlodipine group. The ADMA levels in the candesartan group were 0.57 ± 0.10 nmol/mL (before treatment) and 0.52 ± 0.09 nmol/mL (after treatment). The ADMA level was significantly reduced by the drug treatment in the candesartan group (P=0.014) (**Fig. 2-a**). Meanwhile, ADMA levels in the amlodipine group were 0.45 ± 0.08 nmol/mL (before treatment) and 0.49 ± 0.08 nmol/mL (after treatment), showing no significant change between before and after treatment (P=0.290) (**Fig. 2-b**).

Discussion

We administered candesartan cilexetil and amlodipine to hypertensive patients in the chronic stage of cerebral infarction and researched the changes in their blood pressure and serum ADMA levels. The antihypertensive actions of candesartan and amlodipine appeared to be approximately the same. ADMA levels were significantly reduced after treatment only in the candesartan group.

ARBs are reported to reduce ADMA[3–5]. Our findings confirmed that ARB administration reduced the ADMA level in hypertensive patients with cerebral infarction in the chronic stage.

ADMA levels are higher in diseases known to cause arteriosclerosis. Moreover, the high value of ADMA is related to cerebrovascular infarction[1]. Reduced ADMA levels also have a known relation to improvements in vascular endothelial function[7]. Additionally, ARB has not only an anti-arteriosclerosis effect but also an organ protection effect. ARB is effective for the prevention of cerebral infarction[2]. The findings of our present study may support the notion that ARB confers a secondary preventive effect against cerebral infarction.

By what mechanism does ARB reduce serum ADMA levels? ARBs and ACE inhibitors are reported to reduce ADMA levels independent of depressor effect[5,6]. Our find-

Table Basline Characteristics of Patients

	Candesartan group n=7	Amlodipine group n=6	P-value
Age (years), mean±SD	77±6	80±6	NS
Gender (Male/Female)	5/2	1/5	NS
Clinical types of cerebral infarction			
Atherothrombotic/Lacunar	4/3	3/3	NS
Dyslipidemia	0	3	NS
Diabetes mellitus	0	2	NS
Ischemic heart disease	1	0	NS
Medications			
Statin	3	1	NS
Eicosapentaenoic Acid	0	1	NS
Glimepiride	0	1	NS
Aspirin	2	3	NS
Clopidogrel	4	0	p<0.05
Warfarin	1	2	NS
Systolic blood pressure (mmHg), mean±SD	155±13	156±10	NS
Diastolic blood pressure (mmHg), mean±SD	90±15	87±11	NS
ADMA (nmol/mL), mean±SD	0.57±0.10	0.45±0.08	NS
Creatinine (mg/dL), mean±SD	0.78±0.24	0.72±0.35	NS
Fasting blood sugar (mg/dL), mean±SD	95.29±12.32	152.17±102.74	NS
LDL cholesterol (mg/dL), mean±SD	89.14±20.90	102.50±20.33	NS
HDL cholesterol (mg/dL), mean±SD	50.74±20.87	57.32±8.45	NS
Triglyceride (mg/dL), mean±SD	89.86±30.68	113.50±48.17	NS

NS=not significant
ADMA=Asymmetric dimethylarginine

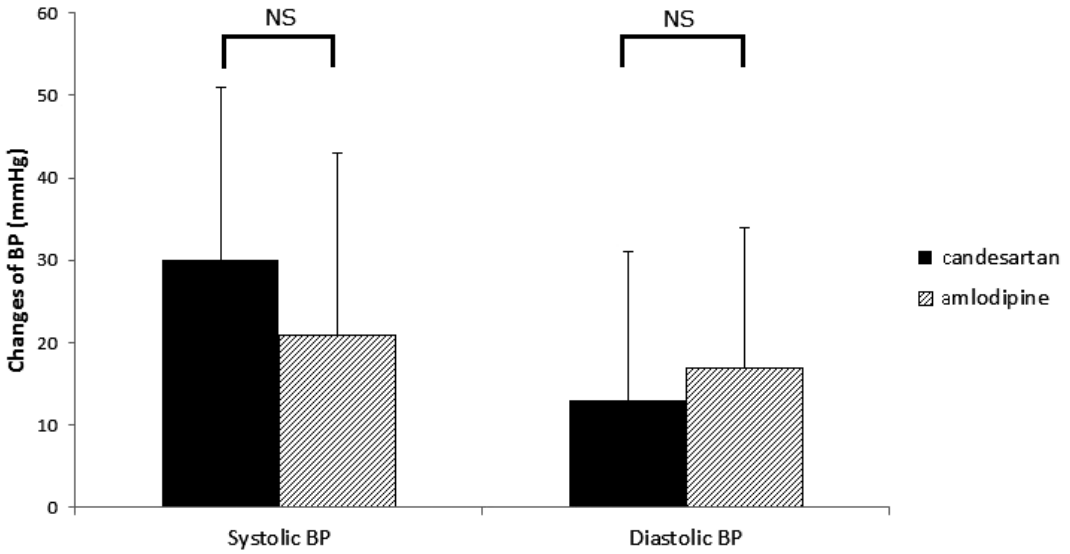

Fig. 1 Changes of blood pressure before and after treatment in the candesartan group and amlodipine group
There were no significant differences between the candesartan group and amlodipine group in the changes of blood pressure before and after treatment. (Unpaired T-test)
Systolic BP=systolic blood pressure, Diastolic BP=diastolic blood pressure
Changes of BP=changes of blood pressure before and after treatment
NS=not significant

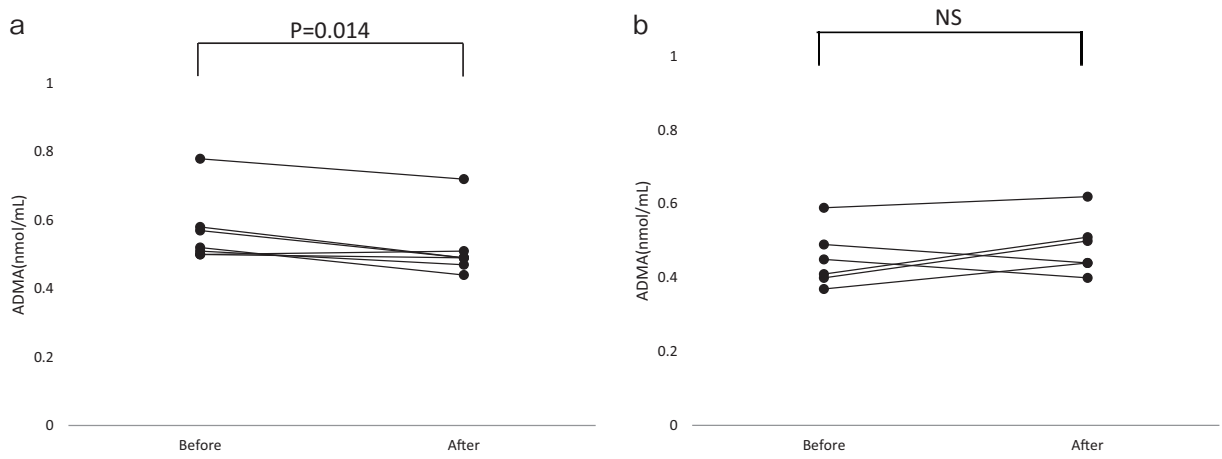

Fig. 2 **a** Asymmetrical dimethylarginine before and after treatment in the candesartan group
Treatment with candesartan cilexetil significantly reduced the serum ADMA level (P<0.05). (Paired T-test) ADMA=asymmetrical dimethylarginine
b Asymmetrical dimethylarginine before and after treatment in the amlodipine group
No significant change was observed in the serum
ADMA levels of the patients given amlodipine. (Paired T-test) ADMA=asymmetrical dimethylarginine; NS=not significant

ing supports the previous conclusion. The renin-angiotensin system is related to the development of arteriosclerosis. Angiotensin II contributes to arteriosclerosis by triggering an inflammatory reaction of the blood vessel walls[8]. This finding confirms that vascular endothelial function is improved by agents that block the renin-angiotensin system[9,10]. It is estimated that the blocking of renin-angiotensin system improves vessel endothelial function and reduces ADMA.

This study had several limitations. The population was randomly divided into two groups — the candesartan group and the amlodipine group, but it was not undertaken with blind manner. As numbers of patients of both groups were extremely small, the finding of this study is inconclusive. Studies with larger numbers of subjects are expected in the years ahead.

Although this study involved a small number of cases, treatment with candesartan cilexetil reduced serum ADMA levels in hypertensive patients with cerebral infarction in the chronic stage. This ADMA reduction by candesartan cilexetil may occur via ARB's specific pharmacological action to protect the vascular endothelial function. ARB treatment at the chronic stage of cerebral infarction is expected to have anti-atherosclerotic effects.

Conflict of Interest: The authors declare no conflict of interest.

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