—Report on Experiments and Clinical Cases—

The Effect of Doxazosin Mesilate on Cerebral Blood Flow in Patients with Hypertension and Chronic Cerebral Infarction

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Abstract

α_1-Adrenoceptor antagonists are useful antihypertensive agents for patients with hypertension who have hyperlipidemia, benign prostatic hyperplasia, or pheochromocytoma. The purpose of this study was to evaluate the effect of the α_1-adrenoceptor antagonist, doxazosin mesilate, on cerebral blood flow (CBF) and flow velocity in the common carotid artery in patients with hypertension and chronic cerebral infarction.

Doxazosin mesilate (1 mg/day) was orally administered for 4 to 8 weeks to 7 patients with hypertension 4 weeks after the onset of cerebral infarction. We determined blood pressure, heart rate, CBF measured with autoradiography single photon emission computed tomography (SPECT) with N-isopropyl-p-[^{123}I] iodoamphetamine (^{123}I-IMP) as a tracer, and the maximum, minimum and mean flow velocities in the common carotid arteries measured with duplex carotid ultrasonography before and 4 to 8 weeks after the beginning of treatment. Mean CBF was defined as the mean count of tracer from the 8 regions of interest (ROIs) in the frontal, parietal, occipital, and temporal cortices of the cerebral hemisphere. Values were analyzed with paired t tests.

With administration of doxazosin mesilate, systolic pressure significantly decreased from 152 ± 11 to 137 ± 7 mmHg ($p<0.01$), but diastolic pressure and heart rate were unchanged. Mean CBF was improved significantly from 32.0 ± 4.1 to 34.7 ± 4.1 mL/100 g brain/min ($p< 0.01$) in the ipsilateral cerebral cortex and from 32.6 ± 6.2 to 36.2 ± 5.1 mL/100 g brain/min ($p< 0.05$) in the contralateral cerebral cortex. The maximum, minimum, and mean flow velocities in the bilateral common carotid arteries were not changed significantly.

In the present study, the improvement of mean CBF in the ipsilateral and contralateral cerebral cortices was demonstrated in patients with hypertension and chronic cerebral infarction after the treatment with doxazosin mesilate. Doxazosin mesilate might be an effective antihypertensive agent for hypertensive chronic cerebral infarction.
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Key words: doxazosin mesilate, cerebral blood flow, hypertension, cerebral infarction

Introduction

Hypertension is an important public health issue. To address this problem, many antihypertensive medicines have been developed to control blood pressure. Recently antihypertensive agents have been shown to have cardiovascular benefits beyond

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Table 1 Patient Profiles

Patient	Age	Sex	Symptoms	Diagnosis	Lesion	Complications
1	59	Male	Right hemiparesis, dysarthria	Lacunar brain infarction	Left caudate body	HT, DM, and HL
2	74	Female	Left hemiparesis	Atherothrombotic brain infarction	Right putamen	HT, HL
3	71	Female	Left hemiparesis	Lacunar brain infarction	Right corona radiata	HT, HL
4	62	Male	Right hemiparesis, dysarthria	Lacunar brain infarction	Left corona radiata	HT, CHF
5	64	Male	Dizziness	Lacunar brain infarction	Pons, left thalamus	HT, DM, HL, and HU
6	75	Male	Left hemiparesis, dysarthria, and dizziness	Lacunar brain infarction	Right corona radiata	HT
7	72	Female	Numbness of left perioral region	Lacunar brain infarction	Right thalamus	HT

HT, hypertension; DM, diabetes mellitus; HL, hyperlipidemia; CHF, congestive heart failure; HU, hyperuricemia.

the reduction of blood pressure[1]. Angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers are widely used antihypertensive medicines in Japan. On the other hand, α_1-adrenoceptor antagonists are the useful antihypertensive medicines for hypertensives who have hyperlipidemia, benign prostatic hyperplasia[2], or pheochromocytoma. Doxazosin mesilate is an antihypertensive quinazoline derivative. Its action is a consequence of selective blocking of postsynaptic α_1-adrenoceptors[3–5]. The treatment of hypertension with doxazosin mesilate results in the improvement of hyperlipidemia, reduction of arterial wall thickness[6], and normalization of alterations in platelet function[7].

In the patients with chronic cerebral infarction, blood pressure must be adequately controlled to prevent cerebrovascular events. Cerebral blood flow (CBF) should be maintained in patients with hypertension who have chronic cerebral infarction when they are treated with antihypertensive agents. The purpose of this study was to evaluate the effects of the α_1-adrenoceptor antagonist, doxazosin mesilate, on CBF and flow velocity in the common carotid artery in patients with hypertension and chronic cerebral infarction.

Materials and Methods

1) Subjects

Among patients who had had cerebral infarction and had been admitted to our institution from December 1997 through January 1999, 7 patients with hypertension who had had cerebral infarction 4 weeks earlier (4 men and 3 women; age, 68.1 ± 6.4 years; mean ± standard deviation), from whom informed consent was obtained, were selected (**Table 1**).

2) Protocol

This study was performed as part of planned medical procedures. Doxazosin mesilate (Cardenalin, Pfizer Japan Inc., Tokyo, Japan) (1 mg/day) was orally administered to the subjects for 4 to 8 weeks with either ticlopidne hydrochloride or aspirin. Agents having effects on cerebral circulation, such as cerebral circulation improvers, and antihypertensive medicines except doxazosin mesilate were prohibited in this study. We determined blood pressure, heart rate, mean CBF in the hemispheric cerebral cortex measured with the single photon emission computed tomography (SPECT) autoradiographic method using N-isopropyl-p-[^{123}I] iodoamphetamine (^{123}I-IMP) as a tracer[8], and the maximum, minimum, and mean flow velocities (Vmax, Vmin and Vmean, respectively) in the common carotid arteries with duplex carotid ultrasonography before and 4 to 8 weeks after the beginning of treatment.

i. Measurement of CBF

SPECT was performed with a triple-head gamma

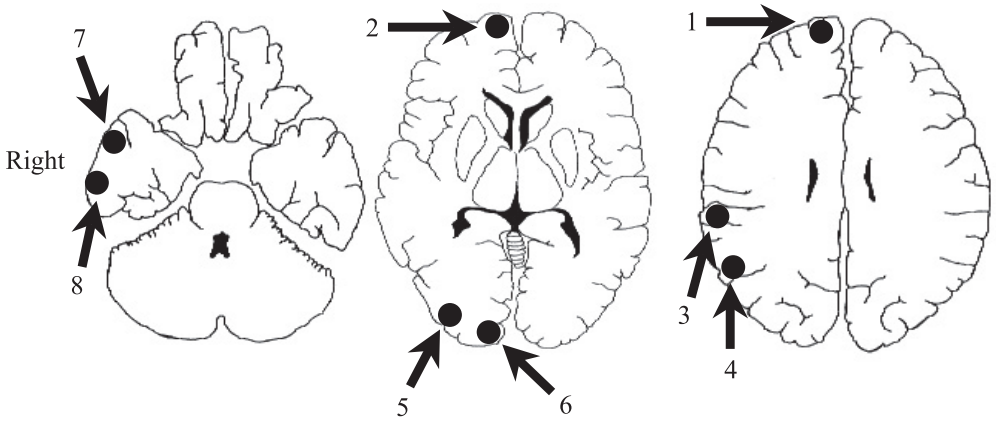

Fig. 1 Regions of interest
The CBF of the frontal cortex was the average of areas 1 and 2. The CBF of the parietal cortex was the average of areas 3 and 4. The CBF of the occipital cortex was the average of areas 5 and 6. The CBF of the temporal cortex was the average of areas 7 and 8.
1 and 2: Frontal cortex
3 and 4: Parietal cortex
5 and 6: Occipital cortex
7 and 8: Temporal cortex

camera (PRISM 3000; PICKER/Shimadzu Corp., Kyoto, Japan). SPECT imaging was performed 12 to 42 minutes after injection of ^{123}I-IMP (222 Mbq) to measure CBF in the 7 patients. The standard input function and Vd value (35) were used as described in a previous study performed at our institution[9]. Round regions of interest (ROIs) consisting of 4 pixels (4.5 mm/pixel) were placed in the frontal, parietal, occipital, and temporal cortices of the ipsilateral or contralateral cerebral hemisphere as described in previous studies performed at our institution[10,11]. Mean CBF was defined as the mean count of tracer from the 8 ROIs in the frontal, parietal, occipital, and temporal cortices of each cerebral hemisphere (**Fig. 1**). The ipsilateral hemisphere and contralateral hemisphere denoted the hemisphere with the main lesions and the other hemisphere, respectively.

ii. Measurement of flow velocity in common carotid artery

Color duplex ultrasound scanning was performed with a Toshiba SSA-270A (Toshiba Medical Systems Corp., Tochigi, Japan) to measure flow velocity in the common carotid artery in the 7 patients. A 7.5-MHz linear array probe was used. The ultrasound beam was corrected within an angle of 60 degrees. The Vmax, Vmin, and Vmean in the common carotid artery were measured 2 to 3 cm from the carotid bifurcation.

3) Statistical Analysis

Blood pressure, heart rate, flow velocity in the common carotid artery, and mean CBF were analyzed with paired t tests. Data are presented as mean ± standard deviation (SD); a P value less than 0.05 was considered to indicate statistical significance.

Results

1) Measurement of Blood Pressure and Heart Rate

With administration of doxazosin mesilate, systolic blood pressure significantly decreased from 152 ± 11 to 137 ± 7 mmHg ($p<0.01$), but diastolic blood pressure and heart rate were unchanged (**Table 2**).

2) Measurement of CBF

Mean CBF was improved significantly from 32.0 ± 4.1 to 34.7 ± 4.1 mL/100 g brain/min ($p<0.01$) in the ipsilateral cerebral cortex and from 32.6 ± 6.2 to 36.2 ± 5.1 mL/100 g brain/min ($p<0.05$) in the contralateral cerebral cortex (**Table 3**).

Table 2 Blood pressure and heart rate

Variable	Before treatment	After treatment	P value
Systolic blood pressure (mmHg)	152 ± 11	137 ± 7	0.002*
Diastolic blood pressure (mmHg)	84 ± 6	82 ± 3	0.4619
Heart rate (beats/minute)	71 ± 8	72 ± 10	0.5986

Data are presented as mean ± standard deviation.
* indicates statistical significance.

Table 3 Mean CBF

Mean CBF	Before treatment	After treatment	P value
Ipsilateral cerebral cortex (mL/100 g brain/min)	32.0 ± 4.1	34.7 ± 4.1	0.0044*
Contralateral cerebral cortex (mL/100 g brain/min)	32.6 ± 6.2	36.2 ± 5.1	0.0123*

Data are presented as mean ± standard deviation.
* indicates statistical significance.

Table 4 Flow velocities in the common carotid artery

Flow velocity (m/s)	Before treatment	After treatment	P value
Ipsilateral Vmax	0.73 ± 0.16	0.78 ± 0.18	0.6392
Ipsilateral Vmin	0.16 ± 0.05	0.17 ± 0.03	0.5788
Ipsilateral Vmean	0.31 ± 0.07	0.33 ± 0.06	0.4241
Contralateral Vmax	0.69 ± 0.17	0.67 ± 0.21	0.7600
Contralateral Vmin	0.17 ± 0.06	0.16 ± 0.05	0.7214
Contralateral Vmean	0.32 ± 0.07	0.30 ± 0.07	0.5130

Vmax, maximum flow velocity; Vmin, minimum flow velocity; Vmean, mean flow velocity. Data are presented as mean ± standard deviation.

3) Measurement of Flow Velocity in the Common Carotid Artery

The Vmax, Vmin, and Vmean values in the ipsilateral common carotid artery before treatment were 0.73 ± 0.16 m/s, 0.16 ± 0.05 m/s, and 0.31 ± 0.07 m/s, respectively, and were not changed significantly with the administration of doxazosin mesilate. The Vmax, Vmin, and Vmean values in the contralateral common carotid artery before treatment were 0.69 ± 0.17 m/s, 0.17 ± 0.06 m/s, and 0.32 ± 0.07 m/s, respectively, and were no changed significantly after treatment (**Table 4**).

Discussion

The quinazoline derivative, doxazosin mesilate, is an antihypertensive agent. Its action is a consequence of selective blocking of postsynaptic α_1-adrenoceptors[3–5].

In this study, doxazosin mesilate was administered to patients with hypertension 4 weeks after the onset of cerebral infarction. Because stroke-related symptoms are stable during this period, it is an appropriate time to assess the effects of agents on CBF. We did not observe worsening of palsy, numbness, speech disturbance, or dizziness during treatment.

In the measurement of CBF, mean CBF in the cerebral cortex was increased in patients with hypertensive chronic cerebral infarction after the treatment with doxazosin mesilate. With administration of doxazosin mesilate, mean CBF improved significantly from 32.0 ± 4.1 to 34.7 ± 4.1 mL/100 g brain/min ($p<0.01$) in the ipsilateral cerebral cortex and from 32.6 ± 6.2 to 36.2 ± 5.1 mL/100 g brain/min ($p<0.05$) in the contralateral cerebral cortex. α_1-Adrenoceptors are present in the central nervous system[12–15], and the side-chains

bound to quinazoline and quinazolinedione core structures may play an important role in the antagonistic potencies of α_1-adrenoceptors in the central nervous system[16], as they do in the peripheral tissues. Doxazosin mesilate decreases total peripheral resistance and blood pressure but also seems to dilate cerebral vessels directly. Consequently, CBF is thought to be maintained or to be increased. It has also been reported that the lower limit of CBF autoregulation shifts to a lower level after the long-term treatment with doxazosin mesilate[17]. This effect is favorable for the maintenance of CBF under hypotensive conditions. Bunazosin, an α_1-adrenoceptor antagonist, also increases cerebral blood flow in patients with hypertension and chronic cerebral infarction[18].

In our study, flow velocity in the common carotid arteries and heart rate were not changed after the treatment with doxazosin mesilate. We speculate that 1 mg/day of doxazosin mesilate for 4 to 8 weeks does not dilate the common carotid arteries and does not have an effect on cardiac output. However, Iijima et al have reported that maximum flow velocity of the internal carotid artery increased with administration of 0.5 to 1 mg/day of doxazosin mesilate for 12 weeks[19]. Further studies should be performed to examine how doxazosin mesilate acts on flow velocity in the carotid artery.

With administration of doxazosin mesilate, systolic pressure significantly decreased from 152 ± 11 to 137 ± 7 mmHg ($p<0.01$), but diastolic pressure and heart rate were unchanged. In our study, we administered 1 mg/day of doxazosin mesilate for 4 to 8 weeks. However, Yamada et al have reported that 1 to 4 mg/day of doxazosin mesilate administered for more than 12 weeks decreased diastolic pressure[20]. The dose and duration of doxazosin mesilate must be considered.

Alpha blockers decrease insulin resistance, whereas diuretics increase insulin resistance. According to the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[21], the treatment of hypertension with doxazosin mesilate in adults with glucose disorders incurs the same risk of coronary heart disease as the treatment with chlorthalidone, a diuretic; however, the treatment with doxazosin mesilate increases the risk of combined cardiovascular disease and heart failure despite lower glucose levels[22]. Furthermore, among patients with hypertension, the risks of stroke and cardiovascular disease were higher in those receiving doxazosin than in those receiving chlorthalidone[21,23]. These findings confirm the superiority of the diuretic-based antihypertensive treatment over the alpha-blocker-based antihypertensive treatment to prevent cardiovascular disease, including heart failure and stroke[21,24].

In contrast, there are some reports in favor of doxazosin mesilate. The lower limit of CBF autoregulation shifts to a lower level after the long-term treatment with doxazosin mesilate[17]. The treatment of hypertension with doxazosin mesilate results in the improvement of hyperlipidemia, reduction of arterial wall thickness[6], and normalization of alterations in platelet function[7]. The morning blood pressure surge is particularly dependent on alpha-adrenergic activity and is closely associated with advanced silent hypertensive cerebrovascular disease in elderly individuals[25]. In the absence of angiotensin II resulting from enalaprilat, doxazosin mesilate has a greater hypotensive action than in the presence of angiotensin II[26].

When doxazosin mesilate is administered to patients with hypertension and chronic cerebral infarction, the risk of cardiovascular disease should be paid attention to, and doxazosin mesilate combined with other antihypertensive agents, such as angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors, must be considered, according to the circumstances.

In conclusion, the present study has clarified the improvement in mean CBF in the ipsilateral and contralateral cerebral cortices in patients with hypertension and chronic cerebral infarction after the treatment with doxazosin mesilate, which is thought to be an effective antihypertensive agent for hypertensive chronic cerebral infarction.

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