Blood Pressure Lowering with Valsartan Is Associated with Maintenance of Cerebral Blood Flow and Cerebral Perfusion Reserve in Hypertensive Patients with Cerebral Small Vessel Disease

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Background: The purpose of this study was to determine the effect of systemic blood pressure–lowering treatment with an angiotensin II receptor blocker, valsartan, on cerebral hemodynamics in patients with hypertension and evidence of cerebral small vessel disease. *Methods:* We used positron emission tomography and acetazolamide challenge tests to measure cerebral blood flow (CBF) and cerebrovascular reserve (CVR) in 8 patients with hypertension (mean age 70.8 years) with lacunar infarcts and white matter lesions before and after valsartan therapy. *Results:* Systemic blood pressure was significantly decreased from baseline after treatment with valsartan. The baseline global CBFs before and after treatment were 38.2 ± 5.6 mL/min/100 g and 39.9 ± 9.0 mL/min/100 g, respectively. The CVRs before and after treatment were 52.2 ± 18.4% and 39.7 ± 18.9%, respectively. Differences in these parameters were not significant. Both regional CBF and CVR in the corona radiata with moderate or severe white matter lesions were also preserved after valsartan therapy compared with those before treatment. *Conclusions:* Cerebral hemodynamics were preserved after blood pressure lowering with valsartan therapy. Valsartan could be a feasible antihypertensive regimen in terms of cerebral circulation in patients with cerebral small vessel disease. **Key Words:** Valsartan—angiotensin II receptor blocker—cerebral infarction—positron emission tomography—cerebral blood flow.

Recent clinical trials have shown that antihypertensive treatments that include inhibitors of the rennin-angiotensin system offer benefits in both primary and secondary prevention of stroke.[1,2] Among angiotensin II receptor blockers (ARBs), losartan,[3] candesartan,[4] and valsartan[5] were shown to decrease occurrence of stroke, and eprosartan[6] was shown to be more effective in secondary prevention of stroke recurrence than calcium channel blocker.

However, there is still some concern about deterioration of cerebral hemodynamics, decreasing cerebral perfusion pressure, and increasing the risk of ischemic stroke when patients with hypertension, especially those with a history of stroke or ischemic white matter lesion, receive an ARB

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with strong antihypertensive action. Previously, positron emission tomography (PET) showed the long-term angiotensin-converting enzyme (ACE) inhibitor perindopril improved cerebral perfusion reserve in patients with ischemic stroke.[7] Losartan was also shown to preserve cerebral blood flow (CBF) in hypertensive patients with[8,9] and without[10] a history of stroke. With recent progress in brain imaging techniques, we can identify patients with silent brain infarcts or white matter lesions without a history of stroke as being at high risk for stroke.[11,12] Although strict management of vascular risk factors, especially hypertension, is recommended in patients with hypertension and these brain lesions,[13] the effect of ARBs on cerebral hemodynamics in such high-risk patients as those with cerebral small vessel disease has not been clarified.

The purpose of this study was to determine the effect of systemic blood pressure–lowering treatment with valsartan on cerebral hemodynamics in patients with hypertension and evidence of lacunar infarcts and white matter lesions using PET and acetazolamide challenge tests.

Methods

Patients with hypertension, lacunar infarcts, and white matter lesions but without significant arterial stenosis in brain magnetic resonance (MR) angiography were enrolled from among outpatients of Osaka University Hospital in Japan. The protocol was approved by the institutional review board and ethics committee.

To eliminate the effect of a recent stroke, only patients who had been stable for more than 6 months after the most recent symptomatic stroke were included when symptomatic patients were nominated. Patients who had already taken ACE inhibitors or ARBs were excluded. Patients who had severe stenosis (≥70%) of the carotid artery, middle cerebral artery, or both were also excluded.

Nine patients were enrolled in the study. The patients agreed to participate in the study and provided written consent after receiving a detailed explanation of the study. One patient was dropped from the study after the first PET scan because he refused the second scan.

All patients had undergone brain MR imaging (MRI). All MRI was performed with a 1.5-T Signa Horizon (GE Yokogawa Medical Systems Ltd, Tokyo, Japan) scanner. The imaging protocol consisted of a T1-, T2-weighted spin-echo and fluid-attenuated inversion-recovery imaging. White matter lesions were scored in periventricular and deep subcortical regions separately according to the rating scale of Fazekas et al.[14] The rating scale of Fazekas et al[14] provides two scores rated on a 0-to-3 scale according to the following criteria: periventricular hyperintensity (PVH) = 0 (absence), 1 ("caps" or pencil-thin lining), 2 (smooth "halo"), or 3 (irregular PVH extending into the deep white matter); and deep white matter hyperintensity (DWMH) = 0 (absence), 1 (punctuate foci), 2 (beginning confluence of foci), or 3 (large confluent areas). The degree of white matter lesion was evaluated as a sum of scales of PVH and DWMH in each side of corona radiata. Mild, moderate, and severe white matter lesions were defined as a scale of 0 to 2, 3 and 4, and more than 5, respectively.

The patients received a daily oral dose of valsartan (DIOVAN, Novartis Pharma K.K., Tokyo, Japan) titrated to 80 mg after an initial PET scan. Follow-up medical examinations were performed every 2 to 4 weeks, and the drug dosage was adjusted between 40 and 160 mg/day to achieve a target sitting blood pressure range between 120/70 and 140/90 mm Hg. When the sitting blood pressure reached the target range and stabilized with valsartan administration, the patient underwent a second PET scan at an interval of 27 ± 5 weeks (ranging from 18-35 weeks).

For CBF measurement, we used PET with an [15]O-labeled water injection.[15] We used a high-performance PET scanner (SET-2400W, Shimadzu Co, Kyoto, Japan) set at 63 slices (slice thickness, 3.1 mm) and a spatial resolution of 3.7 mm full width at half maximum. Regional CBF was quantitatively measured using PET, a [15]O-labeled water injection, and an autoradiographic method. First, two consecutive scans were performed, 10 minutes apart, for the baseline condition. Then, after the intravenous administration of acetazolamide titrated to 1000 mg, two additional scans were again performed, 10 minutes apart, in vasodilated condition. At the end of every scan, the patients' blood pressure, pulse rate, and arterial blood gas tensions were measured. Averaged data of the two measurements were obtained for both baseline and vasodilated conditions.

The regional CBF PET image data sets obtained were realigned and transformed stereotaxically into an identical normal brain template with statistical parametric mapping software (SPM99, Wellcome Department of Cognitive Neurology, University College London, London, United Kingdom) running on MATLAB 5.3 (The MathWorks Inc, Natick, MA) for Windows (Microsoft Inc, Redmond, WA). The regional cerebrovascular reserve (CVR) images were calculated with the realigned sets of CBF images. For CVR, CBF at rest was subtracted from CBF vasodilated, the total divided by the CBF at rest, and the result multiplied by 100. The CVR images were transformed stereotaxically with the same parameters of transformation as the corresponding CBF images. Identical regions of interest (the whole cerebrum, frontal cortex, temporal cortex, occipital cortex, parietal cortex, basal ganglia areas, thalami, corona radiata, and centrum semiovale) were drawn on standardized CBF images. The region of interest for the whole cerebrum was drawn manually on all slices of the standardized MRI T1 template provided by SPM99 and applied to the obtained standardized CBF images. Each of the remaining regions of interest were drawn, and consisted of multiple small