Preventive Treatment with Lomerizine Increases Cerebral Blood Flows during the Interictal Phase of Migraine

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Background: Changes in regional cerebral blood flow (rCBF) were reported in migraineurs. However, little is known how preventive medications of migraine can influence rCBF. Lomerizine, a calcium channel blocker, has been used for migraine prophylaxis in Japan. We examined rCBF after lomerizine treatment. *Subjects and methods:* Migraine was diagnosed according to the criteria of the International Classification of Headache Disorders, Third Edition beta. Migraine subtype was classified into migraine with aura (MA) and migraine without aura (MO). Lomerizine (10 mg/day, per oral) was administered for 3 months. Headache Impact Test-6 (HIT-6) and blood pressure (BP) were compared at baseline and end point. Brain single photon emission computed tomography using ^{99m}Tc-ethyl cysteinate dimer was performed at the interictal period. Brain SPECT data were analyzed according to revised version of 3-dimensional stereotaxic region of interest template. Clinic-radiological variables were analyzed by paired Student's *t* test. *Results:* Ten migraineurs (4 men and 6 women) participated in the present study. Mean age was 54.1 (standard deviation [SD] 10.1) years. Mean duration of migraine was 25.3 (SD 9.8) years. Migraine subtype showed 4 MA and 6 MO patients. Mean score of HIT-6 was 66.3 (SD 11.7). Lomerizine treatment decreased HIT-6 scores significantly ($P < .01$). BP did not differ significantly after lomerizine treatment. Lomerizine treatment increased rCBF 20% approximately in the frontal, the parietal, the temporal, and the occipital region. *Conclusions:* The present study indicated a significant increase in interictal rCBF after lomerizine treatment in migraineurs. The upregulation of rCBF could contribute to the antimigraine mechanism of lomerizine. **Key Words:** Migraine prophylaxis—lomerizine—calcium channel blocker—regional cerebral blood flow—brain single photon emission tomography.

Introduction

Migraine is a common headache disorder in working adults. In particular, preventive therapy of migraine is crucial for sufferers with frequent and severe degree of headache. Lomerizine (1-[bis(4-fluorophenyl)methyl]-4-(2,3,4-trimethoxy-benzyl)-piperazine dihydrochloride) is a voltage-dependent L- and T-type calcium channel blocker. Lomerizine has been used for migraine prophylaxis from 1999 only in Japan. This drug is currently the most popular medication because the frequency of adverse effects is

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low. This calcium channel blocker had little blood pressure (BP)-lowering effects, and also had no severe adverse effects, including extrapyramidal symptoms. In general, the effectiveness of lomerizine was estimated at more than 50%.[1,2]

Many previous studies of brain circulation suggested changes of cerebral blood flow (CBF) in migraineurs during a prodrome, an aura, or a headache attack.[3-9] Subcutaneous injection of sumatriptan (6 mg) did not alter regional CBF (rCBF) significantly during a migraine attack.[3] However, little is known on how preventive migraine medications can influence rCBF. We described previously that lomerizine treatment increased rCBF in an elderly migraineur.[10] Herein we aimed to examine rCBF changes on single photon emission tomography (SPECT) after lomerizine treatment in sufferers with migraine with aura (MA) and without aura (MO).

Subjects and Methods

Study Participants

A board-certificated experienced neurologist with headache professional qualification (K.I.) diagnosed migraine according to the criteria of third edition (beta version) of the International Classification of Headache Disorders.[11] Migraine subtype was classified into MA and MO. All migraineurs visited Department of Neurology, PL Tokyo Health Center, Tokyo, Japan. All participants provided written consent for participation. The study protocol was approved by the Committee on the Ethics of PL Tokyo Health Center.

Lomerizine Administration and Clinical Assessments

After the investigation period of 3 months without preventive treatment, lomerizine (5 mg, b.i.d.) was administered orally for 3 months. Headache Impact Test-6 (HIT-6) was recorded for evaluation of headache severity before treatment (baseline) and 3 months after treatment with lomerizine (end point).[12] The change rate of HIT-6 score was defined as 1 – (end point score/baseline score) × 100%. The change rate was divided into 3 groups of an excellent responder (≥70%), a good responder (50%-69%), and a nonresponder (≤49%). BP was recorded at baseline and end point.

rCBF Measurement and Analysis Using Brain SPECT

Brain SPECT using ^{99m}Tc-ethyl cysteinate dimer (ECD) was performed during the headache-free interictal period. SPECT was scanned at 10 minutes after intravenous bolus injection of 1.5 mL (600 MBq), ^{99m} Tc-ECD SPECT was conducted using a rotating γ-camera (Prism 3000; Picker International Inc., Bedford Heights, OH). Brain SPECT data were analyzed according to the revised version of 3-dimensional stereotaxic region of interest (ROI) template.[13] A total of 636 ROIs were set in bilateral cerebral cortexes and cerebellar hemispheres. SPECT images were divided as rCBF into 24 symmetrical (right and left) regions per patient: the callosomarginal, the precentral, the central, the parietal, the angular, the temporal, the posterior, the pericallosal, the lenticular nucleus, the thalamus, the hippocampus, and the cerebellar hemisphere. Quantification of rCBF was assessed using the noninvasive Patlak plot method without blood sampling.[14] Data of rCBF are shown in mL/100 g/min.

Data Analysis

Clinical variables and rCBF are expressed by the mean value (standard deviation [SD]). All parameters before and after lomerizine treatment were analyzed statistically using paired Student's *t* test. The significance level was set at .05. All data were analyzed by PASW Statistics 18.0 (IBM, Chicago, IL).

Results

Clinical Background of Migraineurs

A total of 10 migraineurs (6 women and 4 men) participated in the present study.

Brain magnetic resonance imaging and angiography showed no pathognomonic lesions in all migraineurs. Clinical background of migraineurs is shown in Table 1. Migraine subtype revealed MA in 4 patients and MO in 6 patients. The mean age was 54.1 (SD 10.1) years. The mean duration of migraine was 25.3 (SD 9.8) years. The mean score (SD) of HIT-6 was 66.3 (11.7) points at baseline and 28.1 (15.0) at end point. HIT-6 scores significantly decreased at end point compared with baseline ($P < .01$). The change rate in HIT-6 score after lomerizine treatment showed excellent response in 5 patients (50%), good response in 3 patients (30%), and nonresponse in 2 patients (20%). Eight patients (80%) responded to lomerizine treatment with a reduction rate in HIT-6 score of greater than or equal to 50%. Hypertension was found in 1 patient (10%). The mean systolic BP (SBP) at baseline was 110.6 (SD 12.2) mm Hg, and diastolic BP (DBP) was 72.7 (SD 10.0) mm Hg. After lomerizine treatment, the mean SBP and DBP were 109.6 (SD 9.9) mm Hg and 70.1 (SD 8.9) mm Hg, respectively. Lomerizine treatment did not alter SBP and DBP at end point significantly compared with baseline. All patients had no adverse events during lomerizine medication.

rCBF Changes before and after Lomerizine Administration

Data of rCBF are summarized in Table 2. Lomerizine treatment potentiated rCBF significantly at end point compared with baseline. Brain perfusion increased 20% approximately in the cerebrocortical regions. rCBF did not increase statistically in the deep brain territory of the lenticular nucleus and the thalamus. Statistical