Intra-arterial Administration of Fasudil Hydrochloride for Vasospasm Following Subarachnoid Hemorrhage

—Analysis of Time-Density Curve With Digital Subtraction Angiography—

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Abstract

The cerebral circulatory dynamics were evaluated before and after intra-arterial administration of fasudil hydrochloride in 20 patients with angiographic vasospasm after subarachnoid hemorrhage (SAH). The region of interest time-density curves obtained before and after intra-arterial administration of fasudil hydrochloride were compared in the proximal portion of the middle cerebral artery in the early arterial phase, the distal portion of the middle cerebral artery in the late arterial phase, and the transverse sinus in the venous phase. In the early arterial phase, the time to peak and the time to half-peak were significantly reduced. In the late arterial phase and venous phase, the time to peak was significantly reduced. These results suggest that intra-arterial administration of fasudil hydrochloride induced dilation of the proximal arteries, and improved cerebral microcirculation. The present study suggests that intra-arterial administration of fasudil hydrochloride is effective as a treatment for vasospasm following SAH.

Key words: subarachnoid hemorrhage, vasospasm, fasudil hydrochloride, intra-arterial administration, time-density curve

Introduction

Fasudil hydrochloride is an inhibitor of myosin light chain kinase, which is essential in smooth muscle contraction. Fasudil hydrochloride also inhibits Rho-associated protein kinase, which affects vascular smooth muscle contraction by inactivating myosin light chain phosphatase. Fasudil hydrochloride is effective to prevent vasospasm following subarachnoid hemorrhage (SAH), and is widely administered intravenously in Japan. However, no significant differences were found in activities of daily living improvement at discharge between patients treated before and after the widespread clinical introduction of fasudil hydrochloride, and no improvement in clinical outcome in patients with severe SAH. Indeed, some patients have residual ischemic lesions and delayed ischemic neurological deficit caused by vasospasm even after administra-

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Table 1 Patient characteristics with intra-arterial administration of fasudil hydrochloride (IAF)

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Materials and Methods

I. Patients
Twenty patients, 13 women and seven men aged 37 to 77 years (mean 55.5 years), underwent radical treatment for ruptured aneurysms within 72 hours of SAH (Table 1). In our hospital, transcranial Doppler ultrasonography, diffusion-weighted magnetic resonance imaging, and single photon emission computed tomography are performed daily for about 7 days after onset to detect the early stage of vasospasm. Cerebral angiography is performed between 7 and 10 days after onset in all patients, including asymptomatic patients. Detection of angiographic vasospasm indicates intra-arterial administration of fasudil hydrochloride through the diagnostic catheter. Cerebral angiography is performed for vasospasm in 32 vessels. Seven patients showed deterioration of level of consciousness or neurological deficits due to vasospasm. The other 13 patients had angiographic vasospasm but no symptoms.

II. Intra-arterial administration of fasudil hydrochloride
A 5-French catheter was inserted via the femoral artery into the cervical portion of the internal carotid artery. Intra-arterial administration of fasudil hydrochloride (Asahi Kasei Corp., Tokyo) injected 15 mg of fasudil hydrochloride dissolved in 20 ml of physiological saline into the patient through the catheter over about 15 minutes following the diagnostic angiography. This procedure was performed once or twice.

III. Digital subtraction angiography (DSA)
Contrast agent (7 ml) was injected into the internal carotid artery at 4 ml/sec by autoinjector. Images were obtained at six frames per second with a DSA unit (KXO-80 C/D, DFP-2000A; Toshiba Medical...
System Co., Ltd., Tokyo) using a pixel matrix of 1024 × 1024. The region of interest (ROI) was defined as the proximal portion of the middle cerebral artery (ROI 1) in the early arterial phase on frontal DSA images taken before and after intra-arterial administration of fasudil hydrochloride (Fig. 1A). The time-density curve of the ROI was calculated before and after intra-arterial administration of fasudil hydrochloride. This time-density curve was used to determine the time to peak opacification and the time to half-peak opacification ($T_{1/2}$), which was defined as the time from peak opacification to half washout of the contrast medium, for comparison before and after intra-arterial administration of fasudil hydrochloride. The ROI was then shifted to the distal portion of the middle cerebral artery (ROI 2) in the late arterial phase and the transverse sinus (ROI 3) in the venous phase (Fig. 1B, C), and the time-density curves and the time to peak values were obtained as above. The patients were then divided into two groups, those given 15 mg fasudil hydrochloride and those given 30 mg fasudil hydrochloride, for comparison of the calculated values. Ten patients without stenotic lesions of either the cervical carotid artery or the large intracranial arteries were used as normal controls.

IV. Statistical analysis
Data are expressed as the mean ± standard deviation. The paired t-test was used for comparison of the cerebral circulation time before and after intra-arterial administration of fasudil hydrochloride. A probability value of less than 0.05 was considered statistically significant. Patients with data that could not be properly compared or evaluated, such as those with varying angiographic conditions or motion artifacts, were excluded from the study.

Results

I. Clinical effects
Three of the seven patients with symptomatic vasospasm showed dramatic clinical improvement. Three of the 20 patients had ischemic lesion on computed tomography at discharge, but these three patients finally achieved either good recovery ($n = 2$) or moderate disability ($n = 1$) according to the Glasgow Outcome Scale. The 13 asymptomatic patients developed no progression of angiographic to symptomatic vasospasm after intra-arterial administration of fasudil hydrochloride (Table 1). No patient showed any significant changes in vital signs, such as lower blood pressure or symptomatic autonomic responses, or any other adverse effects resulting from intra-arterial administration of fasudil hydrochloride.

II. Angiographic effects
ROI 1: The time to peak was 2.95 ± 0.40 seconds ($n = 32$) before intra-arterial administration of fasudil hydrochloride, and was significantly reduced to 2.71 ± 0.42 seconds ($n = 31$) in the 15 mg fasudil hydrochloride group ($p < 0.0001$) and to 2.60 ± 0.40 seconds ($n = 27$) in the 30 mg fasudil hydrochloride group ($p < 0.0001$) (Fig. 2A). The time to peak was significantly shorter in the 30 mg fasudil hydrochloride group ($p < 0.05$) compared with the 15 mg group. The time to peak was 2.70 ± 0.27 seconds in the control group. The $T_{1/2}$ was 2.40 ± 0.84 seconds ($n = 31$) before administration and was significantly reduced to 1.97 ± 0.64 seconds ($n = 31$) in the 15 mg fasudil hydrochloride group ($p < 0.0001$) and 1.83 ± 0.70 seconds ($n = 25$) in the 30 mg fasudil hydrochloride group ($p < 0.01$) (Fig. 2A). The $T_{1/2}$ was slightly
shorter in the 30 mg fasudil hydrochloride group, but the difference was not significant. The T_{1/2} was 1.97 ± 0.69 seconds in the control group.

ROI 2: The time to peak was 4.24 ± 0.47 seconds (n = 16) before administration and was significantly reduced to 3.78 ± 0.47 seconds (n = 16) in the 15 mg fasudil hydrochloride group (p < 0.0001) and 3.48 ± 0.28 seconds (n = 14) in the 30 mg fasudil hydrochloride group (p < 0.0001) (Fig. 2B). The time to peak was significantly shorter in the 30 mg fasudil hydrochloride group (p < 0.05). The time to peak was 4.03 ± 0.57 seconds in the control group.

ROI 3: The time to peak was 8.97 ± 1.06 seconds (n = 16) before administration and was significantly reduced to 8.17 ± 1.11 seconds (n = 16) in the 15 mg fasudil hydrochloride group (p < 0.0001) and 7.88 ± 0.98 seconds (n = 14) in the 30 mg fasudil hydrochloride group (p < 0.0001) (Fig. 2C). The time to peak was significantly shorter in the 30 mg fasudil hydrochloride group (p < 0.05). The time to peak was 6.62 ± 1.35 seconds in the control group.

**Discussion**

The present study showed that the time to peak and T_{1/2} were significantly reduced in the proximal portion of the middle cerebral artery in the early arterial phase after intra-arterial administration of fasudil hydrochloride, and the time to peak was significantly reduced in the distal portion of the middle cerebral artery in the late arterial phase, and the transverse sinus in the venous phase.

Investigation of angiographic changes and cerebral circulation time in ruptured aneurysms with intra-arterial DSA showed that delay in cerebral circulation time may provide an index of vasospasm severity. Prolonged cerebral circulation time during cerebral vasospasm was improved by injecting sodium papaverine, suggesting that dilation of small arteries induced by papaverine administration was attributable to shortening of prolonged cerebral circulation time. In the present study, comparison of ROI time-density curves obtained before and after intra-arterial administration of fasudil hydrochloride showed the circulation time after fasudil hydrochloride administration was significantly shorter, indicating that intra-arterial administration of fasudil hydrochloride clinically improves cerebral ischemia due to vasospasm.

An experimental study found dosage-dependent expansion of the vessel diameter after intravenous administration of fasudil hydrochloride. The present study showed that intra-arterial administration may be useful for elevating the local blood concentration of the agent and can be safely performed.
without significant hypotension or autonomic response symptoms such as pupillary dilation or sweating, which often occur after intra-arterial administration of papaverine hydrochloride.

Autoregulation is impaired during vasospasm, since the autoregulatory response to changes in PaCO$_2$ or acetazolamide administration is reduced.$^{1,2,11,16}$ This weak autoregulatory response has been attributed to maximal dilation of the peripheral arterioles to maintain sufficient cerebral blood flow in the presence of decreased cerebral perfusion pressure due to vasospasm. However, a recent histological study revealed that intraparenchymal small arteries or arterioles show luminal narrowing rather than dilation during cerebral vasospasm after experimental SAH.$^5$ Thus, although whether the peripheral arterioles are dilated or constricted at vasospasm remains unclear, disturbance of the intracerebral microcirculatory system may be involved in cerebral ischemia due to vasospasm. Microcirculatory changes manifesting as prolonged peripheral cerebral circulation time are thought to be involved in cerebral ischemia during cerebral vasospasm,$^5$ and the reduction in regional cerebral blood flow was significantly correlated with prolonged peripheral cerebral circulation time in our patients with angiographic vasospasm.

The present study found that intra-arterial administration of fasudil hydrochloride induced dilation of the proximal arteries, and improved cerebral microcirculation in patients with vasospasm indicating the effectiveness of this procedure as a treatment for vasospasm following SAH.

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References


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Commentary

Vasospasm is the primary cause of death and permanent neurologic disability in patients with subarachnoid hemorrhage. Various treatment modalities have been adopted for the treatment of this devastating complication. These treatments could be categorized into two groups: mechanical angioplasty and chemical angioplasty. Mechanical angioplasty can be applied only to proximal vessel segments. For chemical angioplasty, papaverine was the mainstay for the treatment of the angiographically verified vasospasm. However, many adverse effects of papaverine urged the use of other agents such as nicardipine, nimodipine, and verapamil. The present study shows that intra-arterial administration of fasudil hydrochloride, a potent inhibitor of protein kinases A, G, and C, and myosin light-chain kinase, is effective for the treatment of vasospasm after subarachnoid hemorrhage. By analyzing the time-density curve with digital subtraction angiography, the present study showed intra-arterial fasudil hydrochloride is effective in inducing dilation of the proximal arteries, and improves cerebral microcirculation in patients with vasospasm. It is meaningful that this study adds fasudil hydrochloride to the list of antispasmodic agents. What I would like to demand is more experience for possible complications and another prospective comparative study in the near future.

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Iwabuchi and colleagues examined the effect of fasudil hydrochloride on the time-density change of digital subtraction angiography at the regions of interest placed on the middle cerebral artery and the transverse sinus in patients with angiographic vasospasm following subarachnoid hemorrhage. Intra-arterial infusion of fasudil hydrochloride resulted in significant reduction of the time to peak interval in the early and late arterial phases and the venous phase, and improved both proximal arterial circulation and cerebral microcirculation. Fasudil hydrochloride, a protein kinase inhibitor, may be one of the most widely used agents for vasospasm in Japan, although its intravenous administration may be more popular. The present study supports the previous notion that fasudil hydrochloride effectively dilates vasospastic artery sufficiently to improve cerebral circulation and outcomes of the patients. Since the authors compared the data obtained immediately before and after the administration, they did not mention how long and to what extent fasudil hydrochloride keeps the vasospastic arteries in dilation. We await a further study investigating its effect in detail, and the exact mechanism by which fasudil hydrochloride improves the outcome of patients.

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Iwabuchi et al. reported on their experience with intra-arterial fasudil for the treatment of cerebral vasospasm after SAH. They treated 20 patients with immediate clinical improvement in 3 patients and good recovery in GOS in 80% (16/20) of patients. This is a retrospective, nonrandomized case series, although it set up a normal control which included 10 patients without either cervical carotid artery stenosis or large intracranial artery stenosis. Therefore, the study is subject to the well-known limitation of studies of this nature. Moreover, it is a pity some important information could not be found from the study. For example, except for intra-arterial fasudil, whether intravenous fasudil or nicardipine were used. Readers were not informed of the routine protocols for the treatment of SAH in the author’s institute and the end point time of the study. The trial does, however, provide a new and sound method of ‘time-density curve’ to evaluate the effectiveness of the treatment, and adds positive support to intra-arterial fasudil for the treatment of devastating vasospasm after SAH. Still, a prospective, randomized case control trial is needed.

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