Letter to the Editor

To the editor:

1) Late vasospasm is very difficult to control, since it is caused by strong chemical reaction to the smooth muscle. The authors certified the protective effect with nicardipine prolonged-release implants on the late vasospasm at the proximal portions of main cerebral arteries, that may be effective from arteries to arterioles. But the procedures become meaningless if the infarctions occur at the peripheral portions of the arteries. How about the threshold value of nicardipine protecting against late vasospasm of proximal portions of the main cerebral arteries? Is there a particular difference to maintain the threshold value on the vascular smooth muscle between intrathecal use and systemic use; is there a particular difference for nicardipine to reach the smooth muscle between through the adventitia and through the endothelium?

2) In elderly patients aged over 70 years, it is not seldom that less late vasospasm would be found in spite of severe subarachnoid hemorrhage (Fisher grade III). How about the difference in the protective effect of nicardipine on late vasospasm between elderly patients and younger ones?

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Reply:

We thank Dr. Norio Aoyagi for his valuable comments regarding our drug delivery system for preventing cerebral vasospasm. Our responses to his questions are presented below.

1) Currently, there are no drugs supported by sufficient evidence of efficacy for cerebral vasospasm in patients with subarachnoid hemorrhage, despite abundant evidence of anti-vasospasm drugs at the experimental level. The problem cannot be solved by developing new drugs but by developing methods to maintain an appropriate concentration of the drug in the target cerebral artery and its surrounding environment.²⁾ In the past, in experiments with a canine subarachnoid model using 8 mg of nicardipine pellets, the mean concentration of nicardipine in the clots was 1.5×10^{-4} mol/l on Day 7 and 5.1×10^{-6} on Day 14. This drug delivery system can prevent vasospasm significantly in dogs, while maintaining an appropriate concentration of

nicardipine in the clot adjacent to the arteries, since maximal relaxation is achieved by 10^{-6} mol/l of nicardipine.⁵⁾

We consider that this could not be achieved by systemic administration of drugs but rather by local treatment. We suggest that vasospasm can be completely prevented in arteries in cisterns with thick clots, where vasospasm is highly expected, by placing pellets adjacent to the arteries during surgery. Less efficacy was found for arteries remote from the placement of pellets.^{3,4)} Nicardipine was probably adsorbed by the clot and arterial tissue near the pellets.

2) We did not compare the difference in efficacy between young and elderly patients, because there is no evidence that elderly patients have less vasospasm.¹⁾

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Neurol Med Chir (Tokyo) 47, 389~396, 2007

Nicardipine Prolonged-Release Implants for Preventing Cerebral Vasospasm After Subarachnoid Hemorrhage: Effect and Outcome in the First 100 Patients

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Abstract

Vasospasm following subarachnoid hemorrhage (SAH) remains difficult to prevent despite extensive investigative efforts. Nicardipine prolonged-release implants (NPRIs) have been used to prevent vasospasm in patients with SAH since October 1999. The present study analyzed the efficacy and safety of NPRIs in 100 patients with SAH and thick subarachnoid clot (mainly Fisher group 3) treated with NPRIs (diameter 2 mm, length 10 mm, containing 4 mg of nicardipine) during surgery after clipping of the aneurysm. The number and location of pellets depended on the amount and site of the subarachnoid clot on preoperative computed tomography and on the type of craniotomy. Two to 12 pellets were implanted in the cisterns of the internal carotid artery, middle cerebral artery, and/or anterior cerebral artery, where thick clots were present and vasospasm related to delayed ischemic neurological deficit (DIND) was highly likely. Only seven patients developed DIND and five patients suffered cerebral infarction. Angiography performed on days 7–12 revealed no vasospasm in any of the arteries close to the site of NPRI placement. NPRI placement can completely prevent vasospasm in arteries within the cisterns containing thick clots, but is less effective in remote locations.