Combination Therapy of Fasudil Hydrochloride and Ozagrel Sodium for Cerebral Vasospasm Following Aneurysmal Subarachnoid Hemorrhage

Susumu NAKASHIMA, Kazuo TABUCHI, Shoko SHIMOKAWA, Kouzou FUKUYAMA, Toshihiro MINETA, and Masamitsu ABE

Department of Neurosurgery, Saga Medical School, Saga

Abstract

Fasudil hydrochloride is a new type of intracellular calcium antagonist, different from the calcium entry blockers that are commonly employed for clinical use. Since September 1995, the combination of fasudil hydrochloride and ozagrel sodium, an inhibitor of thromboxane A$_2$ synthesis, has been used to treat 60 patients at risk of cerebral vasospasm after aneurysmal subarachnoid hemorrhage. The effectiveness of this combination therapy was investigated by comparison with the outcome of 57 patients previously treated with only ozagrel sodium. The combination therapy was significantly more effective ($p < 0.01$) in reducing the incidence of low density areas on computed tomography scans, and reduced, but not significantly, the occurrence of symptomatic vasospasm. The combination therapy of fasudil hydrochloride and ozagrel sodium has superior effectiveness over only ozagrel sodium in treating patients at risk of vasospasm after aneurysmal subarachnoid hemorrhage.

Key words: subarachnoid hemorrhage, vasospasm, fasudil hydrochloride, ozagrel sodium, combination therapy

Introduction

Delayed cerebral vasospasm is a serious complication of subarachnoid hemorrhage (SAH) which has resulted in death or severe neurological deficits in 33.5% of cases of vasospasm. Various modalities of therapy and medications have been applied to the treatment of vasospasm such as ozagrel sodium, nizofenone fumarate, dihydropyridine calcium antagonist, or cisternal irrigation using either urokinase or tissue plasminogen activator, but any satisfactory results have not yet been attained. At our institution, ozagrel sodium has been used to suppress vasospasm, since it is known to inhibit the synthesis of thromboxane A$_2$ derived from blood platelets, so is expected to have a potent effect against vascular contraction. Ozagrel sodium alleviates the symptoms accompanying cerebral ischemia due to vasospasm. However, we have not obtained favorable results.

Fasudil hydrochloride is a new chemical compound synthesized in Japan and screened from numerous isoquinoline derivatives. This drug is a new type of calcium antagonist which directly affects intracellular Ca$^{2+}$, in contrast to most commonly used calcium antagonists which are calcium entry blockers. The effectiveness of fasudil hydrochloride has been confirmed in delayed cerebral vasospasm in dogs. A multi-center controlled double-blind study was carried out in Japan, and favorable clinical results obtained in patients with vasospasm after rupture of a cerebral aneurysm. Therefore, fasudil hydrochloride was approved by the Ministry of Health and Public Welfare, Japan for clinical use in September 1995. Since then, we have been administering a combination of fasudil hydrochloride and ozagrel sodium to consecutive patients who underwent clipping surgery within 3 days after aneurysmal SAH.

This study investigated the effectiveness of the combination therapy by comparing the clinical courses of patients treated with combination of fasudil...
hydrochloride and ozagrel sodium and patients treated with only ozagrel sodium.

**Materials and Methods**

A total of 176 patients with SAH due to ruptured cerebral aneurysms were treated between January 1993 and August 1997. We selected 117 patients based on their neurological grades (Hunt and Kosnik grades I-IV) and operative timings. Between January 1993 and August 1995, 57 patients (Group A) who underwent clipping surgery within 72 hours after the onset of SAH were treated with ozagrel sodium (intravenous 80 mg/day) for 14 consecutive days. Since September 1995, 60 patients (Group B) who underwent clipping surgery within 72 hours after the onset of SAH were treated with a combination of fasudil hydrochloride (intravenous 30 mg x 3/day) and ozagrel sodium (intravenous 80 mg/day) for 14 consecutive days.

Subarachnoid hematoma was not actively removed at surgery, and postoperative cisternal drainage was generally performed for 7 to 14 days. Other drugs (i.e. plasma protein fraction, dopamine hydrochloride, etc.) to induce hypertension and hypervolemia were used similarly in both groups.

Possible adverse effects and the effectiveness of this combination therapy were thoroughly explained, and the consent of the patients or their family members was obtained.

The following items were compared between the two groups: neurological grading on admission (Hunt and Kosnik's classification), computed tomography (CT) findings on admission (Fisher's CT classification), occurrence of symptomatic vasospasm during the course of treatment, occurrence of low density areas on CT during the course of treatment, functional outcome at discharge (Glasgow Outcome Scale), and adverse effects caused by the drugs. The presence or absence of symptomatic vasospasm was determined based on the presence or absence of focal signs and/or symptoms such as disturbed consciousness, impaired speech, or hemiparesis. Low density areas on CT scans not detected on the day after surgery, but appearing 1 to 3 weeks later were defined as cerebral infarction caused by vasospasm. Clinical data were analyzed by the chi-square test with Yates' continuity correction. A p value of less than 0.05 was considered significant.

**Results**

There were no significant differences in clinical characteristics between the two groups in age and duration of hospitalization and location of ruptured aneurysms (Table 1). The severity of neurological symptoms on admission (Hunt and Kosnik) showed the incidence of grade I patients was greater in Group A than in Group B, but without significant difference. There was little difference in the incidence of grade III patients between Groups A and B. CT findings on admission (Fisher's system) showed no significant difference between the two groups.

Symptomatic vasospasm was confirmed in 24 of the 57 patients in Group A and in 18 of the 60 patients in Group B. The incidence was lower in Group B, but there was no statistical difference. There was little difference in the incidence of grade III patients between Groups A and B. CT findings on admission (Fisher's system) showed no significant difference between the two groups.

Symptomatic vasospasm was confirmed in 24 of the 57 patients in Group A and in 18 of the 60 patients in Group B. The incidence was lower in Group B, but there was no statistical difference.

Low density areas were detected in 19 patients in Group A and six patients in Group B. There was a statistically significant difference between Groups A and B (p < 0.01).

Figure 1 shows the relationship between occurrence of symptomatic vasospasm and low density areas on CT scans. Although induced hypertension and hypervolemia therapy were actively employed when vasospasm was likely to occur, 19 of the 24 patients in Group A who experienced symptomatic vasospasm eventually developed cerebral infarction. The other five patients had no low density areas or

### Table 1 Characteristics of 117 patients with aneurysmal subarachnoid hemorrhage

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>χ² test</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>57</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Age* (yrs)</td>
<td>58 ± 10.4</td>
<td>58 ± 12.0</td>
<td>NS</td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>ICA</td>
<td>15 (26%)</td>
<td>18 (30%)</td>
<td></td>
</tr>
<tr>
<td>MCA</td>
<td>18 (32%)</td>
<td>14 (23%)</td>
<td></td>
</tr>
<tr>
<td>ACA</td>
<td>24 (42%)</td>
<td>27 (45%)</td>
<td></td>
</tr>
<tr>
<td>VB</td>
<td>0</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Hunt &amp; Kosnik grade</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>I</td>
<td>15 (26%)</td>
<td>4 (7%)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>15 (26%)</td>
<td>26 (43%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>22 (39%)</td>
<td>21 (35%)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>5 (9%)</td>
<td>9 (15%)</td>
<td></td>
</tr>
<tr>
<td>Fisher's CT group</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>2</td>
<td>11 (19%)</td>
<td>12 (20%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>33 (58%)</td>
<td>36 (60%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>13 (23%)</td>
<td>12 (20%)</td>
<td></td>
</tr>
<tr>
<td>Duration of hospitalization* (days)</td>
<td>50 ± 15</td>
<td>47 ± 13</td>
<td>NS</td>
</tr>
</tbody>
</table>

any other sign or symptom related to cerebral infarction. In contrast, 12 of the 18 patients in Group B who developed vasospasm had no signs of cerebral infarction.

Clinical outcome at discharge (Glasgow Outcome Scale) showed a greater incidence of good recovery and moderate disability in Group B than in Group A, but there was no statistically significant difference in summary results (Table 2). The causes of poor outcomes in both groups were further analyzed. Twelve of 21 patients in Group A were affected by vasospasm, four by surgery, three by primary brain damage, and two by systemic complication. In contrast, only three of 13 patients in Group B seemed to be affected by vasospasm, four patients by surgery, four by primary brain damage, and two by severe systemic complication. So in the revised results, by excluding patients whose outcome was worsened by any cause other than vasospasm (Table 2), the incidence of good recovery and moderate disability in the two groups was statistically different (p < 0.01). Group A: treated with ozagrel sodium, Group B: treated with combination of fasudil hydrochloride and ozagrel sodium.

### Discussion

Fasudil hydrochloride is a new type of calcium antagonist synthesized by a Japanese group in the search for various sulfonamide derivatives. Generally, calcium antagonists are classified into two groups: calcium entry blockers, which act primarily by inhibiting the influx of the extracellular Ca$^{2+}$ into cells through the slow channel in the cell membrane; and intracellular calcium antagonists, which interfere with the physiological functions of Ca$^{2+}$. Most calcium antagonists, such as nifedipine, nicardipine, diltiazem, are classified as calcium entry blockers. Fasudil hydrochloride is considered to be an intracellular calcium antagonist, and is assumed to selectively inhibit intracellular calcium ion activity, and to inhibit the protein kinases A, G, and C as well as the myosin light-chain kinase that is essential in smooth-muscle contraction. This action is clearly different from the other calcium entry blockers. Preliminary studies of fasudil hydrochloride$^{2,3,21,29}$ have shown that: Fasudil...
hydrochloride inhibits the phosphorylation of myosin light chains, a calcium-dependent reaction, without decreasing intracellular calcium concentration; fasudil hydrochloride administered intravenously in a canine vasospasm model increases the blood flow of the cerebral cortex by dilating the basilar artery, and the onset of vasospasm is significantly suppressed by continuous administration; and fasudil hydrochloride prevents delayed neuronal death in the rat cerebral ischemia model in which the ischemia is induced by temporary carotid artery occlusion.

This study was a prospective, non-contemporaneous, non-randomized clinical trial, so only the ozagrel sodium group (Group A) and combination of ozagrel sodium and fasudil hydrochloride group (Group B) were simply compared and analyzed. In Group A, low density areas on CT scans were seen in 19 (79.2%) of 24 patients who experienced symptomatic vasospasm, whereas in Group B, low density areas were observed in six (33.3%) of 18 patients who experienced symptomatic vasospasm. So there was no statistically significant difference in the occurrence of symptomatic vasospasm, however, there was statistically significant difference in the incidence of low density areas on CT scans (p < 0.01) between the two groups. The ischemic symptoms related to vasospasm were felt to be more reversible and transient in Group B. Furthermore, with regard to the speed of symptomatic vasospasm development, hemiparesis generally occurred suddenly in Group A, whereas in Group B the onset of symptomatic vasospasm seemed to be more gradual. We conclude that the combination therapy is more effective for treating patients with vasospasm, because the revised clinical outcome at discharge was more favorable in Group B.

We could not evaluate the effect of only fasudil hydrochloride, so Fig. 2 compares our results to a previous study conducted by Takakura et al.23,25 Our administration method of fasudil hydrochloride was the same as that of their study. Since our present study analyzed a limited number of patients, and the characteristics of the patients varied, no definite conclusion can be drawn. Nonetheless, the incidence of low density areas on CT scans was slightly lower when both ozagrel sodium and fasudil hydrochloride were administered. The combination of these two drugs with different action mechanisms is apparently clinically effective for treating patients with vasospasm due to SAH after rupture of a cerebral aneurysm.

Fig. 2 Incidence of symptomatic vasospasm (left) and low density areas on computed tomography scans (right): Comparison between the results of our study (Groups A and B) and those of the fasudil hydrochloride double-blind trial conducted by Takakura et al.23,25 open column: present, shaded column: absent.

References

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Address reprint requests to: S. Nakashima, M.D., Department of Neurosurgery, Okayama Kyokuto Hospital, 567-1 Kurata, Okayama 703-8265, Japan.

Commentary

This study raises important points of principle in the treatment of delayed vasospasm and other conditions. It was, as the authors point out, a comparison of two consecutive groups of patients, rather than a randomized trial. However, the latter would have been much more expensive (and probably not supported by a pharmaceutical company) and difficult to carry out, and would also have taken much longer. Furthermore, if one feels from the evidence of other studies that a new treatment (fasudil in this case) is effective, then it is difficult ethically to justify further trials where some patients do not receive that treatment.

In spite of this deficiency the results are encouraging, with 42% incidence of symptomatic vasospasm in those receiving ozagrel only, and 30% in the group with fasudil as well. The difference in the frequency of CT low density areas (I always have a problem with this rather loose term — if an area of low density, due say to transient edema, appears on a scan one week and is gone a week later, then it is meaningless. A difference in incidence of low density areas that are due to an infarct and persist unchanged would be much more relevant clinically) did reach statistical significance. As noted, the effect of the vasospasm was possibly less severe in the second group; 79% of those with vasospasm in the first group also developed low density areas, compared with 33% in the second group.

From the patient’s point of view these findings are not relevant, but the outcome is. There is a trend, which reaches statistical significance if causes of a poor outcome apart from vasospasm are eliminated (Table 2 of this article), towards a better outcome in the group with combined treatment (the functional outcome at discharge measured here is often not strongly related to capabilities six or 12 months later). Perhaps with more cases a significant difference would have been found between the whole groups in Table 2, but that was not possible in the context of this study.

It should be remembered that delayed vasospasm is a multi-factorial problem, with a complex cascade of biochemical events leading eventually to symptomatic ischemia. It seems eminently reasonable, therefore, to do as this group has done and attack the problem at all possible points along this chain of events. The multi-action calcium antagonist fasudil or AT877 may be especially well suited for such a purpose.

Nicholas W. C. Dorsch, F.R.C.S., F.R.A.C.S.
Department of Neurosurgery
Westmead Hospital
Sydney, Australia

Cerebral vasospasm after subarachnoid hemorrhage is a serious complication which decides the surgical results of ruptured intracranial aneurysms. Although various modalities of therapy and medications have been applied, satisfactory clinical results have not yet been attained. The authors report encouraging results in which combined therapy of fasudil hydrochloride and ozagrel sodium achieved superior effectiveness over only ozagrel sodium for treating this disease. The pathogenesis of vasospasm is considered to be multifactorial, and such a combined therapy of two drugs with different action mechanisms should be an effective clinical approach. However, treatment of vasospasm remains controversial, and this study is a prospective and non-randomized clinical trial in a small series. Scientific documentation of this method will require careful evaluation in a randomized large series. Further studies are expected.

Shunro Endo, M.D.
Department of Neurosurgery
Toyama Medical and Pharmaceutical University
Toyama, Japan

The authors carried out a prospective, non-contemporary, non-randomized clinical trial to study the effectiveness of combination therapy of fasudil hydrochloride (intracellular calcium antagonist) and ozagrel sodium for cerebral vasospasm following aneurysmal subarachnoid hemorrhage. They concluded that the combination therapy of fasudil hydrochloride and ozagrel sodium was significantly more effective in reducing the incidence of low density areas and reduced, but not significantly, the occurrences of symptomatic vasospasm compared to only ozagrel sodium treated group. As they could not evaluate the ef-
fect of fasudil hydrochloride only, we presume that it would be better to perform a randomized study with only fasudil chloride in larger number of Fisher group 3 patients to clarify the effect of an intracellular calcium antagonist on cerebral vasospasm.

Seung Kon HUH, M.D. and Kyu Chang LEE, M.D.
Department of Neurosurgery
Yonsei University College of Medicine
Seoul, R.O.K.