Efficacy of Edaravone, a Free Radical Scavenger, for the Treatment of Acute Lacunar Infarction

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Abstract
The effect of edaravone as an inhibitor of ischemic brain damage in addition to routine treatment was retrospectively examined in 70 patients with lacunar infarction who were admitted within 24 hours of symptom onset. Clinical status was assessed using the National Institutes of Health Stroke Scale (NIHSS). The modified Rankin Scale (MRS) was used to assess clinical outcomes at 3 months after onset, with a good outcome defined as MRS score ≤2. Risk factors were also evaluated, including evidence of hypertension, diabetes mellitus, hyperlipidemia, coronary heart disease, and a history of smoking longer than 2 months. The probability of a good outcome and independence at 3 months was assessed by backward stepwise logistic regression analysis based on the maximum likelihood ratio. Administration of edaravone yielded an odds ratio with multivariate adjustment of 6.49 (95% confidence interval, 1.35 to 50.32; p < 0.05) for a good outcome at 3 months. Higher baseline NIHSS score and higher age also adversely affected the outcome at 3 months (p < 0.005). Administration of edaravone improves the outcome of patients with lacunar infarction.

Key words: edaravone, free radical scavenger, lacunar infarction, heparin, ozagrel sodium

Introduction
Free radicals are thought to be important in the occurrence of neural damage during cerebral infarction.8,23) Methods of neuroprotection against acute stroke have attracted much attention and many neuroprotective agents appeared to work in animals, but most clinical trials have produced negative or disappointing results.2,9) A recent Japanese multicenter study showed that a novel free radical scavenger, edaravone, was efficacious in patients with acute ischemic stroke.7) In vitro and in vivo studies showed that edaravone inhibited brain edema after ischemia,1,19) tissue injury,28) delayed neuronal death,30) and vascular endothelial cell injury.27) However, the effectiveness of edaravone in patients with stroke remains unclear.7) This study investigated the effect of edaravone on the outcomes in patients with acute lacunar infarction in addition to routine treatment.

Materials and Methods

I. Subjects
This study retrospectively evaluated 613 consecutive patients with cerebral infarction who were hospitalized in Nippon Medical School Chiba-Hokusoh Hospital between June 1999 and May 2002 to identify patients with lacunar infarction who were admitted within 24 hours of symptom onset. Edaravone is approved for use within 24 hours of the onset of acute cerebral infarction by the Ministry of Health, Labour and Welfare, Japan, and has been available in Japan since June 2001.

Patients with unclear time of onset were excluded, for example, those who suffered the insult while asleep. Patients who received urokinase, tissue plasminogen activator, or low-molecular dextran during hospitalization, and patients with severe liver or renal dysfunction, recent gastrointestinal
bleeding, or malignant neoplasms were also excluded.

The patient population consisted of 48 men and 22 women aged 38 to 90 years (mean 68.5 ± 11.6 years).

II. Diagnosis

Lacunar infarction was defined according to the criteria of the Trial of Org 10172 in Acute Stroke Treatment classification system. On admission, all patients underwent computed tomography (CT) using a CT-W3000AD instrument (Hitachi Medical Co., Tokyo). Within 3 days of admission, T2-weighted and diffusion-weighted magnetic resonance (MR) imaging was performed to identify fresh lacunar infarction with a Signa Infinity 1.5 Tesla instrument (General Electric Company, Fairfield, Conn., U.S.A.). All patients had one of the conventional clinical lacunar syndromes, normal CT/MR imaging findings or a brainstem or subcortical lesion with a diameter of less than 1.5 cm, no potential cardiac sources of embolism, and no conventional or MR angiography evidence of stenosis greater than 50% in the large extracranial arteries. Two neurologists (M.M. and Y.K.) reviewed the neuroimaging studies to determine a consensus of the stroke subtype, and the anatomical location and topographic extension of the infarct considered to be responsible for the acute neurological deficit.

III. Treatment for lacunar infarction in the acute phase

The routine treatment for acute lacunar infarction until May 31, 2001 was continuous intravenous (iv) infusion of 10,000–15,000 units of heparin per day for 3 days, and iv drip infusion of 200 ml of 10% glycerol and 80 mg ozagrel sodium twice a day for 14 days. Some patients with very mild symptoms received glycerol and ozagrel sodium for only about 1 week. Patients were also treated with oral antiplatelet drugs, i.e. aspirin (81–100 mg) or ticlopidine (100–200 mg) daily. Most patients were examined by a rehabilitation specialist on the day following admission and started rehabilitation on the next day.

Edaravone was added to the conventional regimen used to treat patients with acute lacunar infarction after June 1, 2001. Therefore, all patients who received edaravone were also admitted after June 2001. Patients received 30 mg of edaravone with 100 ml of saline twice daily for 14 days by iv drip infusion. The duration of administration was shortened in the patients with very mild symptoms.

IV. Clinical assessment

Clinical status on arrival in the emergency room was assessed using the National Institutes of Health Stroke Scale (NIHSS). The modified Rankin Scale (MRS) was used to assess their clinical outcome at 3 months after onset, with a good outcome defined as MRS score ≤ 2. Risk factors were also evaluated, including evidence of hypertension, diabetes mellitus, hyperlipidemia, coronary heart disease, and a history of smoking for more than 2 months.

V. Statistical analysis

Analyses were performed using JMP 5.0.1 software (SAS Institute Inc., Cary, N.C., U.S.A.). The statistical significance for intergroup differences was assessed by the two-tailed Fisher’s exact test for categorical variables. The probability of a good outcome and independence at 3 months was assessed by backward stepwise logistic regression analysis based on the maximum likelihood ratio. A level of p < 0.05 was accepted as statistically significant.

Results

The patients’ risk factor profiles and baseline clinical findings are shown in Table 1. There was no significant difference with respect to the risk factors for stroke between the edaravone and non-edaravone groups. The medication period was 13.0 ± 0.4 days in the edaravone group, and 13.4 ± 0.3 days in...
Table 2  Logistic regression results for good outcome and independence (MRS ≤ 2) at 3 months

<table>
<thead>
<tr>
<th>Variable</th>
<th>MRS ≤ 2 (n = 49)</th>
<th>MRS &gt; 2 (n = 21)</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>33</td>
<td>15</td>
<td>0.30</td>
<td>0.04–1.99</td>
<td>0.23</td>
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<tr>
<td>Age ≤ 70 yrs</td>
<td>32</td>
<td>6</td>
<td>9.33</td>
<td>1.76–72.09</td>
<td>0.02</td>
</tr>
<tr>
<td>Hypertension</td>
<td>30</td>
<td>10</td>
<td>8.23</td>
<td>1.4–74.93</td>
<td>0.03</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>19</td>
<td>6</td>
<td>5.36</td>
<td>0.66–75.73</td>
<td>0.15</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>27</td>
<td>4</td>
<td>3.64</td>
<td>0.57–31.27</td>
<td>0.19</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>2</td>
<td>2</td>
<td>0.43</td>
<td>0.01–30.4</td>
<td>0.68</td>
</tr>
<tr>
<td>Smoking</td>
<td>25</td>
<td>9</td>
<td>1.99</td>
<td>0.3–14.73</td>
<td>0.48</td>
</tr>
<tr>
<td>NIHSS ≤ 8</td>
<td>48</td>
<td>13</td>
<td>196.53</td>
<td>9.97–16535.17</td>
<td>0.004</td>
</tr>
<tr>
<td>Interval ≤ 6 hrs</td>
<td>17</td>
<td>11</td>
<td>0.58</td>
<td>0.11–3.01</td>
<td>0.51</td>
</tr>
<tr>
<td>Edaravone</td>
<td>18</td>
<td>3</td>
<td>11.09</td>
<td>1.5–179.42</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*Logistic regression analysis based on the maximum likelihood ratio. CI: confidence interval, MRS: modified Rankin Scale, NIHSS: National Institutes of Health Stroke Scale, OR: odds ratio.

Table 3  Backward stepwise logistic regression analysis for good outcome and independence (MRS ≤ 2) at 3 months

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHSS ≤ 8</td>
<td>59.47</td>
<td>6.66–1607.21</td>
<td>0.002</td>
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<tr>
<td>Age ≤ 70 yrs</td>
<td>8.83</td>
<td>2.26–45.54</td>
<td>0.004</td>
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<tr>
<td>Edaravone</td>
<td>6.49</td>
<td>1.35–50.32</td>
<td>0.035</td>
</tr>
</tbody>
</table>

*Logistic regression analysis based on the maximum likelihood ratio. CI: confidence interval, MRS: modified Rankin Scale, NIHSS: National Institutes of Health Stroke Scale, OR: odds ratio.

Discussion

The previously reported multi-center trial for edaravone avoided the use of ozagrel sodium throughout the study period, although patients received glycerol if necessary.7) In contrast, our study combined the use of edaravone, heparin, glycerol, and ozagrel sodium in the treatment of lacunar infarction. Unfortunately, the earlier trial of edaravone did not assess the relationship between the efficacy of the agent and the stroke subtypes.7) Another multi-center trial also showed that magnesium did not reduce the chance of death or disability in patients with acute stroke, but did improve functional outcomes in patients with lacunar infarction.17) However, the results should be interpreted with caution. The Glycine Antagonist in Neuroprotection Americas trial showed that gavestinel did not improve functional outcome in patients with acute ischemic stroke, although a significant difference was found in younger patients with milder strokes.21) The reason remains unexplained. The neuroprotective agent clomethiazole, which is reported to enhance GABA_A receptor activity, does not improve outcome in patients with any subtype of ischemic stroke.15,26)

Lacunar infarctions often occur in the white matter. MK-801 was neuroprotective against neuronal necrosis,14,31) but did not attenuate white matter damage in a model of focal ischemia.28) The α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid antagonist SPD502 was effective in reducing both white and gray matter damage in rat focal ischemia.16) The white matter, both axons and glia, as well as the neurons are important to protect.6) Our patient group contained patients with lacunar infarction in various regions, such as basal ganglia, thalamus, corona radiata, and pons. Based on the present study, we cannot state that our neuroprotective therapy was particularly effective in patients with lacunar infarction. Studies are currently underway in our laboratory to examine the efficacy of the neuroprotective therapy in other stroke...
subtypes, such as cardiogenic embolism. We should also evaluate the regional difference in efficacy of edaravone.

The NIHSS score is strongly predictive of the likelihood for recovery after stroke. Our results also showed that the baseline NIHSS was significantly related to the functional outcome at 3 months in patients with lacunar infarction. After adjustment for this effect, our results still indicated that edaravone significantly improved the functional outcome. Patients with lacunar infarction have a better prognosis than those with other stroke subtypes, although neurological deterioration was observed in 20–40% of patients with acute lacunar infarction. Effective therapy for patients with lacunar infarction is very desirable, because they are likely to return to normal lives. Edaravone is a promising radical scavenger for the treatment of such patients with acute lacunar stroke.

Acknowledgments

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References


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Commentary

The authors report the efficacy of edaravone for the treatment of acute lacunar infarction. In Japan we neurosurgeons have to manage cerebral stroke in the acute stage even if the stroke is hemorrhagic or ischemic except for some hospitals and institutes. So acute stage management of cerebral stroke is crucial for Japanese neurosurgeons.

By now, many types of anti-ischemic drugs to protect the brain have been introduced, but the clinical results have not been satisfactory. Edaravone is widely known as originally developed in Japan and as having brain protective mechanism against ischemia. Additionally in this paper, outcome of patients with lacunar strokes treated with edaravone 3 months after onset has become much better even if the patients are elderly. This result will reduce the financial cost of our health insurance.

This paper is very beneficial not only for neurosurgeons but also for general physicians to treat patients with lacunar stroke in the acute stage.

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Mishina et al. present a very interesting paper about the efficacy of edaravone for the treatment of acute lacunar infarction. Based on a retrospective clinical series, they assessed the effect of this free radical scavenger on the outcome of patients with this kind of stroke. The main contribution of this paper is to provide clinical evidence in favor of edaravone as a neuroprotective agent combined with the routine treatment used currently worldwide (heparin, glycerol, and ozagrel sodium). Prospective randomized studies in this interesting subject and in other subtypes of stroke are warranted.

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