Effect of Edaravone, a Free Radical Scavenger, on Ischemic Cerebral Edema Assessed by Magnetic Resonance Imaging

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Abstract

The anti-edema effect of edaravone, a free radical scavenger, was evaluated by magnetic resonance imaging in six patients with extensive hemispheric ischemic stroke. T_2 relaxation time in the infarct core, the boundary zone of the infarct, and the noninfarcted hemisphere were calculated, and T_2 mapping was performed before and after edaravone administration. Edaravone administration significantly decreased the mean T_2 relaxation time in the boundary zone of the infarct from 121.5 ± 9.2 (mean $\pm$ standard deviation) to 114.5 ± 9.9 msec ($p = 0.008$), but not in the core from 142.3 ± 13.4 to 142.2 ± 18.5 msec ($p = 0.97$) or the noninfarcted hemisphere from 93.0 ± 3.7 to 93.1 ± 3.8 msec ($p = 0.91$). The T_2 subtraction map clearly demonstrated shortened T_2 relaxation time in the boundary zone of the infarct. The present results indicate that edaravone can salvage the boundary zone of the infarct and is a useful cytoprotective anti-edema agent.

Key words: edaravone, magnetic resonance imaging, free radical scavenger, ischemic cerebral edema, stroke

Introduction

Brain edema is one of the most important factors contributing to the morbidity and mortality associated with large hemispheric ischemic stroke, so effective anti-edema treatment in the acute phase is vitally important. Free radicals are believed to be important in the development of ischemic brain edema.^{4,5,19,22} Edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one) is the first free radical scavenger to have shown therapeutic effects in the treatment of acute ischemic stroke, and has been used clinically in Japan since 2001.⁶ Various cerebral ischemic models have demonstrated the protective effects of edaravone. Edaravone markedly attenuated ischemic brain edema in rats by preventing both nonenzymatic peroxidation and lipoxygenase activity.¹ Edaravone had protective effects against hydrogen peroxide-induced vascular endothelial injury in vitro, and attenuated vasogenic edema caused by

intracerebral microinjection of arachidonic acid in rats.^{16,23,24} Moreover, edaravone showed antioxidant properties as well as anti-inflammatory effects that reduced the induction of inducible nitric oxide synthase.²⁶ Edaravone is thought to protect against ischemic brain edema based upon such experimental findings, but no anti-edema effect has not yet been clearly identified in clinical studies.

T_2 -weighted magnetic resonance (MR) imaging can both visualize and quantify vasogenic edema, so provides a method to assess the efficacy of ischemic stroke therapies against edema.^{3,8,11,17,18} Previously, we characterized the anti-edema effect of glycerol after extensive ischemic stroke by comparing T_2 -weighted MR images obtained before and 1 hour after completing glycerol infusion.¹⁸

The present study examined the anti-edema effect of edaravone in patients with extensive hemisphere ischemic stroke by comparing the T_2 relaxation time and T_2 mapping before and after edaravone administration in the infarct core, the boundary zone of the infarct, and the noninfarcted hemisphere.

Table 1 Clinical summary of six patients

Case No.	Age (yrs)/ Sex	Lesion side	Comorbidities	NIHSS score on admission	Time to treatment with edaravone after stroke onset (hrs)	Time to MR examinations after stroke onset (days)
1	78/M	lt	AF, HT	18	6	3
2	69/M	rt	AF, DM	15	3	2
3	75/M	lt	AF, HT	19	4	3
4	82/F	lt	AF, HL	21	5	3
5	78/F	rt	AF, DM, HT	16	6	3
6	67/M	rt	AF	15	3	4

AF: atrial fibrillation, DM: diabetes mellitus, HL: hyperlipidemia, HT: hypertension, MR: magnetic resonance, NIHSS: National Institutes of Health Stroke Scale.

Methods

This study included six consecutive patients, four males and two females aged 67 to 82 years (mean $\pm$ standard deviation 75 ± 5.8 years) with middle cerebral artery territory infarction who were admitted to the Neurology Department of the Kitamura-yama Hospital between December 2001 and March 2002. The inclusion criteria to ensure informative automatic analysis with co-registration of images were: first stroke onset, nonhemorrhagic infarct, and absence of periventricular areas with marked high T_2 signal intensity that could be interpreted as cerebral infarction. All six patients were treated under diagnoses of cardiogenic embolic infarction. Clinical data for these six patients are summarized in Table 1.

The basic treatment for the first 5 days from admission was continuous intravenous infusion of 10,000 units of heparin per day, intravenous drip infusion of 30 mg of edaravone diluted with 100 ml of saline given over 30 minutes twice daily, and 200 ml of 10% glycerol infused over 2 hours three times daily. Use of fibrinolytic and antiplatelet agents was avoided. All MR images were obtained 12 hours or more after the most recent glycerol injection, since the effect of glycerol is reported to persist for 4 to 6 hours.^{14,15)}

MR imaging was performed at 2 to 4 days (mean 3 days) after symptom onset using a 1.5-T MR system (Visart; Toshiba, Tokyo). Plasma edaravone concentrations after intravenous infusion rapidly reach the maximum at 30 minutes, and then decrease rapidly.^{20,25)} Therefore, MR imaging was performed before and 1 hour after completion of edaravone infusion. Conventional spin-echo pulse sequences were used to calculate the T_2 relaxation times, with other imaging conditions as follows: repetition time (TR) 4000 msec, echo time (TE) 30 or 100 msec for the T_2 map; or TR 300 msec and TE 30

msec for T_1 -weighted images; field of view 256×256 mm; matrix size 256×256 pixels; and slice thickness 5 mm with no gap to obtain 20 contiguous slices. The recorded images were transferred to a workstation (Sparc 20; Sun, Milpitas, Calif., U.S.A.).

Segmentation of infarcted brain, noninfarcted brain, and ventricle was carried out automatically to avoid biasing the data. First, regions representing infarcted brain, ventricle, and normal brain were identified semiautomatically in the pretreatment T_2 -weighted MR image. The signal intensity for each pixel was determined using image-processing software (MR Vision, Menlo Park, Calif., U.S.A.) and transferred offline to a personal computer. Discriminant analysis was then performed using a statistics program (SPSS Inc., Chicago, Ill., U.S.A.) to calculate the threshold value of pixel intensity for reliably distinguishing infarcted brain and ventricle from normal brain on T_2 -weighted images. The threshold value of pixel intensity was calculated similarly for distinguishing ventricle from brain tissues on T_1 -weighted images. Segmentation of MR images into infarcted, noninfarcted, and ventricle could then be performed automatically using these threshold values as in our previous study (Fig. 1).¹⁸⁾

Pre- and posttreatment T_2 maps were constructed from the TR/TE = 4000/30 or 1000 msec images. Three regions of interest, noninfarcted hemisphere, infarct boundary zone (inner 10 mm margin of the infarct), and infarct core, were localized in the pre- and posttreatment T_2 maps (Fig. 1). Mean T_2 relaxation time was calculated for each region from all slices. Finally the changes in T_2 relaxation time were topographically visualized by co-registering the pre- and posttreatment T_2 maps using imaging analysis software (MEDx 3.43; Medical Numerics, Inc., Sterling, Va., U.S.A.) according to image warping theory, and constructing the subtraction images.¹⁰⁾ MR images were evaluated by a neuroradiologist unaware of the clinical information.

Fig. 1 Scatter plot of T_1 and T_2 signal intensities (SI). Vertical and horizontal lines show the thresholds determined by discriminant analysis. Segmentation of magnetic resonance images into infarcted area, noninfarcted area, and ventricle was carried out automatically using these thresholds. The upper right quadrant of the plot includes pixels in the infarcted area, identified at right. Three regions of interest were also defined on the pretreatment T_2 maps: blue area, noninfarcted hemisphere; green area, boundary zone of infarct; and red area, infarct core.

Fig. 2 T_2 relaxation times before and after edaravone administration. T_2 relaxation time was shortened significantly in the boundary zone of the infarct after edaravone administration (upper right, $p = 0.008$). No significant change was seen in the infarct core (upper left, $p = 0.97$) or the noninfarcted hemisphere (lower, $p = 0.91$).

Fig. 3 T_2 maps before (left) and after edaravone administration (center), and T_2 subtraction map (right). The subtraction map clearly demonstrates shortened T_2 relaxation time in the boundary zone of the infarct (arrows).

The mean $\pm$ standard deviation of the T_2 relaxation times in the infarct core, the boundary zone of the infarct, and the noninfarcted hemisphere were compared before and after edaravone administration. The paired t test was used for statistical analysis. A value of p below 0.05 was considered to indicate significance.

Results

T_2 relaxation time declined significantly after edaravone administration in the boundary zone of the infarct from 121.5 ± 9.2 to 114.5 ± 9.9 msec ($p = 0.008$), whereas no significant change was evident in

the infarct core from 142.3 ± 13.4 to 142.2 ± 18.5 msec ($p = 0.97$) or the noninfarcted hemisphere from 93.0 ± 3.7 to 93.1 ± 3.8 msec ($p = 0.91$) (Fig. 2). The T_2 subtraction map clearly demonstrated shortened T_2 relaxation time in the boundary zone of the infarct (Fig. 3).

Discussion

The present study of extensive ischemic cerebral infarcts using T_2 relaxation time and T_2 mapping demonstrated that treatment with edaravone was associated with decreased T_2 relaxation time in the boundary zone, suggesting that this agent may

attenuate ischemic cerebral edema.

In the present study, MR imaging was performed at mean 3 days after symptom onset. Ischemic brain edema in this phase consists mainly of vasogenic edema.¹³⁾ Overall mortality rate in patients with acute middle cerebral artery stroke ranges between 5% and 25%, most often occurring within 1 week of onset in association with vasogenic edema.^{7,12)} Therefore, effective treatment of edema in the acute phase of extensive ischemic stroke is important, as well as thrombolytic, antiplatelet, and anticoagulant therapy.

Cerebral ischemic injury is accompanied by early dysfunction of the blood-brain barrier (BBB), subsequent vasogenic edema formation, and irreversible neuronal damage. Edaravone is thought to protect against ischemic brain edema mainly by inhibiting BBB injury. The present clinical study could not establish the pharmacologic action of edaravone in the clinical anti-edema effect. Further investigation of the molecular mechanisms of edaravone against ischemic cerebral edema is needed. However, the mechanism of the anti-edema effect of edaravone clearly differs from that of hyperosmotic therapy with glycerol or mannitol. Glycerol may decrease the water content of normal brain tissue, as T_2 relaxation time of normal tissue decreased significantly after glycerol administration in a rat infarction model. Unfortunately, such changes in the uninvolved brain could aggravate shift of the midline structures, and actually exacerbate the mass effect of large cerebral infarct.^{8,9)}

The present study showed that the T_2 relaxation time declined significantly after edaravone administration only in the boundary zone of the infarct, not in the contralateral noninfarcted hemisphere, suggesting that edaravone acts only in the ischemic boundary zone of extensive ischemic stroke, and therefore should not exacerbate the mass effect. Treatment with edaravone also did not significantly shorten the T_2 relaxation time in the infarct core. Previous experimental studies demonstrated that edaravone conferred neuroprotective effects only in the border zone.^{2,21)} The pharmacologic action of edaravone suggests that protective effects will only occur in ischemic territories with cells that are still viable.

Limitations of the present study include small sample size and absence of controls. Furthermore, the effect of edaravone against ischemic brain edema could be temporary rather than prolonged, since the time course of T_2 relaxation time after treatment was not investigated. However, the present findings are consistent with those of previous experimental studies indicating that edaravone

can salvage the boundary zone of the infarct, and is a promising cytoprotective anti-edema agent for the treatment of patients with ischemic stroke. Larger, placebo-controlled double-blind trials and investigation of the serial changes of T_2 relaxation time will clarify the role of edaravone in the treatment of ischemic stroke.

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Commentary

Edaravone has been demonstrated in a number of in vitro studies to diminish cerebral edema. This free radical scavenger is thought to protect against ischemic brain edema primarily by inhibiting blood-brain barrier injury. In the current study, the authors have studied six selected patients with ischemic stroke to determine the effects of edaravone on ischemic cerebral edema as determined by T_2 relaxation time on MRI. The patients utilized in the study had all experienced their first non-hemorrhagic stroke, with absence of periventricular involvement, and all were presumed to have cardiogenic embolic infarctions. The patients were treated with both edaravone and 10% glycerol. To eliminate any potential beneficial effects of glycerol on cerebral edema, the MR images were obtained at least twelve hours after glycerol administration, and before and one hour after the administration of edaravone. Segmentation of infarcted brain, noninfarcted brain to ventricle was carried out automatically to avoid bias in interpreting the data.

The authors found that the mean T_2 relaxation time in the boundary zone of the infarct was decreased significantly following the administration of edaravone. No significant change occurred in the infarcted core or in the noninfarcted hemisphere after edaravone administration.

The demonstration that edaravone administration significantly decreases the T_2 relaxation time only in the boundary zone of an infarct and not in the contralateral noninfarcted hemisphere suggests that edaravone may be useful in combating cerebral edema following ischemic infarction. As pointed out by the authors, the current study includes a very small sample size and no controls. These findings, however, should stimulate larger scale investigations to better understand the potential role of edaravone in this setting.

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Edaravone (3-methyl-1-phenyl-pyrazolin-5-one), a newly developed free radical scavenger, has been used in patients with acute brain infarction since April 2001 in Japan. Edaravone shows antioxidant effect through enhancement of prostacyclin production, inhibition of lipoxygenase metabolism of arachidonic acid by hydroxyl radicals, and eradication of active oxygen, leading to protection of endothelial cells against damage.

The present study evaluated the anti-edema effect of edaravone by calculating the T_2 relaxation time in the infarct core, the boundary zone, and the noninfarcted hemisphere. The present results show significant decline in T_2 relaxation time in the boundary zone but not in the infarct core or the noninfarcted hemisphere.

Although the present study demonstrated that edaravone is effective in reducing brain edema in the boundary zone of the infarcted area, it has limitations in demonstrating the actual clinical improvement in patients with edaravone administration. The cytoprotective effect of edaravone couldn't be sufficiently demonstrated by showing simple reduction in brain edema in the boundary zone of infarcted area, but rather could be proved by showing reduction in the final infarcted volume on diffusion magnetic resonance imaging (MRI) or superiority in clinical outcome which are compared with patients who do not have edaravone treatment.

One more thing that should be kept in mind is that the complication of edaravone administration is not negligible, especially in elderly people. Acute renal failure, liver dysfunction, disseminated intravascular coagulation, and thrombocytopenia are observed more than 5% of patients who received edaravone treatment.

Notwithstanding the limitation of this study, the authors successfully demonstrated the efficacy of

edaravone in reducing vasogenic edema in the boundary zone of the infarcted area using MRI T_2 relaxation time. The result of this study will urge many neurosurgeons and neurologists to study the real impact of edaravone in the treatment of ischemic stroke.

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The authors examined the effect of edaravone, a free radical scavenger, on cerebral edema in six patients with middle cerebral artery occlusion due to cardio-genic embolism. MR imaging was performed before and 1 hour after completion of the edaravone treatment between 2 and 4 days after the onset. The T_2 relaxation time in the infarct core, the boundary zone of the infarct, and the noninfarcted hemisphere on the MR images were calculated automatically. The results clearly showed that the T_2 relaxation time significantly declined only in the boundary zone of the infarct after edaravone treatment. They concluded that edaravone can salvage the boundary zone of infarct and is a useful cytoprotective anti-edema agent in cerebral ischemia.

The present study not only supports the previous notion that edaravone can prevent the brain edema following experimental and clinical cerebral infarct but demonstrates that the edaravone improved the pre-existed brain edema in the boundary zone of the infarct. However, the limitations of this study include small sample size, absence of controls, and a lack of feasible mechanism for the edema resolution. I look forward to their further studies to clarify the mechanism of ischemic neuronal damages through the investigation of the protective effect of edaravone on brain edema

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