Reviewer’s report

Title: Free radical scavenger, edaravone, reduces the brain ischemic damage especially in the white matter.

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Reviewer: Paul A. Lapchak

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Nakese and colleagues have revisited the effects of Edaravone in acute ischemic stroke patients by doing a retrospective study using a hospital data base. The primary finding, which is not unlike all published findings to date, is that edaravone is neuroprotective in some stroke patients (see Lapchak, Expert Op. Pharmacotherapy. PMID: 20491547). However, the beneficial effects of edaravone in this study are not as pronounced as in some previous studies.

There are major problems with the paper including the reporting of clinical design, treatment regimen and dose, regulatory information and the stated conclusion "Edaravone may reduce the size of brain ischemic lesion by attenuating the oxidative stress after ischemia." is not justified based upon the data presented. Oxidative stress markers in any form were not studied or presented in this paper. Moreover, the conclusion stating that edaravone "...by attenuating inflammation" is not justified for the same reason.

Should the conclusion of this paper be revised to state that "Edaravone reduced infarct volume without providing statistically significant clinical improvement"?

- Discretionary Revisions
NONE

- Minor Essential Revisions
1) Figure 1 axes are not labeled correctly. In Figure 2, they-axis should have the same increments in all panels. Figure legends are inadequate to describe the figures.

2) Numerous grammatical and typographical errors need to be corrected. The manuscript is not suitable for publication unless extensively revised by an English speaking editor who should be acknowledged in the manuscript with full credentials.

3) The authors have managed to spell edaravone differently (i.e. ederavone) on occasion.

4) What does this sentence mean "Edaravone(+) group showed relatively good outcome compared to edaravone(-) group."

5) Methods- Please describe sequential selection. Why was this not a parallel study design? After all, the authors only accessed a database to write this report?
6) The tense for the methods description is incorrect since this was a retrospective study. Please differentiate between past and present tense.

7) Regarding mRS, why is the term prognosis used? Was actual clinical function not measured and recorded on hospital documents?

- Major Compulsory Revisions

1) I could find no specific statement on adherence to clinical guidelines for treatment, IRB approval, patient consent, or even the exact dosing regimen used. Was edaravone produced by Mitsubishi Tanabe Pharma Corp?

2) Please explain the difference between the n values indicated in the methods [i.e.: edaravone(-) group (n=79) and edaravone(+) group (n=77)] and those reported in the Table [edaravone(-) group (n=83) and edaravone(+) group (n=93)].

3) The following statement made by the authors should be removed or edited. "Of course, it should be reasonable to perform the double blind randomized control trial (RCT) for evaluating the effect of edaravone on both acute and chronic period. However, the edaravone treatment for acute ischemic stroke is generally accepted in Japan in these days, so that the RCT of edaravone is ethically challenging." Is it not ethically challenging for a clinician to treat with a drug where efficacy has not been confirmed in at least 2 international clinical trials? To date, there remains only 1 randomized blinded trial completed between 1993-1996 which included a total of 250 patients. Cerebrovasc Disease 2003;15(3):222-9.

The authors should be aware of the ongoing clinical trial with MCI-186 in subjects with acute ischemic stroke (www.clinicaltrials.gov/ct2/show/NCT00821821).

4) It is surprising that the authors report that there was no clinical improvement in either embolic or atherothrombotic stroke patients. This is in stark contrast to previous studies by Otomo, Inatomi and Shinohara. Please explain the discrepancy.

5) This conclusion is not justified by the data presented and should be removed. "In conclusion, edaravone can reduce the size of stroke lesions by attenuating inflammation following ischemic insult. The effect of edaravone could be optimal in ischemic white matter lesions because of the existing rich substrates for inflammatory response. The acute treatment by free radical scavenger may consecutively improve the outcome in chronic period."

6) The discussion should be more compelling and relevant to treating stroke. 7) Please better define conflicts of interest for each author.

Level of interest: An article of limited interest

Quality of written English: Not suitable for publication unless extensively edited

Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:

'I declare that I have no competing interests'