Dichloroacetate After Incomplete Ischemia

To the Editor:

We would like to comment on the article by Colohan and coworkers1 in the May-June 1986 issue of Stroke regarding the effect of dichloroacetate (DCA) after incomplete ischemia in rats. Using the same model, our evidence that pretreatment with DCA does not decrease the amount of lactic acid build-up in the brain during ischemia is in agreement with the findings of these authors. However, additional data of ours shows that treatment with DCA does result in lower lactates 30 minutes after the termination of ischemia.

We agree with these authors that even though pyruvate dehydrogenase enzyme complex (PDHC) in the brain might be activated by DCA during ischemia, the lack of oxygen is probably what limits the entry of pyruvate (lactate) into the citric acid cycle. Having made this assumption, we measured cerebral cortical lactic acid levels 30 minutes after reperfusion in rats that had been treated with DCA 15 minutes prior to, immediately after, or 15 minutes after ischemia. Our results showed that cerebral lactate is near control levels 30 minutes after reperfusion in fasted rats pretreated with 25 mg/kg DCA. In untreated ischemic rats this resolution takes at least 60 minutes after the start of reperfusion. When treated immediately or 15 minutes after ischemia, there likewise is a significantly faster amelioration of cerebral hyperlactatemia in DCA-treated ischemic rats when compared with untreated rats. Since these effects were achieved with a small dose of DCA (25 mg/kg) that was not effective in resolving systemic acidosis, we also agree with these authors1 and Evans,5 that the control of PDHC activity may be different in the brain than in other tissues.

Since most patients with cerebral ischemia will be fed and since high blood glucose correlates with poor physiological and neurological outcome from cerebral ischemia,6-9 we examined the effect of postischemic treatment with DCA in fed rats. Untreated rats exhibited mean cerebral lactates of 23 μM/g 30 minutes after ischemia. In contrast, the mean lactate level in DCA-treated rats 30 minutes after ischemia was 13 μM/g, significantly less than 18 μM/g that has been shown by other investigators to promote irreversible cell damage.5,12 Since brain ischemia commonly affects nonfasted patients and since treatment will occur after, not prior to, ischemia, we believe these results have important clinical significance. We therefore urge the continued investigation of the use of DCA for the treatment of cerebral hyperlactatemia in ischemic events.

Sincerely,

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References

1. Colohan ART, Welsh FA, Miller ED, Kassel NF: The effect of dichloroacetate on brain lactate levels following incomplete ischemia in the hyperglycemic rat. Stroke 1986;17:525-528

The following letter is sent in response.

To the Editor:

Dichloroacetate is a theoretically attractive agent for treatment of cerebral ischemia. We were quite disappointed when the results of our studies failed to suggest a beneficial action. However, the additional studies cited by Drs. Dimlich and Barsan indicate that dichloroacetate may indeed be useful in the management of ischemic stroke. Our enthusiasm has been rekindled, and we agree completely that further studies should be conducted.

Very truly yours,

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Dichloroacetate after incomplete ischemia.
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