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PRELIMINARY RESULTS OF DEFEROXAMINE AND L1 TREATMENT OF SPINAL CORD ISCHEMIA

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Vascular surgery necessitating aortic occlusion produces spinal cord ischemia, which can subsequently lead to paraplegia. Previous studies suggest lipid-rich central nervous system tissue is sensitive to amplification of ischemic injury by free radical mechanisms that lead to lipid peroxidation [1]. Drugs that prevent free radical production and thus lipid peroxidation offer promise as a way to protect the spinal cord during periods of ischemia [2]. The agents deferoxamine and 1,2-dimethyl-3-hydroxypyrid-4-one (L1) are postulated to inhibit iron-catalyzed lipid peroxidation. Deferoxamine is a water-soluble iron chelator that has been shown to attenuate reperfusion injury in isolated rat hearts [3]. L1 is a novel lipid-soluble iron chelator that has been shown to effectively chelate excess iron in a study of chronic transfusional iron overload (i.e., β -thalassaemia) [4]. Our goal was to use these two drugs to test the hypothesis that iron plays an important role in the pathophysiologic reactions leading to spinal cord damage attendant to ischemia and reperfusion.

Our preliminary study was performed in two stages. We first developed a model of spinal cord ischemia that produced paraplegia in a majority of dogs [5]. The second phase of our study used the initial series of dogs as historical controls to determine if treatment with deferoxamine or L1 would significantly improve the neurologic outcome or histopathologic damage.

In the second phase of our study, 13 mongrel dogs were sequentially divided into a deferoxamine-treated group (n = 5) and an L1 group (n = 8). The dogs were pretreated with atropine sulfate 0.4 mg/kg subcutaneously and acetylpromazine (0.22 mg/kg subcutaneously) and were anesthetized with thiopental (9 to 13 mg/kg intravenously). After intubation, nitrous oxide was delivered by inhalation in a 1:2 ratio with oxygen, and anesthesia was maintained by repeated intravenous boluses of thiopental.

A balloon catheter was inflated in the aorta just distal to the left subclavian artery to achieve spinal cord ischemia, and the duration of ischemia was determined by the amplitude reduction of the mean evoked potential signal, as it was in our initial study. The details of the evoked

potential stimulator, histopathologic scoring, regional blood flow studies, and neurologic assessment are identical to phase 1 of the study [5]. In the first group of dogs, deferoxamine (25 mg/kg) was infused intravenously over a 20-minute period, starting 30 minutes before aortic occlusion. Another 25 mg/kg dose of deferoxamine was administered over a 20-minute period beginning 10 minutes before reperfusion. In the other group, L1 (25 mg/kg) was administered intravenously according to the same protocol. All animals received humane care in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Sciences (NIH Publication No. 80-23, revised 1978). The study was approved by the Purdue University Animal Care and Use Committee.

The mean durations of aortic occlusion in the control, deferoxamine, and L1 groups were 36.1 ± 8.5 , 28.6 ± 9.2 , and 32.6 ± 11.2 , respectively. The correlation between neurologic outcome and histopathologic damage for the three groups of dogs is summarized in Fig. 1. In the nonintervention group, seven of the eight dogs had moderate to severe motor deficits. In the deferoxamine treated group, all five dogs had significantly fewer motor deficits at 24 hours than the control group ($p = 0.005$ by Fisher's exact test) as evidenced by absence of muscle spasticity and no brisk withdrawal to a pinch of the interdigital web. Of the eight dogs in the L1-treated group, six demonstrated normal muscle tone and a brisk withdrawal to a pinch of the interdigital web of the hind limb. There was a significant difference in the neurologic outcome of dogs in the L1-treated group compared with the control group ($p = 0.05$ by Fisher's exact test).

Comparison of histopathologic results from all three groups revealed that there was no significant difference in the extent of microglial cell infiltration and vacuolation of the lumbar gray matter. However, in contrast to the historical controls, the integrity of the neurons in both the deferoxamine and L1 groups appeared to be preserved. Although some swelling and satellitosis of the lower motor neurons were present, fewer pyknotic and necrotic neurons were observed. The exception to this finding was the two dogs in the L1-treated group, which had significant motor deficits. They were found to have severe neuronal damage characterized by neuronophagia and pyknosis at the level of the fourth lumbar vertebra.

The initial model of spinal cord ischemia we developed produced an 88% incidence of paraplegia in a control group of dogs and was thus used to test different pharmacologic interventions. The study presented was designed to evaluate the extent to which iron plays a role in ischemia/reperfusion injury of the spinal cord. The preliminary results of our study suggest that treatment with either deferoxamine or L1 will reduce cellular and functional deficits. In addition, the fact that amelioration of damage was achieved with a water-soluble iron chelator suggests that perhaps it is less crucial that a drug cross the blood-brain barrier and more crucial that the iron chelator be in contact with the central nervous system microvasculature. A prospective, randomized, double blind study is recommended to further elucidate the effectiveness of both deferoxamine and L1 in treating spinal cord ischemia.

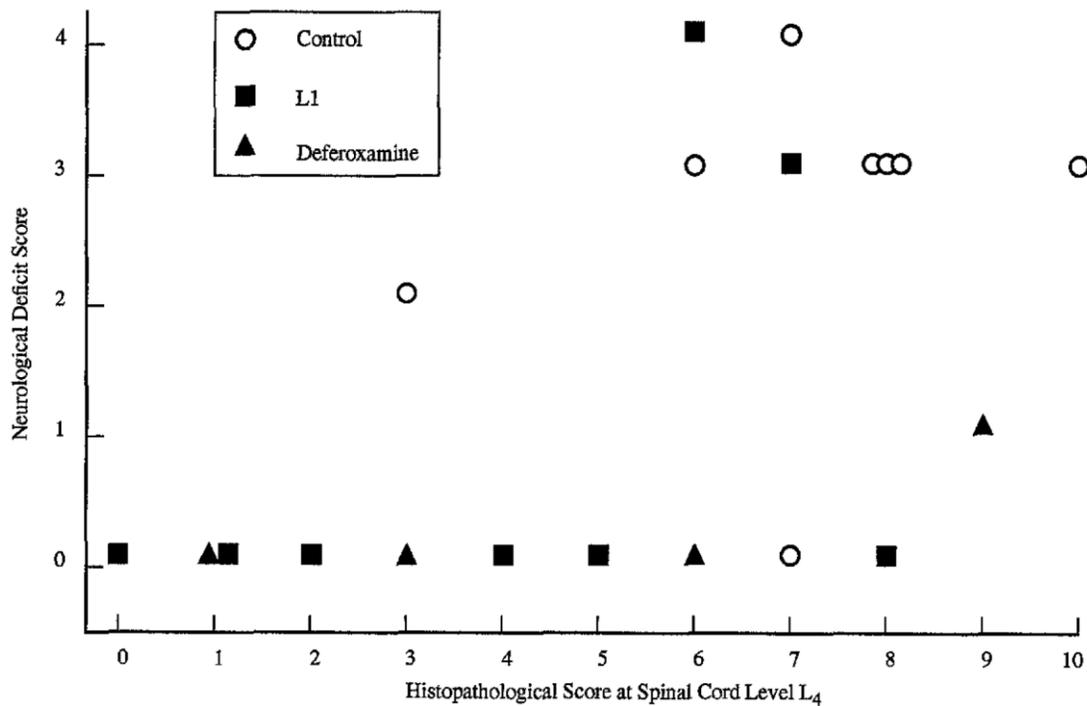


Fig. 1. Correlation of neurologic outcome and histopathologic damage for the historical control, deferoxamine- and L1-treated groups of dogs. On the ordinate, the neurologic outcome is represented semi-quantitatively with different combinations of increasing neurologic deficits. For this axis, the numeric value was obtained by summing the muscle tone and withdrawal reflex results each on a scale of 0 to 2, where normal = 0, hyperreflexia/hyporeflexia and slow withdrawal reflex = 1, and spasticity/atonía and areflexia = 2. The maximal possible score = 4; the minimum score = 0. On the abscissa, the histopathologic damage at level of the fourth lumbar vertebra (L4) is reflected by the damage score (higher number = more severe damage), which was determined by our previously published criteria [5]. All dogs with a neurologic deficit score of 2 to 4 could not walk. Dogs with a deficit score of 0 or 1 could walk. Therefore, note that all but one of the dogs in the control group were paralyzed, whereas only two dogs from the treatment group (L1) could not walk.

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