Deferoxamine Mesylate
A New Hope for Intracerebral Hemorrhage: From Bench to Clinical Trials
Magdy Selim, MD, PhD

Abstract—Iron resulting from hemoglobin degradation is linked to delayed neuronal injury after intracerebral hemorrhage. Extensive preclinical investigations indicate that the iron chelator, deferoxamine mesylate, is effective in limiting hemoglobin- and iron-mediated neurotoxicity. However, clinical studies evaluating the use of deferoxamine in intracerebral hemorrhage are shortcoming. This article reviews the potential role of deferoxamine as a promising neuroprotective agent to target the secondary effects of intracerebral hemorrhage to limit brain injury and improve outcome, and ongoing efforts to translate the preclinical findings into clinical investigations. (Stroke. 2009;40[suppl 1]:S90-S91.)

Key Words: deferoxamine · ICH · edema · neuroprotection

At present, there is no specific treatment for spontaneous intracerebral hemorrhage (ICH) beyond supportive medical care. Therapeutic attempts to target hematoma and its expansion might provide some benefit in carefully selected patients. However, this strategy alone is likely to be of limited usefulness because hematoma expansion often occurs within the first hours after onset. Furthermore, neuronal injury in ICH is not only related to hematoma expansion. Other secondary processes, including apoptosis, necrosis, autophagy, inflammation, and edema formation, have been implicated.1,2 A potential adjunctive approach to the treatment of ICH might be to target hemoglobin- and iron-mediated neurotoxicity.

Iron-Mediated Neurotoxicity
Hemoglobin degradation products resulting from hemolysis after ICH include the iron-containing heme. Iron plays a role in neuronal injury by catalyzing a sequence of reactions “Haber-Weiss reaction” that yield highly reactive toxic hydroxyl radicals leading to oxidative stress and cell death, activating lipid peroxidation, and exacerbating excitotoxicity.3,4 The time course for hemoglobin hemolysis and toxicity after ICH is 2 to 3 days.5,6 This delayed time window can have important therapeutic advantages.

Neuroprotective Properties
Deferoxamine has multiple and diverse neuroprotective properties. It decreases free iron’s availability for the production of hydroxyl radicals; prevents apoptosis induced by glutathione depletion and oxidative stress in embryonic cortical neuronal cultures by activating a signal transduction pathway leading to activation of transcription factor 1/cAMP response element-binding protein (ATF-1/CREB) and expression of genes known to compensate for oxidative stress; induces transcription of heme oxygenase-1, which catalyzes the
degradation of heme; exerts anti-inflammatory effects by stimulating cyclooxygenase; and blocks the neurotoxic effects of hemoglobin through inhibition of glutamate-mediated excitotoxicity.3,8,9

Evidence That Deferoxamine Can Attenuate Neuronal Injury After Hemorrhage

There is extensive preclinical evidence, in vitro and in vivo, by different investigators and in different species to show that deferoxamine can reduce hemoglobin-induced neurotoxicity after hemorrhage.

In Vitro Studies

Regan and Rogers showed that delayed treatment with deferoxamine markedly attenuates the production of reactive oxygen species and neuronal death induced by adding hemoglobin to mixed neuronal and astrocyte cell cultures10 and that deferoxamine attenuates the effects of hemoglobin, which potentiates the neurotoxicity of glutamate agonists in murine cortical cultures.3 Deferoxamine also reduces the production of reactive oxygen species and cell death induced by hemin in human neuron-like cells4 and pheochromocytoma and neuroblastoma cell lines.11

In Vivo Studies

Systemic treatment with deferoxamine reduces brain malondialdehyde content and induces recovery of Na+-K+ ATPase activity after ICH in guinea pigs12 and reduces the pathological changes in the optic nerve after experimental subarachnoid hematoma in rabbits.13 In rat models of ICH, intraperitoneal administration of deferoxamine ameliorates ICH-induced changes in markers of oxidative DNA damage, increases levels of APE/Ref-1, which is involved in DNA repair, significantly attenuates the brain edema induced by stereotactic infusion of hemoglobin and its breakdown products into the brain, and improves neurological and functional recovery with to vehicle-treated controls.14

Human Studies

There are limited data regarding the neuroprotective potential of deferoxamine in human subjects, particularly in patients with ICH. In one study, intravenous infusion of deferoxamine ameliorated free radical production and protected the myocardium against reperfusion injury in cardiac patients.15 We conducted an investigator-initiated pilot study in 4 patients with hemorrhagic and 3 with ischemic stroke and found that treatment with deferoxamine alters serum markers of oxidative stress by decreasing total hydro- and liperoxides and increasing the total radical antitrapping antioxidant capacity in the serum (unpublished results). These exploratory findings suggest that deferoxamine may exert potential antioxidant protective effects in human subjects, including patients with stroke.

Future Directions

Studies are currently underway to further characterize the dose–response curve of deferoxamine and its therapeutic time window in pig models of ICH. A preliminary Phase I, multicenter, dose-finding, safety, and feasibility study funded by the National Institute of Neurological Disorders and Stroke will be launched soon. Its objectives are to assess the safety and tolerability of repeated intravenous infusions of deferoxamine in patients with ICH and to determine the maximal tolerated dose of deferoxamine in this population to be adopted in future Phase II/III studies. The information and knowledge gained from these studies could provide a novel and effective adjunctive therapy for ICH.

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Disclosures

None.

References

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