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.

Deferoxamine Mesylate
Deferoxamine has been used in clinical practice for more than 30 years in iron-overloaded patients with acute iron intoxication or overload due to transfusion-dependent anemia. It is a hydrophilic chelator, which chelates Fe+++ and hemosiderin forming a stable complex that prevents iron from entering into Haber-Weiss reaction. The drug is relatively well tolerated. Serious adverse effects are uncommon. Hypotension and shock occur in 2% of patients, mostly with rapid intravenous administration at high doses. The infusion rate should not exceed 15 mg/kg per hour, and the total amount administered should not exceed 6000 mg in 24 hours.

Pharmacokinetics
Deferoxamine is rapidly absorbed. Plasma concentrations between 80 and 130 μmol/L are recorded 3 minutes after intravenous injections. The drug’s serum protein-binding rate is <10%. It is distributed throughout all body fluids and has a volume of distribution of 0.8 to 1.35 L/kg. The drug is mostly metabolized by oxidative deamination, yielding metabolite B. The drug, its iron chelate complex (ferrioxamine), and metabolite B are excreted by the kidneys within hours. The molecular weight of deferoxamine is 560.7 daltons (656.8 as mesylate). However, there appears to be specific mechanism(s) facilitating the drug’s uptake by neuronal cells.7

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.\textsuperscript{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 cultures\textsuperscript{10} and that deferoxamine attenuates the effects of hemoglobin, which potentiates the neurotoxicity of glutamate agonists in murine cortical cultures.\textsuperscript{3} Deferoxamine also reduces the production of reactive oxygen species and cell death induced by hemin in human neuron-like cells\textsuperscript{4} and pheochromocytoma and neuroblastoma cell lines.\textsuperscript{11}

**In Vivo Studies**

Systemic treatment with deferoxamine reduces brain malondialdehyde content and induces recovery of Na\textsuperscript{+}-K\textsuperscript{+} ATPase activity after ICH in guinea pigs\textsuperscript{12} and reduces the pathological changes in the optic nerve after experimental subarachnoid hematoma in rabbits.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 lipoperoxides 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.

**Sources of Funding**

Grant support was received from the National Institutes of Health/National Institute of Neurological Diseases and Stroke (1R01-NS 057127-01A1, 1R01-NS 045754-01A2, and 5R01-HL46690-14).

**Disclosures**

None.

**References**

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

Stroke. 2009;40:S90-S91; originally published online December 8, 2008;
doi: 10.1161/STROKEAHA.108.533125

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/40/3_suppl_1/S90

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/