

Pharmaceutical Development of a Nitron, NXY-059, for Acute Focal Stroke

Kirk R. Maples

Biopharmaceutical Consultant to the Defense Advanced Research Projects Agency (DARPA), formerly Senior VP, Research at Centaur Pharmaceuticals, Inc, Santa Clara, CA.

NXY-059 (disodium 4-[(tert-butylimino)methyl]benzene-1,3-disulfonate N-oxide) is a nitron with free radical trapping properties and is being developed for the treatment of acute ischemic stroke. NXY-059 possesses proven neuroprotective efficacy in rat transient and permanent models of middle cerebral artery occlusion (MCAO) when administered up to 4-6 hours after the stroke. NXY-059 was also efficacious in a long-term functional disability primate stroke model when administered 5 min after the permanent MCAO and evaluated at 3 and 10 weeks after stroke. NXY-059 substantially lessened the functional disability in these marmosets, and protected both cortical and subcortical structures. Human clinical studies indicate continuous iv infusion of NXY-059, resulting in unbound plasma concentrations up to 200 $\mu\text{mol/L}$ for 72 hours, were well tolerated in healthy volunteers and stroke patients. Plans for evaluation of NXY-059 in global Phase IIb/III efficacy studies are under development.

Although NXY-059 can function as a spin-trapping agent, the relative trapping ability is less than that for phenyl-N-*t*-butyl nitron (PBN) and much less than that for other antioxidants. NXY-059 may have other pharmacological actions, including effects on signal transduction pathways affected by oxidative stress. For instance, NXY-059 prevents neuronal mitochondrial cytochrome C release, maintains activation of the Akt signal transduction pathway, and protects neurons from subsequent death in rat MCAO models.

A succinct overview of the preclinical pharmacology, the potential mechanism of action, and the results of the clinical trials for NXY-059 will be discussed.

(AstraZeneca is developing NXY-059 under a license agreement with Centaur Pharmaceuticals, Inc.)