

Letters to the Editor

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SAINT-I Worked, But the Neuroprotectant Is Not NXY-059

To the Editor:

Testing AstraZeneca's nitron drug NXY-059 against acute stroke, the SAINT-I phase-3 trial¹ showed significant neuroprotectant activity.¹ Moreover, looking at hemorrhagic progression secondary to the "clot-buster" tPA (alteplase) in a parallel trial, symptomatic hemorrhage more than halved in the NXY-059-treated group, to 2.5% versus 6.4% in the controls. Likewise, the rate of asymptomatic hemorrhage was significantly lower in the treatment group (12.9% versus 20.9%). Although the subjective modified Rankin Scale used in the main trial might be open to question, it is hard to dismiss the alteplase findings, based on hard dichotomous radiological data.

Unfortunately, the second (SAINT-II) trial failed. This difference has been ascribed to unspecified methodological problems. But there is a ready alternative explanation. This is that a neuroprotectant was present in SAINT-I, but not in SAINT-II.

Phenylbutyl nitron (PBN) derivatives such as NXY-059 hydrolyze to produce the corresponding benzaldehyde plus *N*-t-butylhydroxylamine (NtBHA).²⁻⁷ Itself a potent radical scavenger, NtBHA readily oxidizes to its parent spintrap, MNP or "2-methyl-2-nitrosopropane", AKA, "t-nitrosobutane". In addition to trapping radicals, MNP is reduced by (say) vitamin-C or mitochondria back to NtBHA. Moreover, on exposure to light or in oxidizing conditions, MNP releases nitric oxide (NO),²⁻⁶ with antiplatelet, antioxidant, neuroprotective and vessel-dilating properties.

Such hydrolysis products might account for the success of the SAINT-I trial and their absence for the failure of SAINT-II. It had similarly proved impossible to replicate earlier results produced with "aged" PBN.⁴ This was later tracked down to NtBHA and MNP production during storage.

A smoking gun? AstraZeneca patent '527⁷ claims methods for inhibiting hydrolysis of NXY-059 to NtBHA and MNP. These methods include antioxidants, limiting light exposure, storage under nitrogen, pH-elevation, decreased headspace, and increasing concentrations. Otherwise, the shelf life of NXY-059 is "unacceptably short",⁷ hydrolyzing a few percent per year. Moreover, NXY-059 in parenteral solutions can hydrolyze up to about 1% per day.⁷ Postulating that the hydrolysis products are the true neuroprotectants, such normally unremarkable variables might explain the rather different results in SAINT-I and SAINT-II.

Sample scenarios: the SAINT-I trial was delayed pending animal toxicity studies. Perhaps the SAINT-I trial was thus done with "old" NXY-059 and SAINT-II with new. Likewise, perhaps the parenteral solutions of NXY-059 used in SAINT-I were not as "fresh" as in SAINT-2 or experienced more light exposure. Alternately, perhaps the differences resulted from the application of the '527 patent's stabilization methodology to SAINT-II.

Most importantly, should any such prove the case, the SAINT/STAIR methodology works well. It not only showed an unexpected neuroprotectant, but also distinguished this from NXY-059. That is, human neuroprotectants are not only possible, but provable.

Disclosures

P.H.P. has patent claims in this area.

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