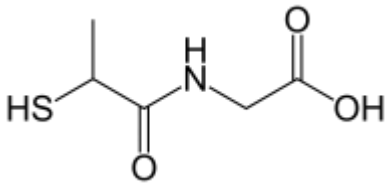
Tiopronin



The neurotoxic aldehyde 3-aminopropanal (3-AP) contributes to brain injury following cerebral ischemia. Tiopronin (N-2-mercaptopropionyl-glycine[N-2-MPG]) is a US Food and Drug Administration (FDA)-approved drug for the treatment of cystinuria and a putative neuroprotective agent that has been shown to bind and neutralize 3-AP and reduce infarct volumes.

The objective of a trial was to establish the safety of tiopronin administration in patients with aneurysmal subarachnoid hemorrhage (aSAH) in preparation for further trials of its efficacy as a neuroprotective agent in this disease process.

This Phase I dose-escalation trial enrolled three-patient cohorts using a conventional “3+3” study design. Tiopronin dose began at 1 g/d until aSAH Day 14. Each subsequent cohort received a dose of tiopronin based on predetermined guidelines. A maximum dose of 3 g/d was selected, because this is the maximum FDA-approved dose for long-term cystinuria treatment. Subjects were monitored for known side effects of tiopronin.

Nine patients were enrolled, the minimum number required based on the study design. None of these patients experienced serious side effects attributable to tiopronin, and no adverse events were noted that could not be attributed to the pathophysiology of aSAH.

The administration of 3 g/d of tiopronin following aSAH for up to 14 days appears to be safe and without the side effects associated with long-term use. Plans for a randomized, placebo-controlled Phase II trial of tiopronin for neuroprotection following aSAH are underway [1)].

A phase II clinical trial evaluated the efficacy of tiopronin in reducing CSF 3-AMINOPROPANAL levels in patients with aSAH.

In a prospective, randomized, double blind, placebo controlled, multicenter clinical trial, 60 patients were assigned to receive tiopronin or placebo in a 1:1 ratio. Treatment was commenced within 96 hours after aSAH onset, administered at a dose of 3 g daily, and continued until 14 days after aSAH or hospital discharge, whichever occurred earlier. The primary efficacy outcome was the CSF 3-AP level at 7 ± 1 days after aSAH.

Of the 60 enrolled patients, 29 (97%) and 27 (93%) in the tiopronin and placebo arms, respectively, received more than one dose of the study drug or placebo. At post-aSAH day 7 ± 1, CSF samples were available in 41% (n = 12/29) and 48% (n = 13/27) of patients in the tiopronin and placebo arms, respectively. No difference in CSF 3-AP levels at post-aSAH day 7 ± 1 was observed between the study arms (11 ± 12 nmol/mL vs 13 ± 18 nmol/mL; p = 0.766). Prespecified adverse events led to early treatment cessation for 4 patients in the tiopronin arm and 2 in the placebo arm.

The power of this study was affected by missing data. Therefore, the authors could not establish or

refute an effect of tiopronin on CSF 3-AP levels. Additional observational studies investigating the role of 3-AP as a biomarker for DCI may be warranted prior to its use as a molecular target in future clinical trials.Clinical trial registration no.: NCT01095731 (ClinicalTrials.gov) [2].

References

1)
Kim GH, Kellner CP, Hickman ZL, Zacharia BE, Starke RM, Hwang BY, Ducruet AF, Fernandez L, Mayer SA, Tracey KJ, Connolly ES Jr. A phase I clinical trial of tiopronin, a putative neuroprotective agent, in aneurysmal subarachnoid hemorrhage. Neurosurgery. 2010 Jul;67(1):182-5; discussion 186. doi: 10.1227/01.NEU.0000370919.93259.3C. PubMed PMID: 20559104; PubMed Central PMCID: PMC4540229.
2)
Ironside N, Christophe B, Bruce S, Carpenter AM, Robison T, Yoh N, Cremers S, Landry D, Frey HP, Chen CJ, Hoh BL, Kim LJ, Claassen J, Connolly ES. A phase II randomized controlled trial of tiopronin for aneurysmal subarachnoid hemorrhage. J Neurosurg. 2019 Jul 12:1-9. doi: 10.3171/2019.4.JNS19478. [Epub ahead of print] PubMed PMID: 31299655.