Ciproxifan in preventing inhalational anesthetic-induced neurotoxicity!

Sir,

Adverse neurological outcomes in pediatric patients when general anesthetic is used before synaptogenesis in the brain is called anesthetic-induced developmental neurotoxicity (AIDN). Even a single exposure of inhalational anesthetics have shown to affect developing the brain in animals. The currently understood mechanism of neurotoxicity is altered expression of ligand-gated ion channels, disturbance to intracellular calcium homeostasis, and mitochondria-mediated apoptotic pathway.[1] Other responsible factors could be concentration of anesthetic, type of anesthetic agent, and duration of exposure.

Of the presently used inhalational anesthetics, nitrous oxide appears to have no role in neurotoxicity. Sevoflurane has the least and isoflurane has the highest possible chances for AIDN in experimental animals. Existing data about role of desflurane and xenon causing neurotoxicity are limited. Xenon has been shown to cause significant neurotoxicity when used as sole anesthetic. However, when xenon is used with 0.75% isoflurane, it has been shown to attenuate AIDN.[2]

The Pediatric Anesthesia Neuro Development Assessment Study by Sun *et al*. studied single exposure to general anesthesia (GA) during inguinal hernia surgery in the exposed sibling versus no anesthesia exposure in the unexposed sibling before 36 months of age in 105 sibling pairs.[3] They prospectively assessed neurocognitive and behavior outcomes with retrospectively documented anesthesia exposure data.

Duration of exposure was 20–240 min. On analysis, they found no statistically significant differences in intelligence quotient scores in later childhood. Davidson *et al*. conducted the GA compared to spinal anesthesia trial in which they randomized infants to receive awake-regional anesthesia versus GA for inguinal herniorraphy.[4] They found no evidence in 1 h of sevoflurane anesthesia increasing the risk of adverse neurodevelopmental outcome at 2 years of age compared with awake regional anesthesia.

Several prophylactic strategies have been tried before using lithium, melatonin, 7-nitroindazole, L-carnitine, dexmedetomidine, and xenon to decrease AIDN but the results were either not encouraging or the exact mechanism was not understood.

Histamine H3 receptor is a presynaptic autoreceptor that inhibits histamine release in the brain and regulates the release of neurotransmitters in the brain. H3 receptor antagonists have been used in treating attention deficit hyperactivity disorder, Alzheimer's disease, and schizophrenia. Ciproxifan is an imidaxole-containing potent H3-receptor antagonist which increases the release of dopamine and norepinephrine

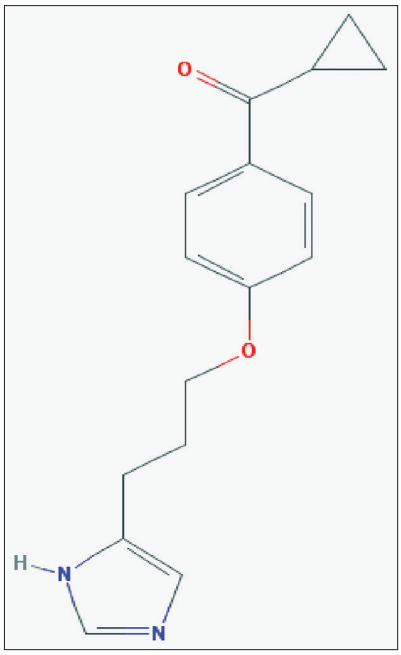

Figure 1: Chemical structure of ciproxifan [Figure source - National Center for Biotechnology Information. PubChem Compound Database; CID = 6422124. Available from: https://www.pubchem.ncbi.nlm.nih.gov/compound/6422124. [Last accessed on 2017 June 13]

in prefrontal cortex along with increase in acetylcholine in hippocampus, prefrontal, and entorhinal cortex [Figure 1].

In a study conducted by Ding *et al*., the authors found that mice who were treated with ciproxifan had improved postanesthesia cognitive memory performance when exposed to isoflurane for about 2 h.[5] The drug at a dose of 1–3 mg/kg intravenous was shown to reverse cognitive changes developed after 24 h exposure in a span of 30 min after injection. Theoretically, ciproxifan appears as a drug that could be either used for prophylaxis for preventing or for treating AIDN. Further studies are required to establish its safety and efficacy for use in humans.

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Conflicts of interest
There are no conflicts of interest.

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