Sedative and Neurotoxic Properties of Brexanolone Compared to Midazolam in the Developing Rodent Brain

Date: April 24th, 2020  
Time: 12:00 p.m. to 2:00 p.m.  
Place: Remote

Abstract
The developing brain is susceptible to extensive neurotoxicity following exposure to sedative/anesthetic drugs (SADs). Every year hundreds of thousands of children around the world are exposed to SADs with no viable non-neurotoxic agents approved for clinical use. Allopregnanolone (AlloP) has neuroprotective capabilities in the adult brain, as well as potent sedative effects in adults and neonates. AlloP and many SADs produce their sedative/anesthetic effects through allosteric modulation of GABAA receptors, which is one of two principal mechanisms behind SAD-induced neurotoxicity. Evidence suggests AlloP has the unique capacity to regulate key apoptotic factors in adults and is widely involved with critical stages of neurodevelopment. Findings with AlloP-analogs indicates the possibility of delivering sedation without neurotoxicity by using non-apoptogenic neurosteroids. Preclinical studies exploring the use of AlloP as a viable sedative and/or neuroprotective agent in the developing brain are sparse. Results of the current study indicate the brexanolone (BRX) formulation of AlloP is more sedative than midazolam (MDZ), producing moderate-to-deep sedation throughout a range of low-to-high doses in neonatal rodents. Lower doses of 10 and 20mg/kg BRX had relatively low impact on vital signs and produced no significant neurotoxic effect compared to controls. Conversely, higher doses of BRX at 40 and 80mg/kg produced greater neurotoxicity, suggesting the apoptogenicity of BRX is dose dependent. Results for MDZ indicate far milder levels of sedation were obtained until high doses of 60 and 120mg/kg. A significant neuroapoptotic response was induced at all reliably sedative doses of MDZ. Similar levels of prolonged light sedation via continuous infusion were also obtained using BRX. Although BRX appeared less deleterious to certain vital signs over time, 6-hour infusion of BRX induced a similar neurotoxic response compared to MDZ. These findings suggest low sedative doses of BRX can be administered without gross impact to vital signs or neurotoxic consequences.