Ketamine Neurotoxicity in a Mechanically Ventilated Mouse Pup Model or Not?

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Introduction:
Anesthetic toxicity in the developing rodent has been demonstrated with several anesthetics, including ketamine. Studies of ketamine-induced neurotoxicity in models of developing rodent brain have been without surgical stimulus and mechanical ventilation. We proposed to investigate the effect of surgical stimulus, tracheostomy and mechanical ventilation, in two paradigms of ketamine exposure 8 and 24 hours.

Methods:
After Institutional approval and according to NIH guidelines for the humane use and treatment of animals, thirty-two neonatal Balb-C mice (PND4) were randomized into control or ketamine exposure groups. Within each of the two study groups were 16 control animals and 16 ketamine anesthetized animals. The control animals were allowed to spontaneously breathe 40% oxygen for 8 (n=8) or 24 (n=8) hours. The ketamine exposed animals underwent tracheotomy (IM: 60mcg/g bw) and were mechanically ventilated with 40% oxygen for 8(n=8) or 24(n=8) hours (Figure 1). Ketamine (IM; 10 mcg/g bw prn) was administered as needed to approximate 1 MAC anesthesia. The ketamine mice were mechanically ventilated with 40% oxygen (microvent 848; Harvard Apparatus; Holliston, MA) at 180 breaths/min and tidal volumes of 7-8ml/kg for 8 or 24 hours at which time the brains were harvested and placed in 4% paraformaldehyde and paraffin embedded for later H&E and caspase-3 staining.

Results:
There was no difference in brain injury (H&E and caspase-3) in the 8 hour ketamine exposure group as compared to 8 hour control. Brain injury (H&E and caspase-3) was noted in the 24 hour ketamine exposure group when compared to the 24 hour control. There was no statistical difference in body weight between the 8 and 24 hour control and the 8 and 24 hr ketamine (3.25 +/- 0.66 control; 3.32+/-.0.49 ketamine) exposure groups. The total amount of ketamine per mouse pup was 0.049 +/--mg/g bw for 8 hour exposure and 0.195 +/- 0.019 mg/g bw. Blood gas analysis in the 8 and 24 hour ketamine groups: pH 7.3 +/- 0.12; PCO2 37 +/- 11.

Discussion:
Our study is similar to other rodent studies using volatile anesthesia at 1.0 MAC to prevent movement. In the present study, brain injury is not observed after 8 hours of exposure to ketamine. It is possible that surgical stimulus, tracheostomy, and/or mechanical ventilation attenuated brain injury as a result of ketamine administration. However, this potential protective effect was not observed with a 24 hour exposure to ketamine. It is difficult to determine whether the total dose or duration of ketamine exposure influenced brain injury. Despite this limitation, the study is novel in its use of surgical stimulus and mechanical ventilation in evaluating ketamine neurotoxicity.

References: