DEX Reduces HVR at Levels Comparable With Propofol in Healthy Male Volunteers

Written by Dennis Bittner

Dexmedetomidine (DEX) is a sedative medication used by anesthesiologists to induce and maintain anesthesia, particularly in intensive care units (ICUs). DEX, like clonidine, is an agonist of α2-adrenergic receptors and is able to provide sedation without causing respiratory depression [Cormack JR et al. *J Clin Neurosci*. 2005]. A recent meta-analysis suggests that DEX may offer advantages over propofol for ICU patient sedation in terms of decrease in the length of ICU stay and the risk of delirium [Xia ZQ et al. *J Surg Res*. 2013]. DEX may also reduce the duration of mechanical ventilation and enhance patient comfort [Jakob SM et al. *JAMA*. 2012], and it can reduce requirements for opioid analgesia [Venn RM et al. *Br J Anaesth*. 2001]. Propofol, the older and more commonly used alternate sedative for ICU applications, is well known to be a respiratory depressant, able to reduce both hypoxic ventilatory response (HVR) and hypercapnic ventilatory response (HCVR).

Åse Danielson, MD, Karolinska University Hospital, Stockholm, Sweden, and colleagues conducted a study aimed at comparing the effect of sedation with DEX or propofol on induced HVR and HCVR in a small group of healthy volunteers. Level of sedation was determined using different sedation scales as well as bispectral index (BIS) electroencephalogram (EEG) measurements. Plasma concentrations of both drugs were recorded, as well as changes in heart rate and blood pressure.

Briefly, after informed consent, 11 healthy male volunteers were randomized to receive DEX or propofol in a crossover study design at doses intended to produce light to moderate sedation, ie, targeting an Observer's Assessment of Alertness and Sedation (OAA/S) score of 3. Of the 11 volunteers, 10 completed the study protocol (age, 28 ± 2 years; body mass index, 24 ± 1 kg/m^2). Doses reported for DEX were a bolus of 0.59 ± 0.25 μg/kg, followed by an infusion of 0.45 ± 0.06 μg/kg/h for a total time of 75 ± 4.0 minutes. Propofol was given as a bolus of 74.51 ± 1.50 μg/kg/min followed by 49.68 ± 10.17 μg/kg/min for a total time of 76.5 ± 3.1 minutes. BIS scores were 82 ± 8 and 75 ± 3 minutes for DEX and propofol, respectively. Following dosing, standard circulatory and respiratory monitoring was conducted, and level of sedation was assessed using both the Richmond Agitation Sedation Scale and OAA/S, as well as BIS recordings. HVR and HCVR were measured at rest, during sedation, and after recovery. Sedative concentrations of DEX or propofol significantly reduced both the HVR and the HCVR to similar degrees.

The researchers said that the results demonstrated that DEX reduced both HVR and HCVR to a similar extent as propofol during light-moderate sedation. Although sedation with DEX preserves resting ventilation, they concluded that it interacts with control of breathing via both the peripheral and central nervous systems during hypoxia and hypercapnia. The authors did not comment on data indicating differences in heart rate and blood pressure observed between patients treated with DEX and those treated with propofol.

BK Channel Blocker Rapidly Reverses OIRD

Written by Rita Buckley

A pharmacokinetic/pharmacodynamic (PK/PD) modeling study on the effect of the BK channel blocker GAL021 found that it produced rapid reversal of opioid-induced respiratory depression (OIRD) in a population of healthy male volunteers [Roozekrans M et al. *Anesthesiology*. 2014].

GAL021—calcium-activated potassium with a stimulatory effect on ventilation at the carotid bodies—reversed OIRD in healthy volunteers without an effect on sedation, analgesia, or hemodynamics [Cotton J. *Anesthesiology*. 2014]. Margot Roozekrans, MD, Leiden University Medical Center, Leiden, The Netherlands, presented results of the study.

The research assessed whether GAL21 stimulates breathing in OIRD and evaluated its safety in a proof-of-concept, double-blind crossover study on isohypercapnic ventilation (study 1) and a subsequent double-blind exploratory study on poikilocapnic ventilation and non-respiratory end points (study 2).

Twelve volunteers were randomized to GAL021 or placebo in the controlled crossover study. Respiratory measurements were obtained under isohypercapnic conditions. The researchers administered intravenous low- and high-dose GAL021 or placebo on top of low- and high-dose alfentanil-induced respiratory depression. Arterial plasma was collected for measurement of GAL021 and alfentanil concentrations.

Data were analyzed with a population PK/PD model in NONMEM in 2 steps. First, the alfentanil and GAL021 PK data were characterized. Next, the PK models were used as inputs of the sigmoid E_{MAX} PD model, in which GAL021 was assumed to increase ventilation in a multiplicative