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

fashion so that the degree of reversal depended on the degree of respiratory depression.

The alfentanil concentration causing 50% respiratory depression was 26.3 ± 3.8 ng/mL (estimate ± SE); the alfentanil blood–effect site equilibration half-life was 1.0 ± 0.5 minutes. At a plasma concentration of 1 µg/mL, GAL021 reversed the OIRD by 37%; at the maximum dose, it reversed ventilation by 53%. For GAL021, the blood–effect site equilibration half-life was not significantly different from zero.

GAL02 produced rapid reversal of OIRD in the volunteers. The rapid onset of effect supports the findings in animals that GAL021 stimulates respiration at a site close to the vascular bed—namely, the peripheral chemoreceptors of the carotid bodies. In the future, studies should assess whether more complete reversal is possible at varying levels of OIRD.

Anesthesiologists routinely administer drugs that compromise a patient's ability to breathe, and dealing with the consequences can be a challenge [Cotton J. *Anesthesiology.* 2014]. Current clinical practice is to treat OIRD with such drugs as the opioid antagonist naloxone, which reverses OIRD as well as analgesia and sometimes has other deleterious side effects [Dahan A et al. *Anesthesiology.* 2010; van Dorp E et al. *Expert Opin Drug Saf.* 2007]. Doxapram is another widely used drug that was developed in the 1960s.

High-risk powerful opioids such as oxycodone, methadone, propofol, and fentanyl are commonly used by anesthesiologists to manage perioperative and postoperative pain. Less-than-complete relief often takes place due to the fear of OIRD.

The therapeutic drug GAL021 offers an alternative to naloxone that promises to restore breathing and reduce morbidity and mortality from OIRD without compromising pain relief or increasing sedation.

Phaxan Proves Superior to Propofol in First-in-Human Study

Written by Rita Buckley

Like propofol, lipid-free Phaxan causes fast-onset, short-duration anesthesia but with less cardiovascular and respiratory depression and no pain on injection. It could serve as an intravenous alternative to propofol for anesthesia, sedation, and intensive care unit practice.

Preclinical studies show that Phaxan has less of an effect on blood pressure than propofol and a higher therapeutic index (>30 vs 6, respectively). In humans, the induction dose and duration of anesthesia are the same as those reported for alphaxalone.

Clear and waterlike, Phaxan is an aqueous solution of alphaxalone (Althesin), a neuroactive steroid anesthetic that preceded Phaxan. A water-insoluble intravenous drug that was widely used from 1972 through 1984, Althesin was withdrawn from the market owing to hypersensitivity to the Cremophor EL used to dissolve it.

Colin S. Goodchild, PhD, Monash Institute of Medical Research, Malvern, Australia, presented results from a first-in-human trial comparing propofol and Phaxan.

The Phase 1c Trial Comparing the Anaesthetic Properties of Phaxan and Propofol [ACTRN 126000343909] was a double-blind study based on a Bayesian algorithm to determine dose equivalents for effects on the bispectral index (BIS). Its aims were to find the dose of Phaxan that caused anesthesia and to compare it with propofol for speed of onset and recovery, cardiovascular and respiratory effects, and other measures of safety and efficacy.

Twenty-four male volunteers with American Society of Anesthesiologists grade 1 (ages, 18 to 33 years; body mass index, 18 to 25 kg/m^2) were randomized to receive Phaxan (n = 12) or propofol (n = 12). The following study parameters were assessed 90 minutes after drug injection (single-bolus dose): blood pressure, BIS, oxygen saturation, need for airway and ventilatory support, pain on injection, involuntary movements, nausea, and measures of recovery (ie, the Richmond Agitation and Sedation Scale and the Digital Substitution Test).

No patients treated with Phaxan complained of pain on injection vs 8 of 12 patients treated with propofol ($P = .0013$); none needed apnea or airway support vs 9 of 12 in the propofol group ($P = .0003$; Fisher exact test). Involuntary muscle movement occurred in the propofol-treated group only (n = 3 of 12). Eleven patients in each group were anesthetized to a BIS value ≤ 50: the Phaxan dose was 0.49 mg/kg (95% CI, 0.55 to 0.46; median, 75% interquartile range [IQR]), and the propofol dose was 2.31 mg/kg (95% CI, 3.00 to 1.76; median, 75% IQR). The lowest average BIS was 28 for both patients treated with Phaxan and propofol, with no difference between fall and recovery of BIS. Nine patients in each group received doses of drugs that were within the IQR.

The data show that Phaxan lowers blood pressure and heart rate to a lesser degree than that of propofol at doses that result in equivalent central nervous system depression. Data also indicate that Phaxan is as safe and effective as propofol. Future clinical trials are needed to validate the findings of this study and assess other benefits of Phaxan.