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.