# The Latest Pharmacologic Ventilator

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AS anesthesiologists, we routinely administer drugs that compromise a patient's ability to breathe, and dealing with the consequences can be a challenge. However, our jobs may be getting easier. In this issue, Roozekrans *et al.*[1] present two small, human studies on male volunteers conducted in The Netherlands on a promising new breathing stimulant compound, GAL021, being developed by Galleon Pharmaceuticals (Horsham, PA). Additional first-in-human safety and pharmacokinetic studies of GAL021 conducted in Belgium are to be published in an upcoming issue of the *British Journal of Anaesthesia*.

***"GAL021 is being developed as an agent to treat [opioid-induced respiratory depression] with no effect on opioid analgesia."***

Opioids are the most effective drugs for acute pain management. However, they cause opioid-induced respiratory depression (OIRD), which is a significant contributor to many adverse perioperative respiratory events.[2] Opioid sensitivity is unpredictable and impacted by polypharmacy, age, and comorbidities, including obesity and sleep apnea. Opioids, along with analgesia, cause sedation, hypoventilation, loss of responsiveness to hypoxia and to hypercapnia, irregular breathing with periods of apnea, and loss of upper airway muscle tone. A drug that minimizes OIRD would have significant clinical utility. Naloxone is effective, reliable, and widely-available to reverse OIRD, but, unfortunately, it reverses analgesia, as well. GAL021 is being developed as an agent to treat OIRD with no effect on opioid analgesia.

In this well-conducted, two-part study, patients received steady-state drug infusions of low- or high-dose alfentanil co-administered with steady-state infusions of placebo or low- or high-dose GAL021. Study 1 tested GAL021 efficacy in reversing established OIRD. Study 2 addressed nonrespiratory endpoints such as hemodynamics, analgesia, and sedation. In short, without altering analgesia, sedation, or hemodynamics, GAL021 reversed some of the hypoventilation induced by alfentanil. GAL021 was well tolerated with "sweating and feeling warm" and "infusion site pain" as its main adverse effects.

## GAL021 and Almitrine

According to Galleon scientists, GAL021 is a second-generation breathing stimulant, conceived by deconstructing the chemical structure of almitrine and other breathing stimulant compounds. Almitrine was approved for human use in some European countries, and intravenous almitrine has been used in perioperative and intensive care settings. Oral almitrine has been used to promote ventilation and blood oxygenation in patients with chronic obstructive pulmonary disease and dementia. Never marketed in the United States, almitrine was recently removed from the European market owing to weight loss and peripheral neuropathy with chronic administration. This toxicity is due to the difluorobenzhydrylpiperadine modification on the drug, which is released with almitrine metabolism. Difluorobenzhydrylpiperadine by itself induces weight loss and neuropathy in rats and was removed in designing GAL021 (fig. 1).[3]

In addition to its breathing effects, almitrine also raises pulmonary artery pressure. This seemingly harmful effect is a double-edged sword as it led to almitrine's use in optimizing lung ventilation–perfusion matching, yielding improved oxygenation in patients undergoing one-lung ventilation and in patients receiving inhaled nitric oxide for acute respiratory distress syndrome. GAL021's effects on pulmonary hemodynamics and ventilation–perfusion matching will need to be addressed.

## GAL021's Mechanism of Action

A number of preclinical studies by Galleon have shed light on GAL021's efficacy, mechanism of action, and potential for clinical utility.[3] In animal studies, GAL021 attenuates morphine-induced respiratory depression but not analgesia, and also reverses respiratory depression produced by isoflurane,

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Corresponding article on page 459.

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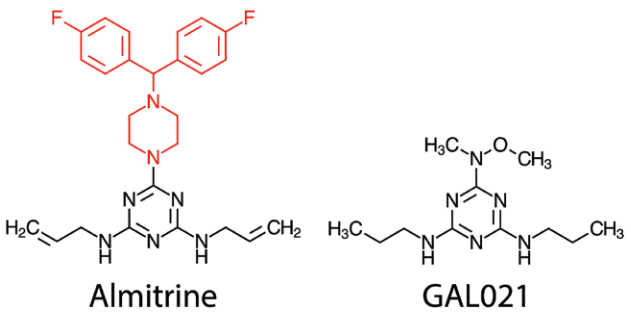


Fig. 1. Chemical structures of the breathing stimulant drugs almitrine and GAL021. The toxic difluorobenzhydrylpiperadine group on almitrine, which causes weight loss and neuropathy, is colored *red*.

propofol, and midazolam. Studies have also shown that GAL021 acts through a peripheral effect on BK potassium channels in the carotid bodies: carotid body denervation eliminates most GAL021 breathing effects in rats, and knockout mice lacking a BK potassium channel protein subunit gene are resistant to GAL021 breathing effects.[3]

The carotid bodies are sentry organs located at bilateral carotid artery bifurcations that monitor low oxygen and low pH levels in blood. In communication with the brainstem, the carotid bodies stimulate breathing. Inhibition of a potassium conductance is an early step in the cellular mechanism by which the carotid bodies sense hypoxia and acidemia. This potassium conductance is provided by BK, TASK, and other types of potassium channels. As a potent BK potassium channel blocker, GAL021 "hijacks" the chemosensing process to increase carotid body sensitivity to hypoxia or acidemia at low doses (*i.e.*, "turns up the chemosensing gain") or to frankly activate the carotid body at higher doses. GAL021 provides physiologic antagonism of OIRD without opioid receptor antagonism as provided by naloxone. GAL021's mechanism of action requires a functioning brainstem to restore breathing normalcy. Since the circuits in the brainstem providing rhythmic breathing are directly compromised by opioids, there is probably a ceiling to GAL021 efficacy. In the current study, GAL021 provides partial reversal of opioid-induced hypoventilation, although higher doses were not studied. Future studies will have to address the limits of GAL021 dosing and efficacy, and its efficacy with bolus opioid administration. Moreover, it will be interesting to learn how GAL021 efficacy compares with centrally acting breathing stimulant drugs that are discussed in the following sections.

## Doxapram Is the One to Beat

Doxapram is one of the best known breathing stimulant drugs already approved for human use and developed in the 1960s. Doxapram, also a potassium channel blocker and a carotid body stimulant, antagonizes OIRD with variable efficacy. GAL021's success likely hinges in part on whether it provides improvements in efficacy or side effects relative to doxapram. Notably, the GAL021 investigators in a separate study using similar methodology were unable to reverse OIRD with doxapram.[4] Doxapram's side effects include panic, agitation, dyspnea, and hypertension; and none of these effects were reported with GAL021 in the current study. Doxapram is a racemic mix of two enantiomers. Trying to eliminate the side effects, Galleon has also conducted preclinical and phase I studies on the doxapram(+) enantiomer, which, relative to doxapram(–), accounts for most of the breathing effects. Doxapram(+), although an improvement over the racemate, unfortunately, retains the pressor effect and likely prompted the company's focus on GAL021.

## Breathing Stimulants, Old and New

GAL021, which is being developed in both intravenous and oral formulations for chronic opioid users, joins almitrine, doxapram, and a number of drugs that promote breathing and antagonize OIRD. GAL021 has an analog with improved bioavailability, GAL160, in development by Galleon primarily for sleep apnea.

Other drugs include Cortex Pharmaceutical's (Irvine, CA) ampakine compounds intended for use in drug-induced respiratory depression. Ampakines act centrally through effects on the AMPA-type glutamate receptors in the brainstem breathing circuitry. The CX1942 ampakine is in preclinical studies and CX1739 has completed phase I trials. CX717, a less potent ampakine precursor to CX1739, antagonizes OIRD in rats and humans. It also reverses opioid suppression of hypoglossal motor neuron activity, suggesting it may improve airway patency (*i.e.*, decreases "snoring").[3,5,6]

Rev-001(tianeptine) is an antidepressant drug in phase II trials repurposed by Revive Therapeutics (Ontario, Canada) for the prevention of OIRD. This drug, interestingly, has also been shown to block opioid tolerance in rats.

Other compounds known to antagonize OIRD to varying degrees include the D1 dopamine and serotonin 1A, 7, and 4A receptor agonists (*e.g.*, buspirone, mosapride, and BIMU8), methylxanthines (*e.g.*, caffeine and theophylline), physostigmine, minocycline, and thyrotropin-releasing hormone. Their use has been limited by side effects, bioavailability, or poor efficacy in humans.[5,6]

The results of the current small study by Roozekrans *et al.* are promising, and pave the way for future studies to understand GAL021's limits, its relative efficacy compared to other agents (*e.g.*, doxapram or ampakines), its tolerability and side effects, and, of course, its clinical utility.



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