Inspire or expire: a matter of life or death

Lemmen, M.A. van

CHAPTER 8

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TAK-925 (danavorexton), an Orexin Receptor 2 Agonist, Reduces Opioid-Induced Respiratory Depression and Sedation Without Affecting Analgesia in Healthy Adult Males

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Anesthesiology. 2025;142(4):628.

Supplemental digital content of this article is available online

ABSTRACT

Background

Orexin neuropeptides help regulate sleep/wake states, respiration, and pain. However, their potential role in regulating breathing, particularly in perioperative settings, is not well understood. TAK-925 (danavorexton), a novel, orexin receptor 2-selective agonist, directly activates neurons associated with respiratory control in the brain and improves respiratory parameters in rodents undergoing fentanyl-induced sedation. This study assessed the safety and effect of danavorexton on ventilation in healthy men in an established remifentanil-induced respiratory depression model.

Methods

This single-center, double-blind, placebo-controlled, two-way crossover, phase 1 trial randomized (1:1) 13 healthy men to danavorexton (11mg [low-dose] then 19mg [high-dose]) or placebo, under remifentanil infusion, on two occasions separated by a ≥36-hour washout period. Remifentanil infusion was titrated under isohypercapnic conditions to achieve ~30% to 40% decrease in minute ventilation (from ~20 to ~14 L/minute) before danavorexton/placebo administration. Assessments included safety, ventilation measurements, sedation, and pain tolerance.

Results

4 (30.8%) danavorexton-treated participants and 1 (8.3%) placebo-treated participant experienced treatment-emergent adverse events (all mild in severity). Insomnia, lasting 1 day, occurred in 1 participant, and was considered related to danavorexton. Compared with placebo, low- and high-dose danavorexton significantly increased ventilation variables (observed mean [95% confidence interval] change, sensitivity analysis model-based p-values) including minute volume (8.2[5.0, 11.4] and 13.0[9.4, 16.5] L/min), tidal volume (312[180, 443] and 483[309, 657] mL), and respiratory rate (3.8[1.9, 5.7] and 5.2[2.7, 7.7] breaths/min) (all P<0.001). High-dose danavorexton significantly decreased sedation on visual analog scale (–29.7[–54.1, –5.3] mm, P<0.001) and Richmond Agitation Sedation Scale (0.4[0.0, 0.7], P<0.001), compared with placebo. Improvements in respiratory variables continued beyond completion of danavorexton infusion. No significant differences in pain tolerance were observed between danavorexton doses or between danavorexton and placebo (~13% increase from baseline; low-dose:P=0.491; high-dose:P=0.140).

Conclusions

Danavorexton has effects on respiration and wakefulness in an opioid-induced respiratory depression setting without reversing opioid analgesia.

Introduction

Many anesthetic drugs, and opioids in particular,[1] affect the brain ventilatory control system and are associated with respiratory depression. The incidence of an adverse respiratory event in the immediate postoperative period is 46% to 84%, depending on patient risk factors.[2, 3] Male sex, older age, opioid naivety, sleep disordered breathing, and chronic heart failure are the main factors predisposing to an opioid-induced respiratory event.[3] The opioid antagonist naloxone is currently the only treatment available to reverse opioid-induced respiratory depression but its use can also reverse analgesia and induce other side-effects.[4-6]

Emerging evidence suggests that the orexin system, central to the regulation of arousal and wakefulness,[7] has a role in the stimulation of respiratory function. Orexin A and B neuropeptides are produced by orexin neurons in the brain [8, 9] and, through activation of orexin receptors 1 and 2 (OX1R and OX2R), have been found to activate hypoglossal motoneurons and enhance genioglossus muscle activity in rats.[10, 11] TAK-925 (danavorexton) is a novel, highly selective OX2R agonist that has been shown to modulate both diaphragm and genioglossus muscle activity[12, 13] and promote recovery from propofol- and fentanyl-induced sedation in rats and monkeys.[14] These findings suggest that there is potential for OX2R agonists to improve respiratory function in patients with opioid-induced respiratory depression in the postanesthesia setting.

The aim of the current study was to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of intravenous danavorexton administered to healthy participants during remifentanil-induced respiratory depression under isohypercapnic conditions, an established human model [15] of opioid-induced respiratory depression. The reason for choosing the isohypercapnic model was its sensitivity in detecting opioid effects on the ventilatory control system.[16]

Materials and Methods

Ethics and Registration

This was a randomized, double-blind, placebo-controlled, 2-way crossover phase 1 trial in healthy volunteers conducted at a single site (Leiden University Medical Center, Leiden, the Netherlands) between March 10 and May 20, 2022. The study was registered at the International Standard Randomized Controlled Trial Number Registry (ISRCTN63027076; https://www.isrctn.com/ISRCTN63027076) on April 20, 2022, and the principal investigator was Albert Dahan, M.D., Ph.D. This trial was approved by the ethics committee at the study site (BEBO Foundation for the Assessment of Ethics of Biomedical Research, Assen, the

Netherlands) and performed in accordance with International Council for Harmonization guidelines, ethical principles of the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice (E6) guidelines, and applicable local or regional regulatory requirements. The study protocol was also approved by the National Competent Authority, the Central Committee on Research Involving Human Subjects (CCMO, the Hague, the Netherlands). All participants provided written informed consent prior to enrollment.

Study Design and Procedures

This work discusses the investigational compound danavorexton, an orexin receptor 2-selective agonist; danavorexton is not yet approved by the United States Food & Drug Administration. The study assessed the safety, tolerability, pharmacokinetics, and pharmacodynamics of an intravenous infusion of danavorexton administered to healthy participants during remifentanil-induced respiratory depression in an opioid-induced isohypercapnic hyperventilation model. Healthy volunteers were randomized 1:1 to one of two treatment sequences: danavorexton (11 mg and 19 mg sequential single dose, 90-min intravenous infusions) on one session and placebo (two sequential single dose 90-min intravenous infusions) on a second session, or vice versa, with a washout period of at least 36 hours between treatment periods (fig. 1). Danavorexton pharmacokinetic samples were drawn on Day 3 to confirm washout after dosing on Day 1.

Study drugs were prepared by the pharmacy and dispensed to the study team in identical, unmarked, numbered flacons on the morning of the experiment. Upon arrival in the research unit, the participants were screened for the use of illicit substances using a urine dipstick (Alere Toxicology Plc., Oxfordshire, United Kingdom) and screened for alcohol use. Furthermore, full hematology, serum chemistry, and urinalysis were determined before dosing. Thereafter, participants received two intravenous catheters in the cubital vein of the left and the right arm, an arterial line in the left or right radial artery (preferably right) and an Intellivue 5-lead electrocardiogram (Philips, Amsterdam, the Netherlands). The arterial line was connected to a FloTrac Sensor and HemoSphere (Edwards Lifesciences, Irvine, US) for hemodynamic monitoring. Additionally, a finger probe Masimo pulse oximeter (Masimo Corporation, USA) was placed.

Ventilation was assessed on a breath-to-breath basis against a background of isohypercapnia, which was induced before remifentanil administration.[15] The isohypercapnic model was chosen for its sensitivity in detecting opioid effects on the ventilatory control system. For this purpose, varying levels of inhaled oxygen, carbon dioxide, and nitrogen were administered

to the volunteers via computer-controlled mass flow controllers (Bronkhorst Nederland B.V., Veenendaal, the Netherlands) ensuring the strict control of the end-tidal levels of oxygen and carbon dioxide. The increase in end-tidal pCO_2 was such that the initial baseline ventilation levels were 20 ± 2 L/min. Throughout the study, the end-tidal PO_2 was maintained at 100 mmHg. During each treatment period, participants received remifentanil intravenous infusion over approximately 210 mins, titrated to achieve approximately 30% to 40% depression of isohypercapnic ventilation (target ventilation level, 14 L/min) prior to danavorexton/placebo administration. Participants' vital signs were continuously monitored using pulse oximetry and electrocardiographic measurements.

Participants

Healthy male volunteers aged 18 to 55 years with a body mass index ≥18 and ≤35 kg/mg2, who had been nonsmokers for ≥6 months, with regular sleep-wake habits, were eligible for participation in this study. Additional eligibility criteria included no history of hypertension, systolic blood pressure (SBP) <140 mmHg, diastolic blood pressure (DBP) <90 mmHg, and a heart rate of 50 to 90 beats/min at the screening visit. Participants were excluded if they had a current or previous history of behavioral or psychiatric disorder requiring daily medication, substance abuse disorder, pulmonary or cardiovascular diseases.

Assessments

The primary safety outcome was the number of participants with at least one treatment-emergent adverse event. The observed plasma concentration of danavorexton at the end of infusion was a secondary outcome. Prespecified exploratory safety outcomes were the number of participants with at least one predefined markedly abnormal value for laboratory values, vital signs (i.e., SBP <90 or ≥160 mmHg, DBP <50 or ≥100 mmHg, or any >20 or >30 mmHg change from baseline in SBP or DBP), or electrocardiogram measurements (i.e., PR interval ≥200 ms or QRS duration ≤80 ms) after the start of danavorexton/placebo infusion. Additional exploratory assessments included 1-min ventilatory averages (minute volume, tidal volume, and respiratory rate), level of sedation assessed by the participant-reported visual analog scale (VAS) and the clinician-reported Richmond Agitation Sedation Scale (RASS), and pain tolerance. Minute volume, tidal volume, and respiratory rate were measured continuously during baseline (time window 1), after application of the end-tidal forcing technique (time window 2), and from start until end of infusion (time windows 3 to 6; fig. 1). The sedation VAS is a subjective questionnaire utilizing a visual rating scale from 0 to 100 mm, where 0 = no sedation and 100 = maximum sedation. The RASS assessment ranges from +4 to −5, where a score of +4 represents a very combative, violent patient, a score of 0 represents an alert

and calm patient, and a score of −5 represents an unarousable patient. Pain tolerance was measured using an electrical pain assessment, whereby an electrical stimulus was delivered via two electrodes applied to the participant's skin over the shinbone of the leg.[17] The current was increased from 0 by 0.5 mA/s. The participant pressed a button when pain was first experienced and a second button that ended the electrical stimulus when pain could no longer be tolerated. The latter value was determined three times with a 1-min interval and the average was used as the pain tolerance level. RASS, sedation VAS, and pain assessments were performed two to three times within each time window. The average of these three measurements was used in the analysis.

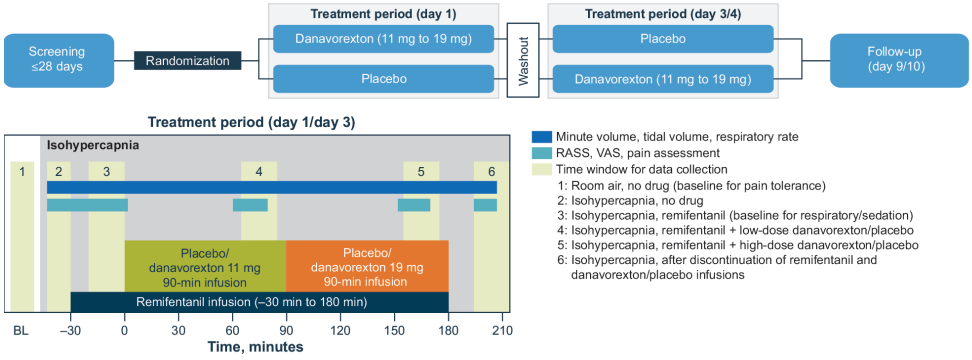

Fig. 1. Study design. Healthy participants were randomized 1:1 to receive danavorexton (11 mg [low-dose] and 19 mg [high-dose]) followed by placebo, or vice versa. Treatment periods were separated by a ≥36-hour washout period. Danavorexton 11 mg and 19 mg and placebo were administered as sequential 90-min intravenous infusions within each treatment period. Remifentanil was administered over 210 mins under isohypercapnic conditions throughout danavorexton/placebo infusion and was titrated to achieve 30% to 40% respiratory depression prior to danavorexton/placebo administration. Minute volume, tidal volume, and respiratory rate were assessed continuously throughout end-tidal forcing, averages were calculated in the first 10 mins of each assessment time window. The RASS, the VAS and pain assessments were performed 2 to 3 times within each time window (−20 to 0 minutes, 65 to 85 minutes, 155 to 175 minutes, and 195 to 215 minutes from start of infusion) and the average values were used. BL, baseline; RASS, Richmond Agitation Sedation Scale; VAS, visual analog scale.

Statistical Analysis

Up to 16 participants were planned to be randomized equally, to achieve up to eight participants in each treatment sequence. Assuming a ~75% completion rate, this sample size was considered sufficient to assess the primary and secondary outcomes of safety, tolerability, and pharmacokinetics. For pharmacodynamic outcomes, a sample size of 12 participants had >90% power to detect a difference in ventilation rate between danavorexton and placebo of 6 L/min (5% two-sided significance level) assuming a within subject SD of 5.5 L/min. The full analysis set (pharmacodynamic endpoints), and safety analysis set (safety endpoints) both included all randomized patients who received at least one dose of study drug.

For the analyses of minute volume, tidal volume, and respiratory rate, the average over all the values collected during the first 10 mins of each assessment time window was calculated. All assessments except for pain tolerance used time window 3 as baseline. For the prespecified method, pharmacodynamic outcomes other than pain tolerance (i.e., minute volume, tidal volume, respiratory rate, sedation VAS, RASS, partial pressure of carbon dioxide [$PaCO_2$], and partial pressure of oxygen [PaO_2]) were analyzed using a mixed-effects analysis of covariance over all post-randomization time windows, with the change from baseline (time window 3; fig. 1) as the outcome, with treatment (danavorexton or placebo), time window (baseline, time windows 4, 5, and 6; fig. 1), and treatment-by-time window (excluding baseline) as fixed effects, and with subject, subject-by-treatment, and subject-by-time window as random effects. Observed means, standard deviations and 95% confidence intervals (CIs) are reported. Model-based P-values, least squares means and model-based 95% CIs are reported in Supplemental Table 1.

For analysis of pain tolerance via the prespecified method, a similar mixed-effects analysis of covariance was used, but with log-transformed values, and time window 1 as baseline (fig. 1). Observed means are reported. Least squares means and model-based 95% CIs are included in Supplemental Table 1.

This statistical model is based on Roozekrans, et al. 2014[15] and the results of the prespecified method are presented in Supplemental Table 1. For some of the parameters, SAS automatically set a random effect to 0. Per request of a reviewer, a sensitivity analysis was run including only subject as a random effect and there were no meaningful differences from the prespecified method (Supplemental Table 1). The inference method was also changed from restricted maximum likelihood (REML) to maximum likelihood (ML), per request of the reviewer, and did not meaningfully affect the results and conclusions of this study (Supplemental Table 1). The sensitivity analysis method-based P-values are presented in the body of this paper.

All continuous variables were summarized using descriptive statistics. No adjustments for multiplicity were made and all P-values are considered exploratory. All analyses were prespecified prior to unblinding via a statistical analysis plan, except for those that were requested by the reviewers, as stated above. SAS v9.4 was used for analyses (SAS; SAS Institute Inc., Cary, NC).

Results

Participants

Of 14 volunteers screened, 13 met inclusion criteria and were randomized, and 12 completed the study (fig. 2). One participant prematurely discontinued from the study after receiving the first sequence of danavorexton and did not return on the second day to receive placebo; the withdrawal was due to a treatment-emergent adverse event of influenza-like illness that was considered unrelated to study medication. Baseline and clinical characteristics were similar between the two treatment groups (table 1). Participants had a mean (SD, range) age of 25 (2.18, 23 to 30) years.

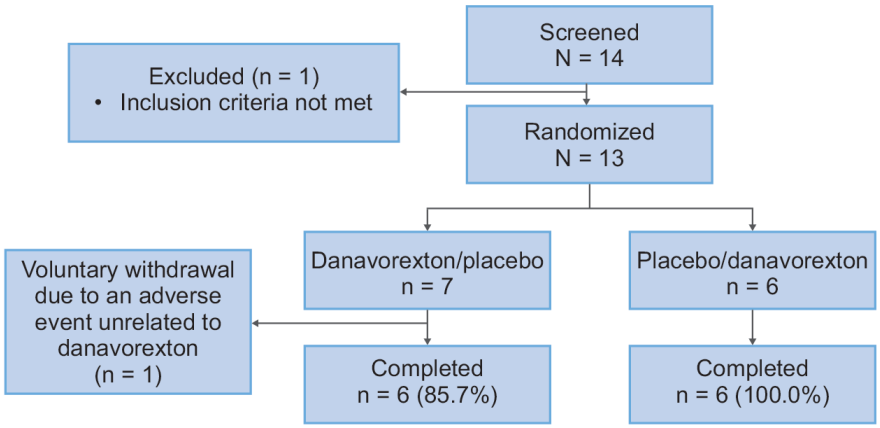

Fig. 2. Flow diagram for study participants. The participant who withdrew consent discontinued on the first treatment day after receiving the first sequence of danavorexton and did not return on the second day for placebo.

Safety

Four of 13 (30.8%) participants in the danavorexton treatment periods and one of 12 (8.3%) participants in the placebo treatment periods experienced seven mild treatment-emergent adverse events. One (7.7%) participant experienced insomnia that was considered related to danavorexton and resolved in less than 24 hours. This adverse event was characterized by difficulty falling asleep at 8 pm on the day of danavorexton infusion and waking early the next day (i.e., 1 hour before their alarm). Prior to danavorexton/placebo infusion, one (7.7%) participant experienced remifentanil-related mild nausea and vomiting. Apart from the one participant who withdrew prematurely (see above), two participants experienced three events of mild headache that were unrelated to study drug and resolved in both the danavorexton and placebo treatment periods (table 2). No serious or severe treatment-emergent adverse

events were reported during the study.

Prespecified markedly abnormal values for vital signs were related to dose-dependent transient increases in blood pressure (fig. 3). Mean blood pressure values returned to baseline or near baseline values after the end of infusion. Nine (69.2%) participants had an increased systolic blood pressure of >20 mmHg from baseline (i.e., before end-tidal forcing) with danavorexton compared with 2 (16.7%) with placebo, and 4 (30.8%) participants had an increased DBP of >20 mmHg with danavorexton versus none with placebo; however, no participant experienced hypertension as a treatment-emergent adverse event. Markedly abnormal values for electrocardiogram parameters were recorded for PR interval ≥200 msec (2/13 [15.4%] participants with danavorexton versus 2/12 [16.7%] participants with placebo) and QRS duration of ≤80 msec (1/13 [7.7%] participants with danavorexton and 1/12 [8.3%] participants with placebo). These were recorded during remifentanil infusion without any difference between danavorexton and placebo. No other clinically meaningful changes in electrocardiogram parameters were observed throughout the study. There were no markedly abnormal values in serum chemistry, hematology, or urinalysis parameters (table 3).

Pharmacokinetics

The dose of remifentanil versus time is shown across both treatment arms for individual participants in Supplemental fig. 1. Following two sequential 90-min intravenous infusions of danavorexton in participants on remifentanil, mean (SD) danavorexton concentrations at the end of infusion were 78.5 (20.7) and 82.4 (14.1) ng/mL during lowdose loading and maintenance period, respectively, and 144 (36.0) and 155 (28.5) ng/mL during high-dose loading and maintenance period. Maximum danavorexton concentrations were achieved at approximately 180 mins, at the end of the high dose infusion. Danavorexton pharmacokinetics were below the limit of quantification at each pre-remifentanil infusion. Danavorexton had no apparent effect on remifentanil pharmacokinetics when co-administered (Supplemental fig. 2).

	Danavorexton/Placebo* (n = 7)	Placebo/Danavorexton† (n = 6)
Age, years		
Mean, SD	24.1 (0.7)	26.8 (2.5)
Median, range	24.0 (23, 25)	26.5 (24, 30)
Male, n (%)	7 (100)	6 (100)
Body mass index, kg/m^2		
Mean, SD	22.6 (1.3)	23.7 (2.6)
Median, range	23.1 (20.5, 24.0)	22.9 (20.9, 26.9)
Smoking history, n (%)		
Never	3 (42.9)	3 (50.0)
Former	4 (57.1)	3 (50.0)
Systolic blood pressure, mmHg		
Mean, SD	129.0 (4.2)	131.5 (11.8)
Median, range	129.0 (123, 136)	131.5 (115, 149)
Diastolic blood pressure, mmHg		
Mean, SD	68.7 (7.2)	72.5 (4.4)
Median, range	67.0 (58, 81)	70.5 (69, 79)

Table continues on next page

	Danavorexton/Placebo* (n = 7)	Placebo/Danavorexton† (n = 6)
Respiratory rate, breaths/min‡		
Mean, SD	13.9 (2.4)	16.3 (3.5)
Median, range	14.0 (10.9, 17.6)	17.1 (10.6, 20.7)
Tidal volume, mL		
Mean, SD	658.4 (171.2)	576.5 (126.2)
Median, range	637.5 (460.7, 955.7)	551.3 (456.6, 771.9)
Minute volume, L/min§		
Mean, SD	7.7 (1.1)	8.0 (0.9)
Median, range	7.5 (6.4, 9.7)	8.0 (6.8, 9.2)
RASS assessment		
Mean, SD	0 (0)	0 (0)
Median, range	0 (0, 0)	0 (0, 0)
Sedation VAS		
Mean, SD	5.4 (6.7)	3.1 (2.8)
Median, range	5.0 (0.0, 18.5)	3.5 (0.0, 6.5)
Pain tolerance, mAmp¶		
Mean, SD	17.7 (8.4)	18.9 (9.8)
Median, range	14.3 (8.5, 28.0)	15.6 (9.0, 35.8)

Table 1. Baseline Demographics
Baseline is defined as the last measurement collected prior to the application of the end-tidal forcing technique on study day 1. *Danavorexton/placebo: participants received danavorexton on Session 1 and placebo on Session 2. †Placebo/danavorexton: participants received placebo on Session 1 and danavorexton on Session 2. ‡Respiratory rate = (minute volume/tidal volume) * 1,000. §Minute volume = tidal volume / (inspiratory time + expiratory time) * 60. ¶Pain tolerance is mAmp when pain can no longer be tolerated, averaged over 2 to 3 assessments in each measurement period. RASS, Richmond Agitation Sedation Scale; VAS, visual analog scale.

	Placebo (N = 12)		Danavorexton (N = 13)	
	Events	Participants, n (%)	Events	Participants, n (%)
Any treatment-emergent adverse event*	1	1 (8.3)	6	4 (30.8)
Related	0	0	1	1 (7.7)
Insomnia	0	0	1	1 (7.7)
Mild	1	1 (8.3)	6	4 (30.8)
Headache	1	1 (8.3)	2	2 (15.4)
Nausea	0	0	1	1 (7.7)
Vomiting	0	0	1	1 (7.7)
Moderate	0	0	0	0
Severe	0	0	0	0
Leading to study drug discontinuation	0	0	1	1 (7.7)
Influenza-like illness†	0	0	1	1 (7.7)
Serious treatment-emergent adverse event	0	0	0	0
Deaths	0	0	0	0

Table 2. Summary of Treatment-Emergent Adverse Events
Percentages are based on all subjects in the safety analysis set within each column. Adverse events were classified using MedDRA version 24.1.
*Treatment-emergent adverse events are those that occur after the start of the danavorexton/placebo infusion within a treatment period and before the start of danavorexton/placebo infusion within the next period. If a treatment-emergent adverse event began during one treatment period and continued into the next treatment period, the treatment-emergent adverse event was attributed to the periods in which it began and where it worsened (if applicable). †Event was determined to not be related to study drug and led to voluntary withdrawal from study.

Pharmacodynamics

No statistically significant difference was observed between placebo and danavorexton for partial pressure of carbon dioxide or partial pressure of oxygen (Supplemental fig. 3). Greater increases in minute volume, tidal volume, and respiratory rate were observed in remifentanil-infused participants with danavorexton versus placebo (fig. 4). Compared with placebo, mean (95% CI) change in minute volume increased by 8.2 (5.0, 11.4) L/min (P < 0.001) with low-dose and by 13.0 (9.4, 16.5) L/min (P < 0.001) with high-dose danavorexton. The improvement in minute volume was commensurate with statistically significant increases in both tidal volume (mean [95% CI] change: low-dose 312 [180, 443] mL, P < 0.001 and high-dose 483 [309, 657] mL, P < 0.001) and respiratory rate (mean [95% CI] change: low-dose 3.8 [1.9, 5.7] breaths/min, P < 0.001 and high-dose 5.2 [2.7, 7.7] breaths/min, P < 0.001) during danavorexton infusion, and was sustained for at least 35 mins after the infusion was discontinued.

	Placebo (N = 12)	**Danavorexton (N = 13)**
Systolic blood pressure (mmHg), n (%)		
<90	0	0
≥160	1 (8.3)	3 (23.1)
Change from baseline >20	2 (16.7)	9 (69.2)
Change from baseline >30	0	3 (23.1)
Diastolic blood pressure (mmHg), n (%)		
<50	0	0
≥100	0	0
Change from baseline >20	0	4 (30.8)
Change from baseline >30	0	1 (7.7)

Table 3. Summary of Markedly Abnormal Vital Signs
Baseline is defined as the last measurement before administration of study drug for a given treatment period. For vital sign assessments, this corresponds to prior to dynamic end-tidal forcing.
Participants with measurements represent the number of participants with a non-missing result for a given parameter at that category. Percentages are based on the number of participants in the safety analysis set within each column.

Decreased levels of sedation were observed in remifentanil-infused participants with danavorexton versus placebo (fig. 5). Mean (95% CI) sedation on the VAS decreased by –18.5 (–45.2, 8.2) mm (P = 0.002) with low-dose and by –29.7 (–54.1, –5.3) mm (P < 0.001) with high-dose danavorexton compared with placebo. Mean (95% CI) change in RASS scores from baseline were 0.1 (–0.4, 0.6) (P = 0.018) with low-dose and 0.4 (0.0, 0.7) (P < 0.001) with high-dose danavorexton compared with placebo. During the danavorexton period, participants returned to a baseline alertness state during high-dose danavorexton infusions; in the placebo period, participants returned to baseline alertness state in the post-infusion stage (table 4).

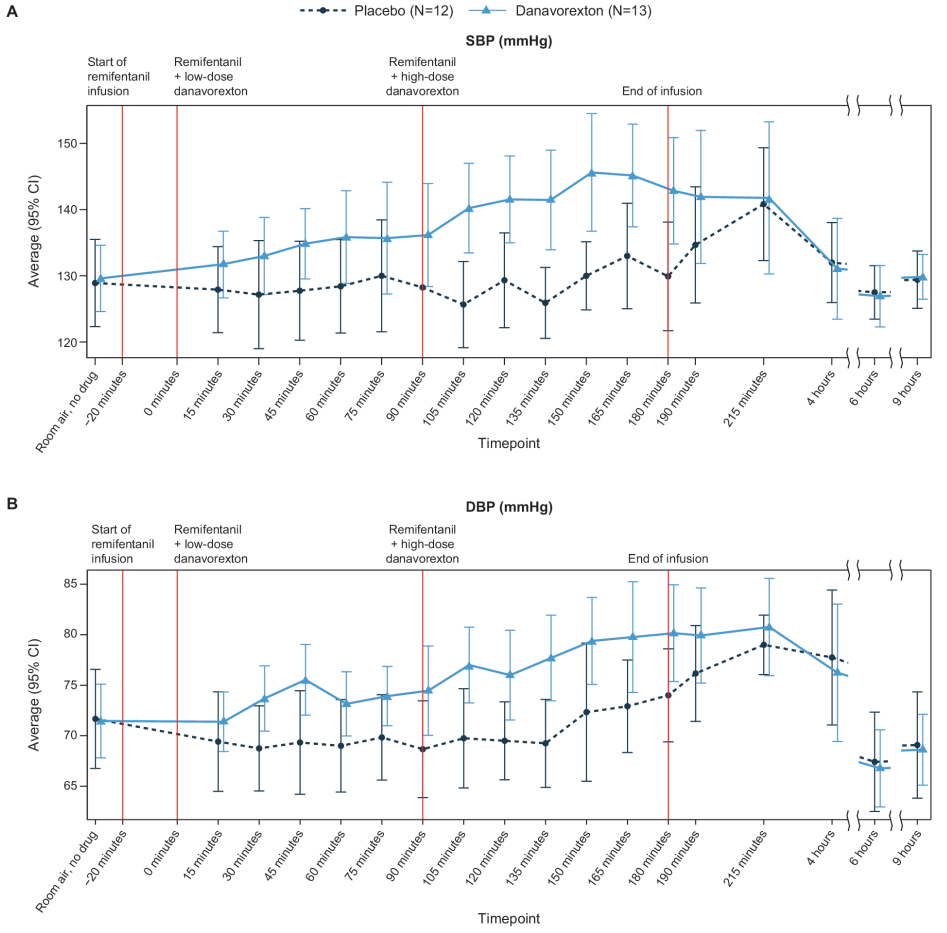

Fig. 3. Effect of danavorexton, in the context of remifentanil infusion, on blood pressure over time. (A) SBP and (B) DBP were measured from prior to the start of remifentanil infusion (room air, no drug) to 9 hours after the start of danavorexton/placebo infusions. CI, confidence interval; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Pain tolerance did not differ significantly between placebo and danavorexton treatment periods under comparable remifentanil concentrations (P = 0.491 for low-dose and P = 0.140 for high-dose danavorexton). Pain tolerance increased in the placebo and danavorexton treatment periods, with an approximate increase of 13% to 21% from baseline during infusions.

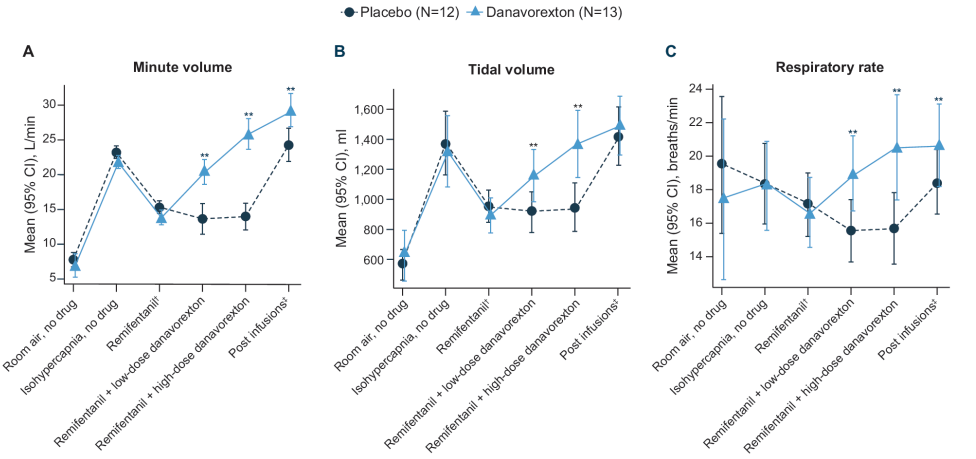

Fig. 4. Effect of danavorexton, in the context of remifentanil infusion, on minute volume, tidal volume, and respiratory rate. Statistically significant increases in (A) minute volume, (B) tidal volume, and (C) respiratory rate were observed with danavorexton versus placebo infusions across treatment periods and the improvement in minute volume was sustained even after danavorexton infusion was discontinued. Values shown are based on summary statistics and may differ from the least squares means from a model-based analysis (Supplemental Table 1). **P ≤ 0.001 from the mixed-effects model with the change from baseline as the outcome, and with baseline, treatment, time window, and treatment-by-time window as fixed effects, and with subject as the only random effect, using Maximum Likelihood (ML) for estimation (i.e., sensitivity analysis). There was no adjustment for multiplicity, and these values are nominal. †Under isohypercapnia with remifentanil infusion, pre-danavorexton/placebo infusion. ‡Under isohypercapnia after discontinuation of remifentanil and danavorexton/placebo infusions.

Discussion

Lowering the risk of respiratory complications, such as opioid-induced respiratory depression, is clinically meaningful to patients and clinicians and remains an unmet need in the postanesthesia care setting. Reducing opioid-induced respiratory depression without affecting the quality of analgesia could contribute to this treatment goal. This randomized, placebo-controlled, phase 1 trial investigated the OX2R-selective agonist danavorexton in healthy volunteers undergoing opioid-induced respiratory depression. There were no serious, severe, or danavorexton-related TEAEs and no discontinuations were caused by danavorexton. Moreover, danavorexton significantly improved respiration and reduced sedation in healthy participants undergoing remifentanil-induced respiratory depression under isohypercapnic conditions, without affecting pain tolerance, thereby preserving analgesia.

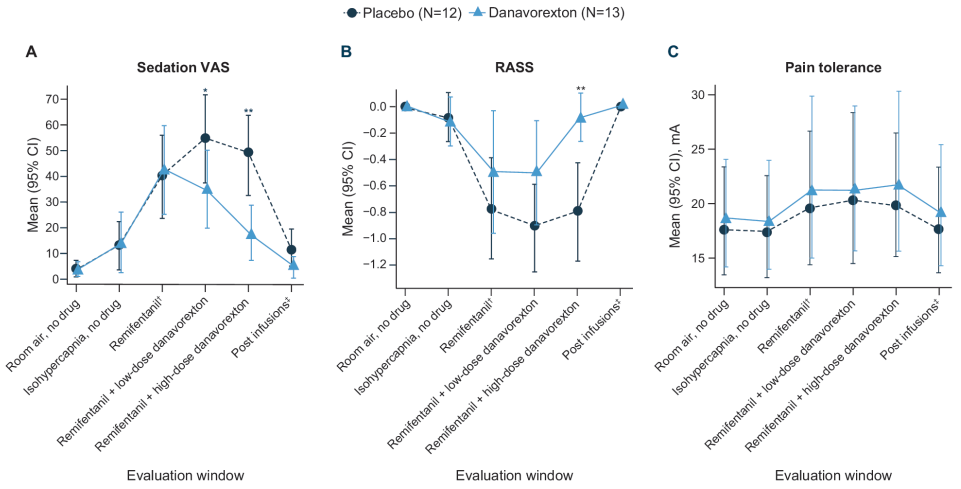

Fig. 5. Effect of danavorexton, in the context of remifentanil infusion, on sedation and pain tolerance. Significant differences in (A) sedation VAS and (B) RASS were observed with danavorexton compared with placebo. (C) There was no statistical difference in pain measurements between danavorexton doses and placebo. RASS, Richmond Agitation Sedation Scale: from +4 to –5, where a score of +4 represents a very combative, violent patient; a score of 0 represents an alert and calm patient; and a score of –5 represents an unarousable patient. VAS, visual analog scale: subjective questionnaire about degree of sedation – visual rating scale from 0 to 100 mm, where 0 = no sedation, 100 = maximum sedation. For pain tolerance, the room air no drug time window was used as the baseline. Values shown are based on summary statistics and may differ from the least squares means from a model-based analysis (Supplemental Table 1). *P < 0.01, **P ≤ 0.001 from the mixed-effects model with the change from baseline as the outcome, and with baseline, treatment, time window, and treatment-by-time window as fixed effects, and with subject as the only random effect, using Maximum Likelihood (ML) for estimation (i.e., sensitivity analysis). There was no adjustment for multiplicity, and these values are nominal. †Under isohypercapnia with remifentanil infusion, pre-danavorexton/placebo. ‡Under isohypercapnia after remifentanil and danavorexton/placebo discontinuation. RASS, Richmond Agitation Sedation Scale; VAS, visual analog scale.

Stimulation of the orexin system with OX2R agonists promoted wakefulness, enhanced respiratory function, and accelerated emergence from anesthesia in preclinical and clinical studies.[10, 11, 14, 18-22] This suggests potential for OX2R agonists to improve respiratory function in the postanesthesia setting and oppose the respiratory-depressant effects of opioids in subjects with opioid-induced respiratory depression. The latter has been successfully demonstrated in the current study. Our current results are also consistent with findings from preclinical studies with danavorexton that demonstrated its activation of neurons in the pre-Bötzinger complex, which contribute to respiratory rhythmogenesis and sustained respiratory activity. In a recent study in rats, Suzuki et al. showed that danavorexton reduced fentanyl-induced respiratory depression without compromising fentanyl analgesia.[14] These same authors further showed that, apart from its respiratory effects, danavorexton shortened emergence from isoflurane, propofol, and fentanyl-induced anesthesia in rats and monkeys.[14]

	Placebo (N = 12)	Danavorexton (N = 13)
VAS, mean (95% CI)		
Room air, no drug	4.7 (1.9, 7.6)	3.4 (0.1, 6.6)
Isohypercapnia, no drug	12.4 (2.6, 22.3)	13.8 (1.8, 25.8)
Remifentanil†	39.5 (23.1, 55.9)	42.1 (24.8, 59.5)
Remifentanil + low-dose danavorexton	54.6 (37.3, 71.9)	34.7 (19.4, 49.9)
Remifentanil + high-dose danavorexton	48.0 (32.2, 63.8)	17.5 (6.8, 28.3)
Post-infusions‡	11.5 (3.8, 19.2)	4.15 (0.0, 8.3)
RASS, mean (95% CI)		
Room air, no drug	0.0 (N/A)	0.0 (N/A)
Isohypercapnia, no drug	–0.08 (–0.3, 0.1)	–0.12 (–0.3, 0.1)
Remifentanil†	–0.8 (–1.2, –0.4)	–0.5 (–1.0, 0.0)
Remifentanil + low-dose danavorexton	–0.9 (–1.2, –0.6)	–0.5 (–0.9, –0.1)
Remifentanil + high-dose danavorexton	–0.8 (–1.2, –0.4)	–0.1 (–0.3, 0.1)
Post-infusions‡	0.0 (NA)	0.0 (NA)

Table 4. Summary of VAS and RASS Assessments
Mean (95% CI) for VAS and RASS assessments across all time windows for placebo and danavorexton treatment periods. Note, baseline for RASS was taken after remifentanil administration under isohypercapnic conditions. †Under isohypercapnia with remifentanil infusion, pre-danavorexton/placebo. ‡Under isohypercapnia after remifentanil and danavorexton/placebo discontinuation. CI, confidence interval; RASS, Richmond Agitation Sedation Scale; VAS, visual analog scale.

Together these findings provide new insights into the role of the orexin system in the control of breathing, and shows that activation of orexin receptors effectively reverses opioid-induced respiratory depression and may also accelerate emergence from anesthetics. These mechanisms of emergence should be described as an arousal network that progresses from a state of unconsciousness to a state of wakefulness and restored consciousness as well as respiratory arousal.

Opioids negatively affect breathing through activation of mu-opioid receptors in the pre-Bötzinger complex, located in the medulla, and the Kölliker-Fuse nucleus and the parabrachial nucleus, the so-called parabrachial complex, in the pons. Whilst naloxone, an opioid receptor antagonist, can reverse the effects of opioid-induced respiratory depression, its effects are non-selective, reverse analgesic effects, and may provoke withdrawal symptoms, particularly in individuals that use large amounts of opioids for treatment of chronic pain or individuals with an opioid use disorder. Such patients are becoming an increasing part of the surgical population that require postoperative pain relief. Since danavorexton has no known effects on mu-opioid receptors within the pons or brainstem, but agnostically reverses opioid-related deleterious respiratory effects, no negative adverse effects from danavorexton treatment are expected with respect to pain relief or provoking withdrawal symptoms. Accordingly, danavorexton reduced opioid-induced respiratory depression without reducing analgesic responses in our study.

The safety and tolerability of a single administration of danavorexton in remifentanil-infused participants was consistent with that of other danavorexton studies with single administration.[20-22] Overall, there were no deaths, serious or severe treatment-emergent adverse events, and few markedly abnormal vital signs associated with danavorexton infusion. Dose-dependent mean increases in blood pressure were observed during the infusion period, which, consistent with previous studies,[20-22] returned to baseline after completion of danavorexton infusion. Individual BP elevations, while regarded as markedly abnormal in this study, were not clinically significant since none fulfilled the standardized criteria for hypertension.[23] Although danavorexton in healthy volunteers did not lead to clinically significant increases in blood pressure, danavorexton may have to be used cautiously and with close monitoring in individuals with cardiovascular comorbidities undergoing major surgery. The degree of blood pressure increase and clinical significance of such elevations in a perioperative population needs further investigation.

There are a few limitations to this study. One key limitation is that this study was performed under experimental isohypercapnic conditions, so the observed effects of danavorexton in the clinical setting may differ from the effects observed in this previously validated model[15]. The reason for choosing the isohypercapnic model was its superior sensitivity in detecting opioid effects on the ventilatory control system.[16] Moreover, findings from this study are based upon 13 healthy male volunteers. Whilst some results are statistically significant, they are not generalizable and should be evaluated in much larger trials.

This study investigated respiratory depression induced by remifentanil and the generalizability of the results in this study to respiratory depression induced by other opioids, such as fentanyl, and other drug classes is not fully known. Remifentanil is a very short-acting opioid, and the dose was relatively low, so the duration of effect of danavorexton when administered with longer-acting opioids and higher doses remains uncertain. Moreover, the last post-dose assessment was too early to quantify the longer duration of effect with danavorexton infusion. The longer duration is likely attributable to rapid disappearance of the opioid-induced respiratory depression effect as remifentanil clears from the body coupled with lingering danavorexton exposure following cessation of infusion. The small sample size of this phase 1 study was appropriate to fulfill the study objectives, and follow-up with additional studies in a larger population is now warranted to explore the effect of danavorexton on postanesthesia recovery including respiratory recovery and emergence. Further, the study population was comprised of healthy male volunteers, which may differ from more real-world populations experiencing respiratory depression in the postanesthesia care unit or in the ward following surgery. Further investigation will determine the appropriate therapeutic dosing levels of danavorexton in the postanesthesia setting.

In conclusion, findings from this study suggest that danavorexton, a novel and highly selective OX2R agonist administered intravenously, has potential to decrease opioid-induced respiratory depression and reverse sedation in the remifentanil-induced postanesthesia setting without reversing analgesia.

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