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Clinical Investigation

RESPIRATION AND THE AIRWAY

Effect of midazolam co-administered with oxycodone on ventilation: a randomised clinical trial in healthy volunteers

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Abstract

Background: Benzodiazepines can exacerbate opioid-induced respiratory depression by furthering the decrease in central respiratory drive and causing loss of upper airway patency potentially leading to airway obstruction. This study aimed to determine if co-administration of benzodiazepines and opioids significantly decreases hypercapnic ventilation compared with opioids alone.

Methods: We conducted a randomised, double-blind, four-period crossover trial in 20 healthy participants to assess whether i.v. midazolam (0.0375 mg kg^{-1} in the first five participants; 0.075 mg kg^{-1} in 15 participants) plus oral oxycodone (10 mg), compared with oxycodone alone, decreases minute ventilation at an end-tidal carbon dioxide (P_{CO_2}) of 7.3 kPa using modified Read rebreathing methodology.

Results: Midazolam administered with oxycodone, compared with oxycodone alone, did not significantly decrease minute ventilation at an end-tidal P_{CO_2} of 7.3 kPa (23.5 *vs* 25.2 L min^{-1}; mean difference −1.7 L min^{-1}, one-sided 95% confidence interval −∞ to 1.6; P=0.21). However, midazolam plus oxycodone increased resting end-tidal P_{CO_2} compared with oxycodone alone (5.8 *vs* 5.6 kPa; mean difference 0.2 kPa, 95% confidence interval 0.0–0.4). Nine of 15 (60%) participants fell asleep or snored on midazolam plus oxycodone, compared with 0 of 15 (0%) on oxycodone alone.

Conclusions: Midazolam co-administered with oxycodone did not decrease hypercapnic ventilation, compared with oxycodone alone, but did affect tidal volume, ventilatory frequency, and resting end-tidal P_{CO_2}. These findings support the hypothesis that benzodiazepines influence ventilation by inducing relaxation of the respiratory muscles and highlight the need for additional investigations to elucidate the potential for upper airway obstruction when benzodiazepines and opioids are co-administered.

Clinical trial registration: NCT 04310579.

Keywords: breathing; benzodiazepines; opioids; pharmacodynamics; pharmacokinetics; respiratory depression

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Editor's key points

- Benzodiazepines can worsen opioid-induced respiratory depression by effects on central respiratory drive and upper airway patency.
- Healthy volunteers were administered oxycodone with or without midazolam to determine if co-administration of benzodiazepines and opioids decreases hypercapnic ventilation compared with opioids alone.
- Midazolam co-administered with oxycodone did not further decrease hypercapnic ventilation compared with oxycodone alone, but did decrease tidal volume, increase ventilatory frequency, and increase resting end-tidal P_{CO_2}.
- Future studies should investigate the potential for upper airway obstruction when benzodiazepines and oxycodone are co-administered, especially in at-risk populations.

There is increased risk of mortality secondary to overdose-related respiratory depression with concurrent use of opioids and benzodiazepines, with deaths among patients concomitantly using benzodiazepines and opioids 10-fold higher than those treated with opioids alone.[1–3] This information prompted the US Food and Drug Administration to make safety labelling changes for benzodiazepines and opioids to include boxed warnings about increased potential for respiratory depression with their co-use in August 2016.[4–6]

Under normal conditions, when chemoreceptors sense increased carbon dioxide (CO_2) levels in the body, ventilation increases.[7] Benzodiazepines might increase the risk of opioid-induced respiratory depression by decreasing this chemoreceptor responsiveness to hypercapnia, thereby decreasing central respiratory drive.[8,9] An alternate hypothesis is that benzodiazepines negatively affect upper airway patency by decreasing diaphragmatic contraction and respiratory muscle strength, which cause airway obstruction and increase risk of respiratory depression.[10,11] To investigate the mechanism by which benzodiazepines and opioids on their own and co-administered affect ventilation, this clinical trial evaluated whether co-administration of oxycodone and midazolam resulted in differences in hypercapnic ventilatory response compared with oxycodone alone in healthy participants.

Methods

We conducted a randomised, double-blind, four-period crossover trial in healthy participants at a clinical pharmacology unit (Spaulding Clinical Research, West Bend, WI, USA) to assess whether relatively low doses of an opioid (oxycodone) and benzodiazepine (midazolam) decrease the ventilatory response to hypercapnia compared with oxycodone alone. This trial was approved by the local institutional review board (Advarra [https://www.advarra.com]) on March 6, 2020, and registered on ClinicalTrials.gov (NCT 04310579) on March 17, 2020. All participants provided written informed consent.

Key inclusion criteria were age 18–50 yr, nonsmoking, and negative tests for alcohol or drugs of abuse. Key exclusion criteria were a history of sleep disorder, panic disorder, panic attacks, generalised anxiety disorder, hypoventilation syndrome or obstructive sleep apnoea, opioid or psychotropic drug use within 60 days of beginning the trial, and inability to tolerate the ventilatory assessment procedure during screening. Participants were randomised to one of four treatment sequences using a random number generator in R statistical software (The R Project for Statistical Computing, Vienna, Austria [https://www.R-project.org]) (Fig. 1).

Study procedures and interventions

On day 1 of each period, study participants received one of the following treatments: oxycodone, midazolam, oxycodone and midazolam, or placebo. Based on prior studies, a 10 mg oral dose of immediate-release oxycodone was administered at 0 h to achieve a measurable effect while keeping safety considerations, especially in conjunction with benzodiazepines.[12,13] To align the time of maximum concentration, midazolam was infused i.v. over 2 min starting at 1.92 h (115 min) at 0.0375 mg kg^{-1} for the first five participants and increased to 0.075 mg kg^{-1} for the remaining 15 participants. Because midazolam administration was timed to ensure that rebreathing procedure was during the time of maximum concentration for both oxycodone and midazolam, resting measures at 2 h were collected before midazolam administration, and rebreathing measures were collected after midazolam administration (Fig. 1c). All participants received ondansetron 4 mg orally 30 min before oxycodone or placebo administration. A modification was made after the higher midazolam dose caused substantial sedation (based on physician assessment) and O_2 saturation to decrease below 90% for the first two participants given midazolam 0.075 mg kg^{-1}. Subsequently, a nasal cannula was preemptively given to the participants across all treatments after rebreathing at the 2-h and 3-h time points and at other times at the clinician discretion.

Ventilatory assessments

Ventilatory measures, including minute ventilation, end-tidal partial pressure of carbon dioxide (P_{CO_2}), ventilatory frequency, tidal volume, and oxygen saturation, were assessed at 0, 1, 2, 3, 4, 6, and 24 h. During each assessment, the modified Read rebreathing technique was used to assess ventilatory response to gradually increasing CO_2 levels (described in detail in Supplementary Figs S1 and S2). Participants sat in a semi-supine position fitted with a face mask attached to a pneumotachometer (Hans Rudolph, Shawnee, KS, USA) and went through the ventilatory procedure, which featured breathing room air, breathing 100% oxygen, hyperventilation, and, finally, rebreathing.[14,15] The procedure continued until end-tidal P_{CO_2} reached 8%, minute ventilation reached 60 L min^{-1}, the participant signalled to terminate the test, the rebreathing bag deflated, or rebreathing lasted >15 min. Data from all stages were reviewed by two independent assessors blinded to the study arm and time of assessments to evaluate the completeness of data for study outcomes (the excluded assessments are in Supplementary Table S1). The primary outcome was minute ventilation at an end-tidal P_{CO_2} of 7.3 kPa for midazolam co-administered with oxycodone *vs* oxycodone alone at the 2-h time point for all subjects treated with the higher-dose midazolam. Similar comparisons between midazolam or oxycodone alone and placebo were secondary outcomes.

Pharmacokinetic assessments

Plasma concentrations of midazolam, oxycodone, and its metabolite oxymorphone were measured by validated liquid chromatography-tandem mass spectrometry methods (LC-MS/MS) at 0, 1, 2, 3, 4, 6, 8, 12, and 24 h after dosing (Supplementary Tables S2 and S3). Maximum plasma concentration (C_{max}) and area under the curve (AUC) for oxycodone were secondary outcomes.

Data analysis

This study was powered with consideration of the effect of oxycodone plus midazolam *vs* oxycodone alone. A sample size of 20 participants was determined to have 90% power at a one-sided significance level to detect a 4 L min^{-1} decrease in the primary endpoint assuming a standard deviation of 5 L min^{-1}, based on prior studies.[12,13]

Minute ventilation at an end-tidal P_{CO_2} of 7.3 kPa was calculated for each rebreathing procedure by fitting individual minute ventilation and end-tidal P_{CO_2} data to linear regression and interpolating the model-predicted value (Supplementary Fig. S1). The *x*-axis intercept and slope of this linear regression were also analysed.[14,15]

All data from participants receiving placebo, oxycodone, and midazolam 0.075 mg kg^{-1} who finished more than one study period and completed rebreathing assessments at the 2-h time point were included in the primary analysis without imputation of missing data. Study arms were compared using a linear mixed-effects model with participant as a random effect and fixed effects for treatment order, period, and baseline minute ventilation at an end-tidal P_{CO_2} of 7.3 kPa. Tidal volume at an end-tidal P_{CO_2} of 7.3 kPa, ventilatory frequency at an end-tidal P_{CO_2} of 7.3 kPa, *x*-axis intercept, and slope were compared using a linear mixed-effects model with participant as a random effect at 2 h, whereas sedation and resting respiratory measures (minute ventilation, ventilatory frequency, end-tidal P_{CO_2}, and oxygen saturation) were compared at 3 h. For pharmacokinetic analyses, all concentrations below the lower limit of quantification were considered zero. C_{max} and AUC_{∞} were calculated using R noncompartmental analysis. Patient characteristics are reported with standard descriptive statistics.

A prespecified interim analysis was performed after the first five participants to determine that the midazolam dose needed to be increased to 0.075 mg kg^{-1} for the remaining 15 participants and the oxycodone dose should be kept at 10 mg. To account for this, a multiplicity adjustment was made based on alpha spending allocation following the O'Brien–Fleming approach for two planned analyses (i.e. 0.05 for k=1 and 0.0492 for k=2). Based on this, a one-sided *P*-value of <0.049 was considered significant for the primary outcome. For all other measures, the 95% confidence intervals (CIs) have not been corrected for multiplicity and should not be used to infer statistical significance. Statistical analyses were performed in R (version 4.2.2; The R Project for Statistical Computing).

Results

Study participants

Fifty-four participants were screened, and 20 participants were enrolled and randomised, with all 20 participants completing the trial (Fig. 1). Participant and baseline characteristics are summarised in Table 1.

Minute ventilation

Table 2 summarises mean minute ventilation at an end-tidal P_{CO_2} of 7.3 kPa for all treatment conditions at 2 h, with full-time courses of minute ventilation at 7.3 kPa end-tidal P_{CO_2} and drug plasma concentrations presented in Figure 2 and individual-level data in Supplementary Figure S3. Compared with placebo, oxycodone 10 mg alone significantly decreased minute ventilation at 7.3 kPa end-tidal P_{CO_2} (difference −7.0 L min^{-1}, one-sided 95% CI −∞ to −4.0), whereas midazolam 0.075 mg kg^{-1} did not decrease minute ventilation at 7.3 kPa end-tidal P_{CO_2} (difference −1.4 L min^{-1}, one-sided 95% CI −∞ to 1.8). Compared with oxycodone alone, midazolam 0.075 mg kg^{-1} co-administered with oxycodone did not significantly decrease minute ventilation at 7.3 kPa end-tidal P_{CO_2} (difference −1.7 L min^{-1}, one-sided 95% CI −∞ to 1.6).

Other ventilatory measures

Figure 3 depicts the population-level hypercapnic ventilatory response curves for each treatment group at 2 h and a sample individual-patient hypercapnic ventilatory response curve. The slope of the hypercapnic ventilatory response curve was increased for midazolam compared with placebo (difference 4.7, 95% CI 2.0–7.4) (Table 2). The *x*-axis intercept for participants treated with midazolam (mean 5.9 kPa, 95% CI 5.5–6.4) was significantly higher than that for those treated with placebo (mean 4.8 kPa, 95% CI 4.4–5.2; difference 1.1 kPa, 95% CI 0.3–1.9). The co-administration of oxycodone and midazolam (mean 6.1 kPa, 95% CI 5.6–6.5) had a slightly higher *x*-axis intercept than oxycodone alone (mean 5.2 kPa, 95% CI 4.8–5.7; difference 0.8 kPa, 95% CI −0.1 to 1.7).

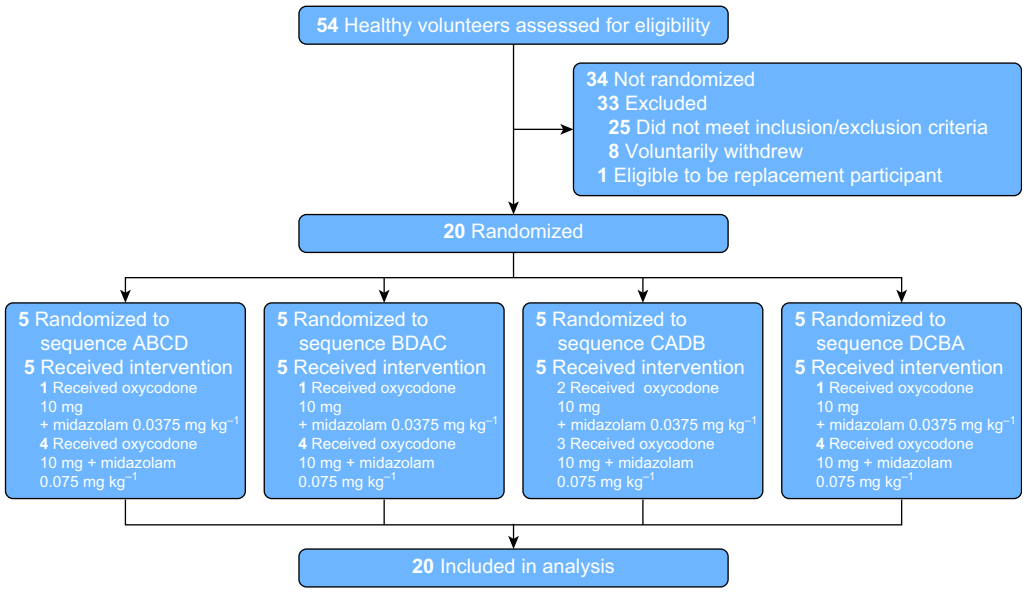
Table 2 summarises the mean tidal volume and ventilatory frequency at an end-tidal P_{CO_2} of 7.3 kPa for all treatment conditions at 2 h, with individual changes from placebo for each treatment presented in Supplementary Figure S4. Midazolam increased ventilatory frequency (difference 6.7 bpm, 95% CI 4.7–8.7) and decreased tidal volume (difference −886 ml, 95% CI −1191 to −580) compared with placebo, and midazolam co-administered with oxycodone increased ventilatory frequency (difference 3.9 bpm, 95% CI 1.9–5.9) and decreased tidal volume (difference −811 ml, 95% CI −1116 to −505) compared with oxycodone alone.

Resting respiratory measures including ventilatory frequency, end-tidal P_{CO_2}, oxygen saturation, and minute ventilation are summarised in Supplementary Figure S5 and Table S4. Midazolam co-administered with oxycodone increased resting end-tidal P_{CO_2} compared with oxycodone alone (difference 0.2 kPa, 95% CI 0.0–0.4), but midazolam alone did not reduce end-tidal P_{CO_2} compared with placebo (difference 0.1 kPa, 95% CI −0.1 to 0.3) 1 h after midazolam treatment.

Sedation

Participant-reported sedation (Fig. 4), as measured by a 0–100 mm visual analogue scale, was higher in participants treated with midazolam compared with placebo (difference 13.5, 95% CI 4.9–21.9) and oxycodone compared with oxycodone alone (difference 25.7, 95% CI 17.2–34.2) at the 3-h time point. Oxycodone alone increased sedation compared with placebo at 2 h (difference 11.3, 95% CI 3.4–19.1) and at 3 h (difference 7.9, 95% CI 0.1–15.7). Immediately after midazolam administration, six out of 15 (40%) participants given higher-dose midazolam and nine out of 15 (60%) participants given both midazolam and

a **Flow of participants in study**



b **Study 4- period crossover design and study drug interventions by treatment group**

Day 1	Days 2–3	Day 4	Days 5–6	Day 7	Days 8–9	Days 10
Period 1	Washout	Period 2	Washout	Period 3	Washout	Period 4

Treatment group	Study drugs[f]
A	Oxycodone + placebo i.v.
B	Oral placebo + midazolam i.v.
C	Oxycodone + midazolam i.v.
D	Oral placebo + placebo i.v.

c **Time course of data collection**

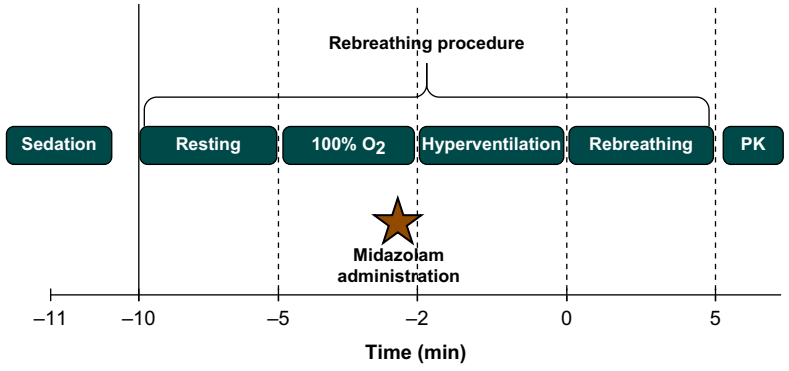


Fig 1. Flow of participants in the study, interventions, and overall study design. (a) Participant consort diagram for the study. (b) Study design and drug interventions for each treatment group. (c) Ordering of assessments at scheduled sampling time points relative to the beginning of the rebreathing procedure. Sedation was collected before the beginning of the data collection for respiratory measures. Resting respiratory measures were collected while breathing room air for 5 min, followed by 3 min of breathing 100% oxygen (O_2). For the 2-h time point, midazolam i.v. was administered during the last 2 min of the 100% O_2 administration. After breathing 100% O_2, participants were asked to take deep breaths for 2 min, and then the rebreathing stage began. After the stopping criteria for rebreathing were met, pharmacokinetic (PK) data were collected.

Table 1 Trial participant and baseline characteristics.*Self-identified race and ethnicity were collected in an open-ended format by clinical staff.

Characteristic	Value (N=20)
Age (yr), median (range)	36 (22–47)
Female sex, n (%)	7 (35)
Race, n (%)*	
Black or African American	14 (70)
White	6 (30)
Hispanic or Latino ethnicity, n (%)	2 (10)
Body weight (kg), median (range)	80 (43–92)
Height (m), median (range)	1.76 (1.46–1.92)
Body mass index (kg m^{-2}), median (range)	27.4 (20.5–29.6)
Resting respiratory measurements	
Minute ventilation (L min^{-1}), median (range)	8.0 (5.3–18.0)
Ventilatory frequency (bpm), median (range)	15.3 (8.2–21.3)
End-tidal P_{CO_2} (kPa), median (range)	5.3 (3.8–5.9)
Oxygen saturation (%), median (range)	96.4 (93.9–98.9)

oxycodone were reported by the clinician as falling asleep or snoring. In contrast, 0 out of 20 participants dosed with oxycodone or placebo were falling asleep or snoring.

Pharmacokinetics

Figure 2 depicts plasma concentrations of oxycodone and midazolam (additional data in Supplementary Fig. S6). The oxycodone C_{max} for participants treated with oxycodone was 21.8 ng ml^{-1} (36.6 CV%), and AUC_{∞} was 132.2 ng ml^{-1} h^{-1} (37.0 CV%). The midazolam C_{max} for participants treated with midazolam was 125.6 ng ml^{-1} (62.5 CV%), and the AUC_{∞} was 316.0 ng ml^{-1} $h-^{1}$ (49.1 CV%). There was no significant change in the pharmacokinetics of either drug (or metabolites) from the co-administration of midazolam and oxycodone (details in Supplementary Table S5).

Safety

No serious adverse events occurred. Fifteen participants (75%) experienced one or more adverse events; the most common adverse events were puncture site pain (40%), headache (35%), and nausea (30%). Supplementary Table S6 presents the incidence and number of adverse events by study arm.

Discussion

In this randomised, double-blind, four-period crossover clinical trial involving healthy participants, oxycodone 10 mg significantly decreased hypercapnic ventilation 2 h after administration compared with placebo, midazolam 0.075 mg kg^{-1} did not decrease hypercapnic ventilation compared with placebo, and co-administration of oxycodone and midazolam did not significantly decrease minute ventilation at an end-tidal carbon dioxide of 7.3 kPa compared with oxycodone alone.

The concurrent use of opioids and benzodiazepines is associated with a significantly increased risk of mortality attributed to overdose-related respiratory depression.[1–3] Co-administration of midazolam and oxycodone might have detrimental effects on respiration. This trial shows that oxycodone decreases chemoreceptor responsiveness to hypercapnia, thereby decreasing central respiratory drive, consistent with the hypothesised mechanism of opioid-induced respiratory depression.[12,13,16,17] Conversely, midazolam alone did not decrease hypercapnic ventilation, suggesting that its deleterious effects on respiration occur via a different mechanism.[10,11,18] Exploratory analyses found that midazolam caused a decrease in tidal volume, consistent with reported effects of benzodiazepines in the literature and the hypothesis that benzodiazepines impact ventilation through relaxation of respiratory muscles (summarised in Supplementary Table S7).[19–21] One explanation for these observations is decreased diaphragmatic contraction and decreased inspiratory and expiratory respiratory muscle strength, which could lead to increased airway resistance and possibly obstruction, a known clinical effect of benzodiazepines. However, minute ventilation at an end-tidal P_{CO_2} of 7.3 kPa remained unchanged despite this decreased tidal volume owing to a compensatory increase in ventilatory frequency, as seen in other studies.[21–24] We relate the effect on ventilatory frequency to a $GABA_A$-mediated mechanism.[25] When both drugs were co-administered, no additional effect on minute ventilation at an end-tidal carbon dioxide of 7.3 kPa was seen compared with oxycodone alone.

Exploratory analysis showed that participants given both midazolam and oxycodone had higher resting end-tidal P_{CO_2} compared with oxycodone alone, but those treated with midazolam did not have increased resting end-tidal P_{CO_2} compared with placebo. This might indicate a pharmacodynamic interaction whereby co-administration causes greater airway narrowing or even airway obstruction than with either drug alone. These findings are consistent with those of Vodovar and colleagues,[19] in which buprenorphine or diazepam on their own did not increase arterial P_{CO_2} in rats, but co-administration led to an increase in arterial P_{CO_2} compared with diazepam alone. In humans, Mora and colleagues[20] observed that compared with pretreatment values, co-administration of a benzodiazepine and opioid increased end-tidal P_{CO_2} but did not decrease the slope of the CO_2 response curve or minute ventilation after treatment with fentanyl 50 μg i.v. and midazolam 2 mg i.v. followed by a variable-rate midazolam infusion of 0.3–0.5 mg min^{-1}. Other studies observed different outcomes with respect to the effects of co-administration of benzodiazepines and opioids on ventilation.[19,26–31] These discrepancies likely stem from differences in the drugs studied, doses, routes of administration, methodologies to quantify ventilation, and timing of assessments across studies.

Co-administration of midazolam and oxycodone increased the *x*-axis intercept, suggesting an increased apnoeic threshold, resulting in higher carbon dioxide levels before ventilation increased to counteract hypercapnia, which could lead to increased risk of respiratory depression in patients with conditions such as obstructive sleep apnoea or chronic obstructive pulmonary disease. In our trial, of those participants who fell asleep, 67% of those treated with midazolam and 78% of those treated with midazolam and oxycodone concomitantly were observed to snore during the rebreathing stage, which might indicate an increase in upper airway resistance and possibly even airway occlusion.[32] This is further supported by epidemiologic studies showing that treatment with benzodiazepines is associated with a higher

Table 2 Hypercapnic ventilatory response outcomes. *n corresponds to the number of subjects included in each analysis. †A one-sided $P<0.049$ was considered significant for ventilation at P_{CO_2} 7.3 kPa because the trial aim was to evaluate if the study drugs decreased ventilation. The 94.9% CI for oxycodone alone compared with placebo difference is −∞ to −4.0; midazolam alone compared with placebo difference is −∞ to 1.9; and midazolam co-administered with oxycodone compared with oxycodone alone difference is −∞ to 1.7. CI, confidence interval.

Mean (95% CI)		n*	Mean difference (one-sided 95% CI)	P-value†
Minute ventilation at 7.3 kPa end-tidal P_{CO_2} (L min^{-1})				
Oxycodone + midazolam	Oxycodone			
23.5 (19.4–27.6)	25.2 (21.5–28.9)	15	−1.7 (−∞ to 1.6)†	0.21
Oxycodone	Placebo			
25.2 (21.5–28.9)	32.2 (28.6–35.9)	20	−7.0 (−∞ to −4.0)†	<0.001
Midazolam	Placebo			
30.8 (26.8–34.8)	32.2 (28.6–35.9)	15	−1.4 (−∞ to 1.8)†	0.24
Oxycodone + midazolam	Placebo			
23.5 (19.4–27.6)	32.2 (28.6–35.9)	15	−8.7 (−∞ to −4.6)†	<0.001
Oxycodone + midazolam	Midazolam			
23.5 (19.4–27.6)	30.8 (26.8–34.8)	15	−7.3 (−∞ to −3.8)†	<0.001
Mean (95% CI)		n	Mean difference (95% CI)	
Hypercapnic ventilatory response slope (L min^{-1} kPa^{-1})				
Oxycodone + midazolam	Oxycodone			
12.1 (9. 0 to 15.2)	9.6 (6.7–12.4)	15	2.6 (0.2–5.3)	
Oxycodone	Placebo			
9.6 (6.7–12.4)	10.3 (7.5–13.2)	20	−0.8 (−3.3 to 1.7)	
Midazolam	Placebo			
15. 0 (12. 0 to 18. 1)	10.3 (7.5–13.2)	15	4.7 (2.0–7.4)	
Oxycodone + midazolam	Placebo			
12.1 (9. 0 to 15.2)	10.3 (7.5–13.2)	15	1.8 (−1.0 to 4.5)	
Oxycodone + midazolam	Midazolam			
12.1 (9. 0 to 15.2)	15. 0 (12. 0 to 18. 1)	15	−2. 9 (−5. 8 to 0.0)	
X-axis intercept (kPa)				
Oxycodone + midazolam	Oxycodone			
6.1 (5.6–6.5)	5.2 (4.8–5.7)	15	0.8 (−0.1 to 1.7)	
Oxycodone	Placebo			
5.2 (4.8–5.7)	4.8 (4.4–5.2)	20	0.4 (−0.3 to 1.2)	
Midazolam	Placebo			
5.9 (5.5–6.4)	4.8 (4.4–5.2)	15	1.1 (0.3–1.9)	
Oxycodone + midazolam	Placebo			
6.1 (5.6–6.5)	4.8 (4.4–5.2)	15	1.3 (0.8–1.8)	
Oxycodone + midazolam	Midazolam			
6.1 (5.6–6.5)	5.9 (5.5–6.4)	15	0.2 (−0.4 to 0.7)	
Ventilatory frequency at 7.3 kPa end-tidal P_{CO_2} (bpm)				
Oxycodone + midazolam	Oxycodone			
16.7 (14.8–18.7)	12.8 (11.0–14.6)	15	3.9 (1.9–5.9)	
Oxycodone	Placebo			
12.8 (11.0–14.6)	14.0 (12.2–15.8)	20	−1.2 (−3.0 to 0.7)	
Midazolam	Placebo			
20.7 (18.7–22.7)	14.0 (12.2–15.8)	15	6.7 (4.7–8.7)	
Oxycodone + midazolam	Placebo			
16.7 (14.8–18.7)	14.0 (12.2–15.8)	15	2.7 (0.7–4.7)	
Oxycodone + midazolam	Midazolam			
16.7 (14.8–18.7)	20.7 (18.7–22.7)	15	−4.0 (−6.1 to −1.9)	
Tidal volume at 7.3 kPa end-tidal P_{CO_2} (ml)				
Oxycodone + midazolam	Oxycodone			
1030 (718–1342)	1841 (1560–2122)	15	−811 (−1116 to −505)	
Oxycodone	Placebo			
1841 (1560–2122)	2100 (1819–2381)	20	−260 (−536 to 17)	
Midazolam	Placebo			
1214 (903–1526)	2100 (1819–2381)	15	−886 (−1191 to −580)	
Oxycodone + midazolam	Placebo			
1030 (718–1342)	2100 (1819–2381)	15	−1070 (−1376 to −746)	
Oxycodone + midazolam	Midazolam			
1030 (718–1342)	1214 (903–1526)	15	−184 (−504 to 136)	

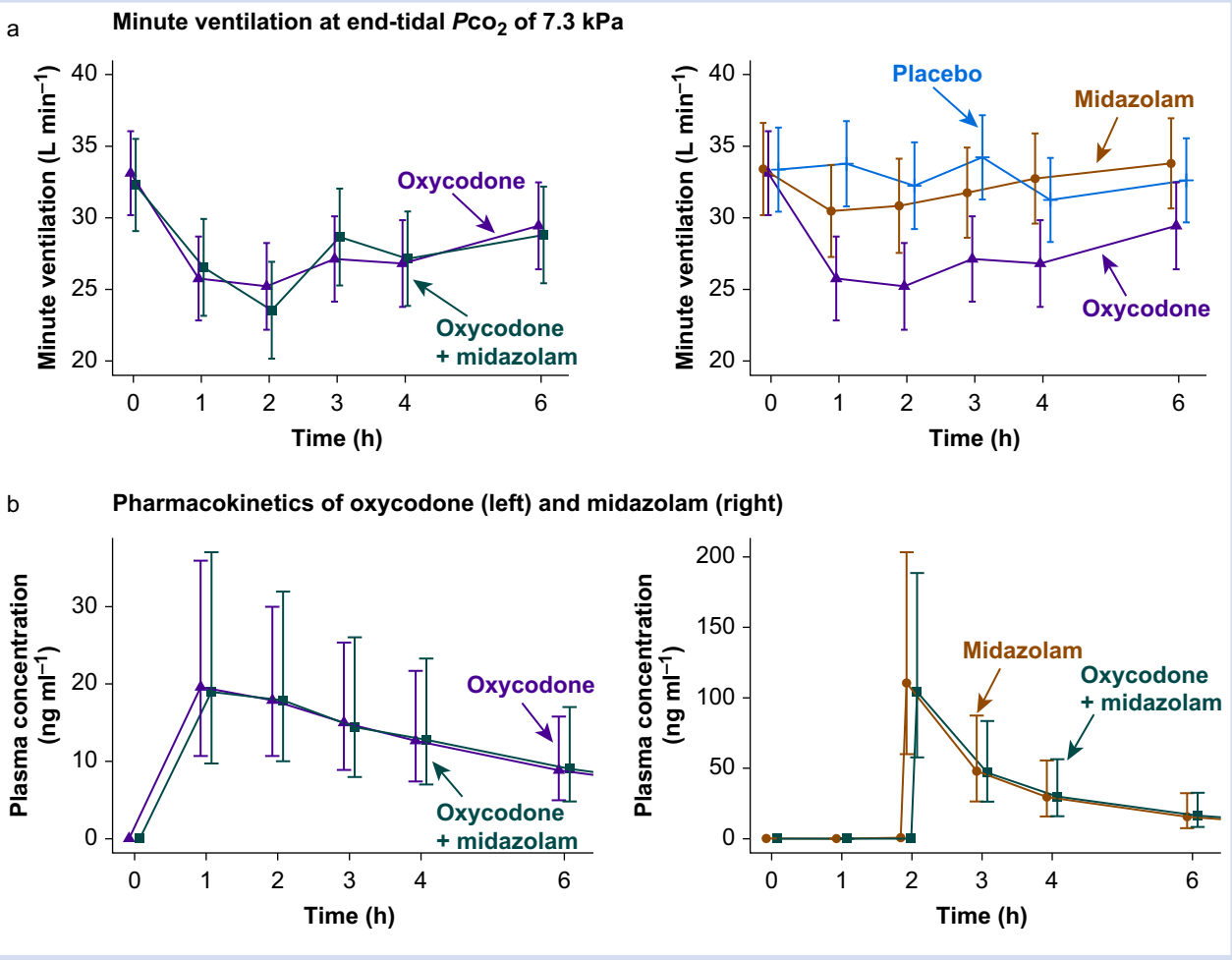


Fig 2. Primary and secondary outcomes. (a) Model-predicted minute ventilation at an end-tidal P_{CO_2} of 7.3 kPa during 6 h after oxycodone treatment for the primary endpoint (left) and secondary outcomes (right). The points indicate model-estimated means, and error bars indicate two-sided 95% confidence intervals. (b) Geometric mean plasma concentration of oxycodone (left) and midazolam (right) from treatment with oxycodone alone and the combination of oxycodone and midazolam. Error bars indicate two-sided 95% confidence intervals. A total of 20 participants per arm were included for the oxycodone and placebo groups, and 15 participants per arm were included in the analysis for the midazolam and oxycodone + midazolam groups.

risk of obstructive sleep apnoea and an increased prevalence of acute respiratory failure in those with obstructive sleep apnoea.[10,33]

This trial is a part of the US FDA's proactive work to address the opioid crisis and help reduce opioid overdoses and deaths and, more specifically, to better understand the mechanism for increased risk of respiratory depression with co-use of benzodiazepines and opioids. In addition, this trial evaluated an established procedure for studying the effects of other drugs on exacerbating opioid-induced respiratory depression. This methodology could be prospectively used for evaluating the effects of investigational drugs alone or in co-administration with other drugs on ventilation.

A limitation of this trial was the time of data collection relative to treatment with midazolam. At 1 h after midazolam administration (3 h), summarised in Supplementary Table S4, resting oxygen saturation, resting minute ventilation, and ventilatory frequency were not different between co-administration of oxycodone and midazolam or oxycodone alone. At this time point, the pharmacodynamic effects of oxycodone were also not different compared with placebo. Collecting these measures closer to the time of administration of oxycodone and midazolam could have allowed for the detection of differences in other ventilatory measures where opioid-induced effects were exacerbated by benzodiazepines in prior studies. Another limitation was that the benzodiazepine dose did not maximise the effect and the route of administration did not lead to consistent exposures, which prevented sustained effects on ventilation. In case of sedation or sleep, staff provided stimulation and coaching to encourage participants to breathe. This could have interfered with the natural behavioural control of ventilation and hindered the ability to detect an effect of midazolam on ventilation. Because consciousness significantly influences both respiratory drive and upper airway muscle strength, by rousing subjects a key effect of the co-administration of benzodiazepines and opioids might have been missed.[34,35] Finally, this trial was a relatively small, healthy participant cohort. With

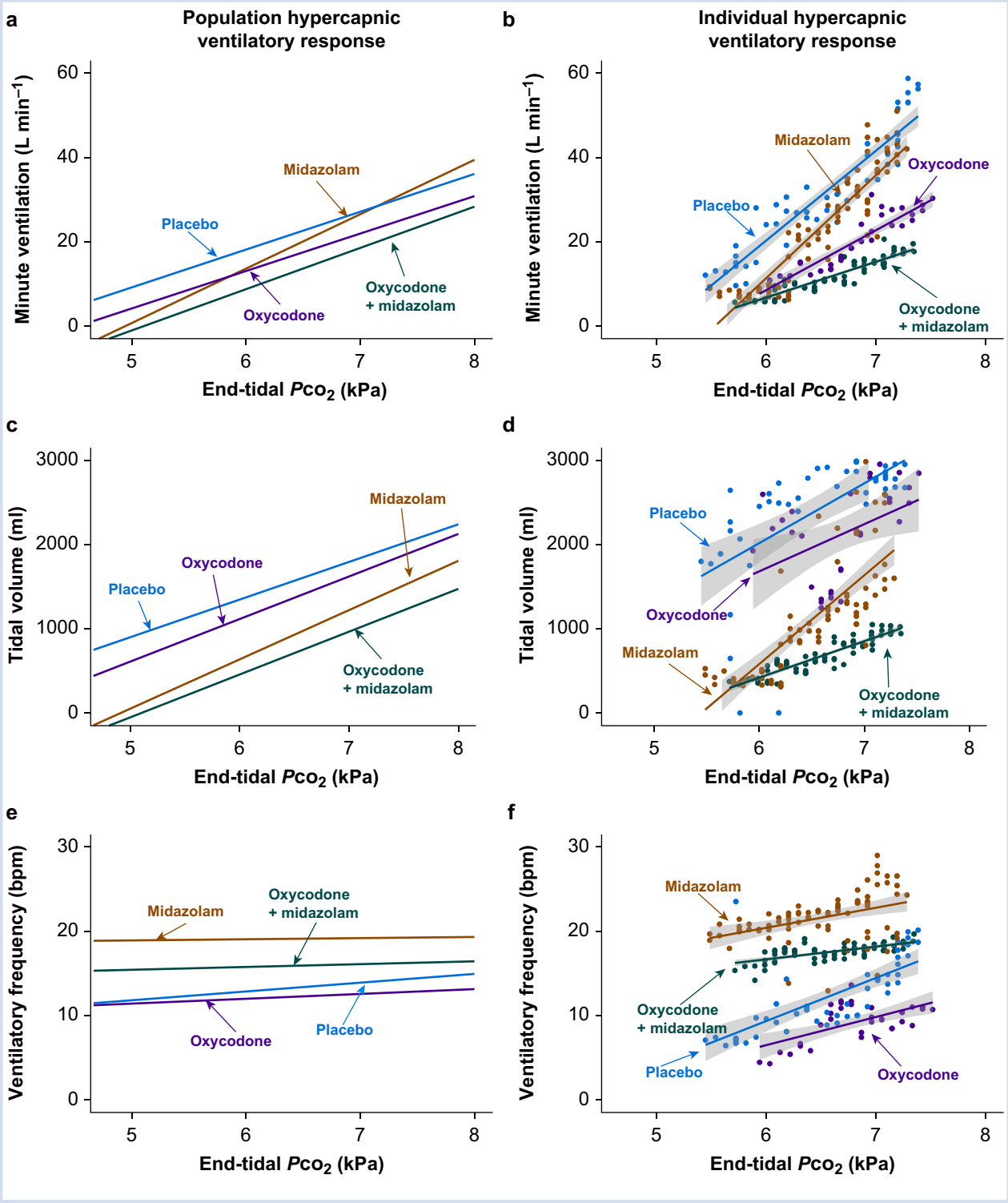


Fig 3. Relationship between end-tidal P_{CO_2} and minute ventilation. (a) Hypercapnic ventilatory response curves by treatment group based on the 2-h time point rebreathing data for the whole population (left) and a sample participant (right). A linear mixed-effect model using all data with participant as a random effect was used to predict the linear relationship between end-tidal P_{CO_2} and minute ventilation (top), tidal volume (middle), and ventilatory frequency (bottom). A total of 20 participants per arm were included for the oxycodone and placebo groups, and 15 participants per arm were included in the analysis for the midazolam and oxycodone + midazolam groups. (b) Data points represent all the sample participant measurements collected during the rebreathing stage, lines represent the linear regression for each treatment for one participant based on measurements during the rebreathing stage, and shaded areas represent the 95% confidence intervals for the linear regression for minute volume (top), tidal volume (middle), and ventilatory frequency (bottom).

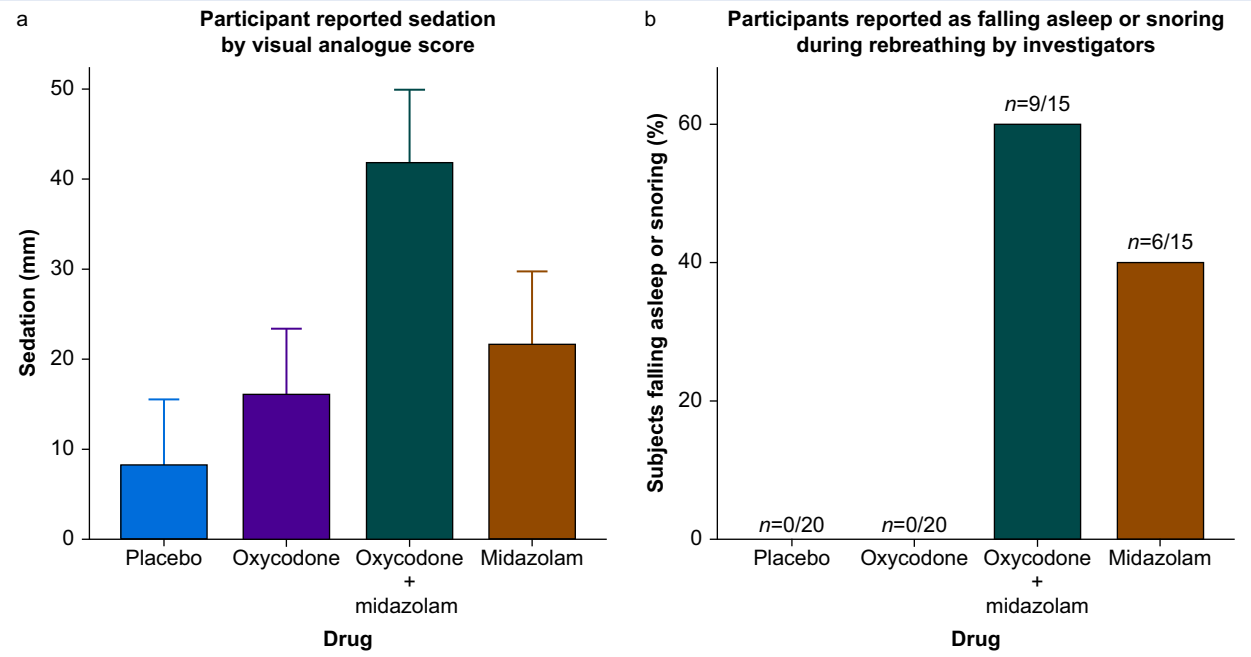


Fig 4. Sedation effects on participants. (a) Linear mixed-effects model-predicted sedation at 3 h for each treatment group. The error bars indicate two-sided 95% confidence intervals. (b) Number and percent of participants reported as falling asleep or snoring by the investigator at the 2-h assessment during the rebreathing stage. A total of 20 participants per arm were included in the analysis for the oxycodone and placebo groups, and 15 participants per arm were included for the midazolam and oxycodone + midazolam groups.

the number of subjects whose rebreathing data were not usable at the primary time point, only 10 subjects had no missing data for the primary analysis, making the results underpowered to detect a difference in minute ventilation at 7.3 kPa if there truly was one. By using healthy volunteers, this study excluded those at highest risk for an overdose with co-administration of benzodiazepines and opioids.

In conclusion, although midazolam co-administered with oxycodone did not further decrease hypercapnic ventilation compared with oxycodone alone, it decreased tidal volume, increased ventilatory frequency, and increased resting end-tidal P_{CO_2} in healthy subjects, which suggests that the combination influences ventilation by inducing relaxation of the respiratory muscles. This is an important foundation for understanding the underlying mechanisms. However, additional investigations are necessary to elucidate the potential for upper airway obstruction when benzodiazepines and oxycodone are co-administered, especially in at-risk populations.

Authors' contributions

Had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis: VG, JF, DGS
Concept and design: JF, RvdS, MCD, KB, KP, VP, MM, KAF, RRo, MS, AD, DGS
Acquisition, analysis, or interpretation of data: VG, JF, RvdS, MCD, PS, CW, KB, AS, RRa, VP, MM, OI, RB, KAF, CS, AD, DGS
Drafting of the manuscript: VG, JF, DGS
Critical revision of the manuscript for important intellectual content: all authors
Statistical analysis: VG, JF, RvdS, CW
Obtained funding: DGS
Administrative, technical, or material support: JF, RvdS, MCD, PS, KP, AS, MM, OI, KAF, RRo, CS, AD
Supervision: JF, VP, AD, DGS

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Declarations of interest

RvdS reported receiving a research contract from the FDA. AD reported receiving grants or research contracts from ZonMW (Dutch Research Council), the FDA, Medtronic, LTS Lohmann, AMO Pharma, Bedrocan BV, Grunenthal GmbH, and Merck Sharp & Dohme BV; consulting fees from Enalare Therapeutics and Trevena; speaker fees from Grunenthal BV; stock options from Enalare Therapeutics; and nociception devices for research from Medasense Biometrics. No other disclosures were reported.

Disclaimer

The opinions expressed in this manuscript are those of the authors and should not be interpreted as the position of the US Food and Drug Administration.

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US Food and Drug Administration (FDA), which oversaw the design and overall conduct of the study including overseeing the management, analysis, and interpretation of the data. The FDA prepared, reviewed, and approved the manuscript for submission for publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2024.11.047.

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