High Therapeutic Buprenorphine Levels Reduce IV Fentanyl Respiratory Depression

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Background

- The number of US drug overdose deaths exceeded 70,000 in 2017, partially driven by an increase in deaths involving potent synthetic opioids such as fentanyl[1]
  - Fentanyl overdose can cause respiratory depression, followed by decreased mental status, brain damage, and death
- Patients who enter medication-assisted treatment (MAT) programs for opioid use disorder (OUD) have reduced risk of overdose and death,[2] but are still often exposed to fentanyl via illicit drug use[3]
- Buprenorphine, a partial agonist at the mu-opioid receptor (MOR), is used for the MAT of OUD
  - Buprenorphine has high affinity for the MOR; prior studies indicate that plasma concentrations of buprenorphine ≥2 ng/mL achieve 70%-80% brain MOR occupancy and block the subjective drug-liking effect of full opioid agonists, such as hydromorphone[4,5]
  - As a partial agonist, buprenorphine has a ceiling effect on respiratory depression such that it does not cause apnoea when administered alone and minute ventilation (MV) is not suppressed beyond 50% to 60%[4]
- The hypothesis is that sustained plasma concentrations of buprenorphine ≥2 ng/mL will competitively inhibit the effects of potent, short-acting MOR agonists like fentanyl and carfentanil that can result in apnoea and death

Objective

- To examine the effects of sustained buprenorphine concentrations on respiratory depression induced by intravenous (IV) fentanyl injection

Methods

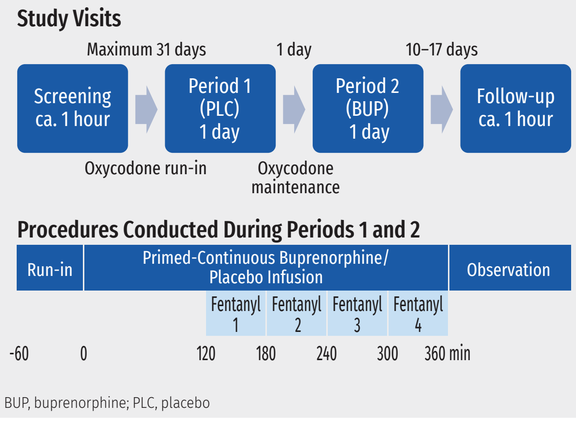
Key Inclusion Criteria

- Males and females, age 18 to 55 years
- BMI 18 to 32 kg/m^2
- Opioid-tolerant participants who were using opioids at daily doses ≥90 mg oral morphine equivalents
- No current use of any central nervous system depressants besides opioids, unless cleared by principal investigator
- Stable, as defined by the investigator and based on a full medical evaluation)

Study Design

- Open-label, placebo-controlled, 2-period crossover design
- Total trial duration was about 8 weeks, including Screening, Period 1, Period 2 and End of Study follow-up (**Figure 1**)
- Participants received placebo + fentanyl during Period 1 (Day 1) and buprenorphine + fentanyl during Period 2 (Day 3)

Figure 1. Study Design



BUP, buprenorphine; PLC, placebo

Ventilation Measurements

- To study ventilation on Day 1 and Day 3, the dynamic end-tidal forcing technique was used[4]
- End-tidal PCO_2 and PO_2 were clamped to approximately 7 and 14.5 kPa, respectively, until MV (tidal volume x respiratory rate) reached 20 to 24 L/min
- Participants breathed through a face mask and received fresh gas with O_2, CO_2 and N_2 adjusted to obtain the desired end-tidal concentrations
- The inspired and expired gas flows were measured using a pneumotachograph, and the O_2 and CO_2 concentrations were measured using a gas monitor; a pulse oximeter continuously measured the oxygen saturation
- For these preliminary analyses, drug effects were measured as a decrease in MV, number/duration of apnoeic events (lasting >20 seconds), need for ventilatory stimulation and changes in oxygen saturation

Drug Dosing

- Once baseline ventilation was stable at 20-24 L/min, participants received ondansetron 4 mg IV and a primed-continuous IV buprenorphine (or placebo) infusion was initiated
- Buprenorphine infusion targeted plasma concentrations of 1 ng/mL (Low-Dose), 2 ng/mL (Middle-Dose) and 5 ng/mL (High-Dose), consistent with levels achieved with the two approved doses of SUBLOCADE™, the first buprenorphine extended-release monthly injection for subcutaneous use approved by the US Food and Drug Administration
- Buprenorphine infusion continued for 360 min and fentanyl boluses were administered at 120, 180, 240 and 300 minutes to complete a 4-step IV bolus dose escalation (**Table 1**)
- Fentanyl dose escalation was discontinued at the investigator's discretion if participants experienced apnoea that required ventilatory stimulation or had a significant fall in oxygen saturation or other unstable breathing pattern

Table 1. Listing of Buprenorphine Primed-Continuous Infusion Doses and Fentanyl Bolus Doses

	Buprenorphine Dosing		Fentanyl Dosing	
	Prime (mg/70 kg)	Continuous (mg/70 kg/h)		Bolus (mg/70 kg)
Low-Dose	0.25	0.10	Fentanyl Dose 1	0.25
Middle-Dose	0.50	0.20	Fentanyl Dose 2	0.35
High-Dose	1.25	0.50	Fentanyl Dose 3	0.50
			Fentanyl Dose 4	0.70

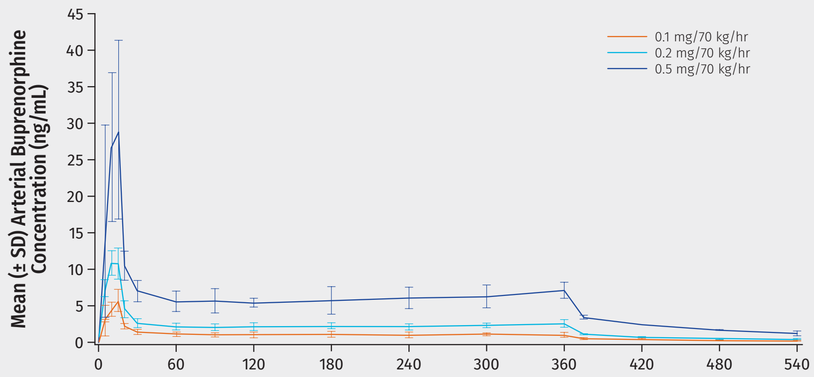
Results

- Eight opioid-tolerant participants were enrolled and received both placebo and buprenorphine infusionse

Table 2. Patient Demographic and Clinical Characteristics

Dose	Patient	Sex	Age	BMI	Drug Usage at Screening Visit
Low	201	F	44	23.6	Oxycodone 60 mg/d
	205	M	46	29.6	Fentanyl patch 25 mcg/h/Oxycodone 60 mg/d/Marijuana
Middle	206	F	33	30.8	Fentanyl patch 75 mcg/h/Oxycodone 90 mg/d/Tapentadol 50 mg/d
	208	M	43	22.0	Buprenorphine 16 mg/d/Cocaine/Marijuana
	1207	F	31	23.2	Oxycodone 60 mg/d/Marijuana
High	202	M	52	25.1	Heroin 250 mg/day (smoke)/Cocaine/Marijuana
	203	F	52	31.5	Fentanyl patch 50 mcg/h
	204	F	34	21.0	Fentanyl patch 75 mcg/h/Oxycodone 60 mg/d/Marijuana

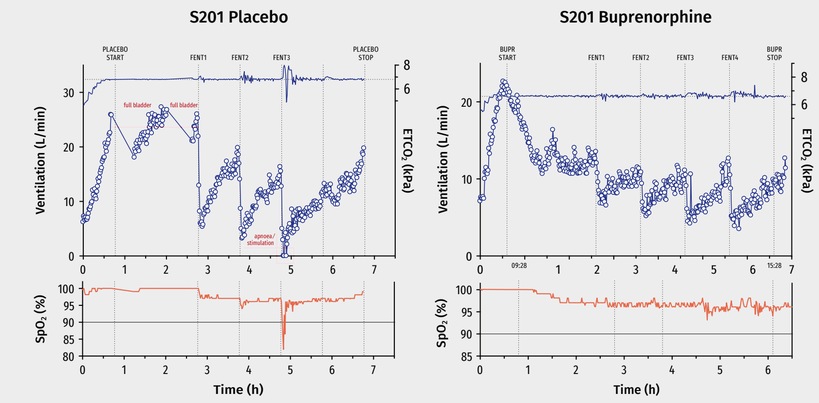
Figure 2. Mean Arterial Plasma Buprenorphine Concentrations



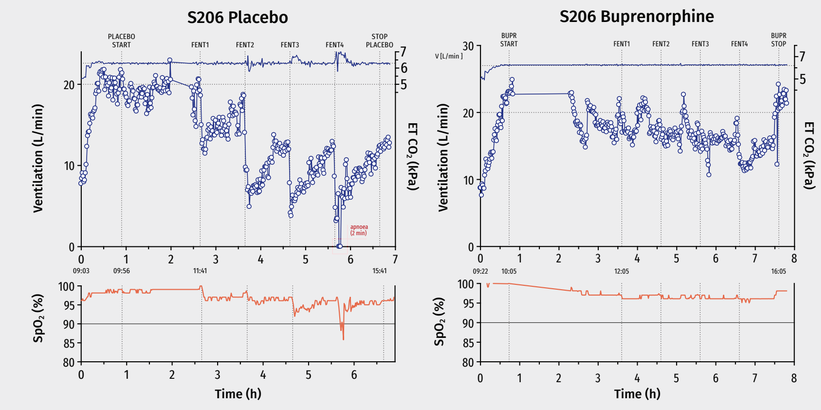
Low-Dose (n=2), Middle-Dose (n=3) and High-Dose (n=3) infusions yielded mean arterial plasma concentrations of 1.1 ng/mL, 2.3 ng/mL and 6.1 ng/mL, respectively.

Figure 3. End-Tidal CO_2, Minute Ventilation and Oxygen Saturation (SpO_2) of the First Participant Who Received Low-Dose (A), Middle-Dose (B) and High-Dose (C) Buprenorphine With Fentanyl Boluses

A. Low-Dose Buprenorphine



B. Middle-Dose Buprenorphine



C. High-Dose Buprenorphine

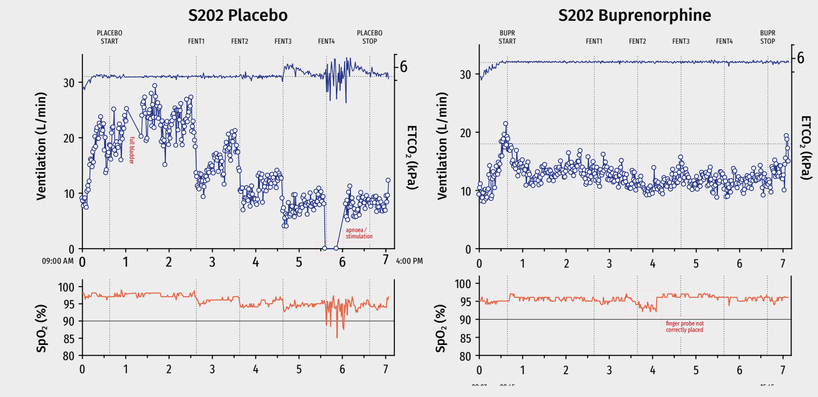


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Table 3. Summary of Fentanyl Boluses Administered With Associated Apnoea and Verbal Stimulation Events

Subject	Dose	# boluses	Notes
201	Placebo	3	Apnoea after 3rd bolus. Intermittent for 5 minutes with verbal stimulations. ↓ O_2 sat.
	Low-dose	4	No apnoea events.
205	Placebo	2	Prolonged apnoea after 2nd bolus. Lasted ~10 minutes and required verbal stimulation. ↓ O_2 sat.
	Low-dose	4	Apnoea after 3rd bolus. No verbal stimulation. Intermittent apnoea after 4th bolus but no verbal stimulation required and O_2 sat stable.
206	Placebo	4	Apnoea after 4th bolus for 2 minutes with verbal stimulations required. ↓ O_2 sat.
	Middle-dose	4	No apnoea events.
208	Placebo	4	No apnoea events.
	Middle-dose	4	No apnoea events.
1207	Placebo	4	Prolonged apnoea after 4th bolus. Lasted 25 minutes with verbal stimulation required. ↓ O_2 sat
	Middle-dose	4	No apnoea events.
202	Placebo	4	Prolonged apnoea after 4th bolus. Lasted 25 minutes with verbal stimulation required. ↓ O_2 sat
	High-dose	4	No apnoea events.
203	Placebo	2	Apnoea after 2nd bolus. Two events with verbal stimulation.
	High-dose	4	Brief apnoea only after 2nd bolus and verbal stimulation was not required.
204	Placebo	3	Apnoea after 3rd bolus. Intermittent for 5 minutes with unstable breathing pattern.
	High-dose	4	No apnoea events.

Summary

- Placebo session
  - Abrupt declines in MV were generally evident following each fentanyl bolus
  - 6 of 8 participants (75%) experienced 1 or more apnoeic events requiring verbal ventilatory stimulation
  - IV fentanyl dose escalation was stopped early after the 2nd (n=2) or 3rd bolus (n=2) in 4 participants because of prolonged apnoea or changes in oxygen saturation
  - 5 participants had oxygen saturation values <90%
- Buprenorphine session
  - Each participant completed all 4 fentanyl boluses
  - Only 1 participant experienced an apnoeic episode after the 3rd and 4th boluses
  - Verbal ventilatory stimulation was not required
  - Oxygen saturation did not drop below 90%
- Buprenorphine dose response
  - 1 ng/mL – declines in MV were evident after fentanyl boluses; the 1 participant with fentanyl-related apnoeic events during buprenorphine infusion was in this group
  - 5 ng/mL – marked changes in MV did not occur after the fentanyl infusions and repeated apnoeic events did not occur

Conclusions

- These data suggest buprenorphine acts as a competitive inhibitor of fentanyl boluses at doses up to 0.70 mg/70 kg
- This competitive inhibition reduces the magnitude of fentanyl-induced respiratory depression, most notably at buprenorphine concentrations ≥2 and 5 ng/mL
- Although this is a small patient sample, the potential protective effect of ≥2 ng/mL and 5 ng/mL sustained plasma concentrations against fentanyl-induced respiratory depression warrants additional investigation

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Conflict of Interest Statement

MF and RD are employees of Indivior, Inc. KW is a site PI for selected Indivior trails and was an Indivior, Inc. advisory committee member in 2018. HA, LM, and MV have no conflict of interests to disclose.

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