High Therapeutic Buprenorphine Levels Reduce IV Fentanyl Respiratory Depression

Katharina Wiest[1] | **M. Hyke Algera**[2] | **Laurence Moss**[3] | **Geert Jan Groeneveld**[3] | **Jules Heuberger**[3] | **Albert Dahan**[2] | **Frank Gray**[4] | **Stephanie Strafford**[4] | **Monique van Velzen**[2] | **Robert Dobbins**[3] | [1]CODA, Inc., Portland, OR, USA | [2]Leiden University Medical Center, Leiden, NLD | [3]Centre for Human Drug Research, Leiden, NLD | [4]Indivior Inc., North Chesterfield, VA, USA

Goal

- 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

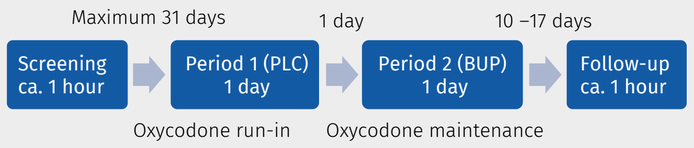
- Males and females, age 18 to 55 years
- BMI 18 to 32 kg/m^2
- Opioid-tolerant participants who were using opioids at daily doses ≥90 mg oral morphine equivalents
- No current use of any central nervous system depressants besides opioids, unless cleared by principal investigator
- Stable, as defined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

Study Design

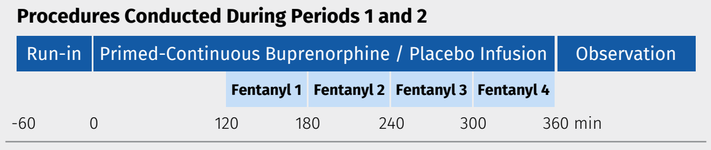
- Open-label, placebo-controlled, 2-period crossover design (NCT03747341; EUdra CT 2017-004858-42)
- Total trial duration was about 8 weeks, including Screening, Period 1, Period 2 and End of Study follow-up (**Figure 1**)
- Participants received placebo + fentanyl during Period 1 (Day 1) and buprenorphine + fentanyl during Period 2 (Day 3)

Figure 1. Study Design

Study Visits



Procedures Conducted During Periods 1 and 2



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

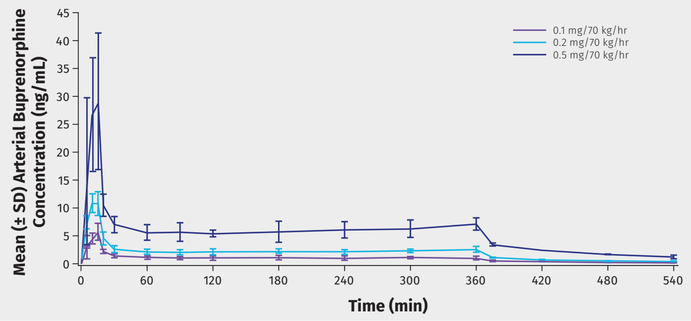
Results

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

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

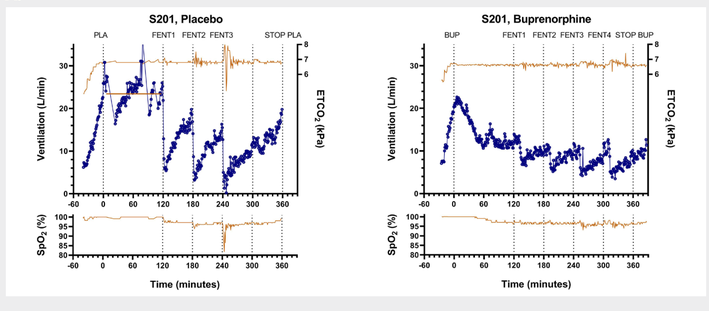
Figure 2. Mean Arterial Plasma Buprenorphine Concentrations



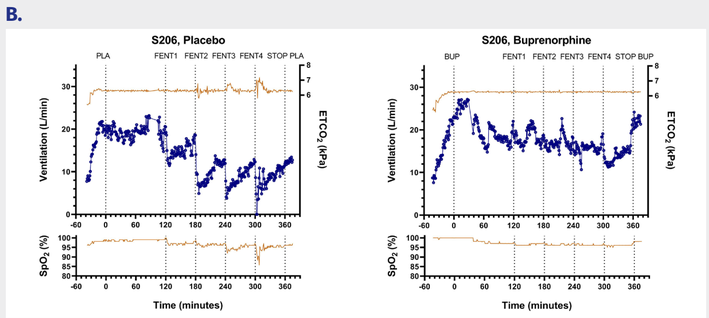
Low-Dose (n=2), Middle-Dose (n=3) and High-Dose (n=3) infusions yielded mean arterial plasma concentrations of 1.1 ng/mL, 2.3 ng/mL and 6.1 ng/mL, respectively.

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

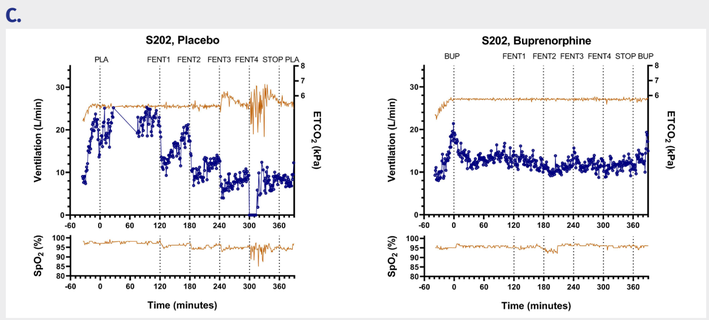
A.



B.



C.



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.

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	Prolonged apnoea after 4th bolus. Lasted 12 minutes with verbal stimulation required. ↓ O_2 sat.
	Middle-Dose	4	No apnoea events.
1207	Placebo	4	No apnoea events.
	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

Conclusion

- These data suggest buprenorphine acts as a competitive inhibitor of fentanyl boluses at doses up to 700 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

References

1. Hedegaard H, et al. Drug overdose deaths in the United States, 1999-2017, NCHS Data Brief. 2018; 329:1-8.
2. Dupouy J, et al. Mortality associated with time in and out of buprenorphine treatment in French office-based general practice: A 7-year cohort study. *Ann Fam Med.* 2017; 15:355-8.
3. Ochalek TA, et al. Fentanyl exposure among participants seeking opioid treatment. *J Subst Abuse Treat.* 2019; 96:23-4.
4. Yassen A, et al. Mechanism-based PK/PD modeling of the respiratory depressant effect of buprenorphine and fentanyl in healthy volunteers. *Clin Pharmacol Therapeut.* 2007; 81:50-8.
5. Nasser AF, et al. Sustained-release buprenorphine (RBP-6000) blocks the effects of opioid challenge with hydromorphone in participants with opioid use disorder. *J Clin Psychopharmacol.* 2016; 36:18-26.

Disclosures

KW is a site PI for selected Indivior trials and was an Indivior Inc. advisory committee member in 2018. MHA is an employee of LUMC. LM, MVV, GJG, JH, and AD report no conflicts of interest. FG, SS, and RD are employees of Indivior Inc.

Acknowledgements

The authors would like to thank S Strafford, F Gray, A Heath from Indivior Inc, GJ Groeneveld and JAAC Heuberger from the Centre for Human Drug Research, and A Dahan from Leiden University Medical Center. Funded by Indivior Inc. Graphic design provided by Prescott Medical Communications Group, Chicago, IL.

PRESENTED AT THE ANNUAL CONFERENCE OF THE SOCIETY FOR THE STUDY OF ADDICTION, NOVEMBER 7-8, 2019 • NEWCASTLE UPON TYNE, UNITED KINGDOM