High Sustained Therapeutic Buprenorphine Plasma Levels Reduce Respiratory Depression Induced by IV Fentanyl

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Disclosure

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- Speaker honoraria:
  - D&A Pharma, Gilead Sciences, Reckitt Benckiser; Indivior, Abbvie, Merk
- Consulting fees:
  - Gilead Sciences, Indivior, Laboratorio Farmaceutico CT, Merck Serono, Molteni Farmaceutici, Mundipharma Pharmaceuticals, Reckitt Benckiser
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Background

- **The number of Italian drug overdose deaths is underestimated[1],** altough according to EMCDDA, in 2017, the special register (Police Forces and Prefettures) reported an increase of 10% in the number of drug-induced deaths in Italy[2]

- Patients who enter medication-assisted treatment **(MAT)** programs for opioid use disorder **(OUD) have a reduced risk of overdose and death[3,4]**

1. Italian annual report to Parliament on drug addiction, 2018. Available at: http://www.politicheantidroga.gov.it/it/attivita-e-progetti/relazioni-annuali-al-parlamento/relazione-annuale-al-parlamento-sul-fenomeno-delle-tossicodipendenze-in-italia-anno-2018-dati-2017.
2. Italy, Country Drug Report 2019. EMCDDA, June 2019. Available at: http://www.emcdda.europa.eu/publications/country-drug-reports/2019/italy.
3. Hedegaard H, et al. NCHS Data Brief. 2018; 329:1-8. **4.** Dupouy J, et al. *Ann Fam Med.* 2017*;* 15:355-8.

Background and Hypothesis

- **Buprenorphine, a partial agonist at the mu-opioid receptor (MOR) used for the MAT of OUD, 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[1,2]
- As a partial agonist, buprenorphine has a ceiling effect on respiratory depression[1]
- **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**

1. Yassen A, et al. *Clin Pharmacol Therapeut.* 2007; 81:50-8. 2. Nasser AF, et al. *J Clin Psychopharmacol.* 2016; 36:18-26.

Objective

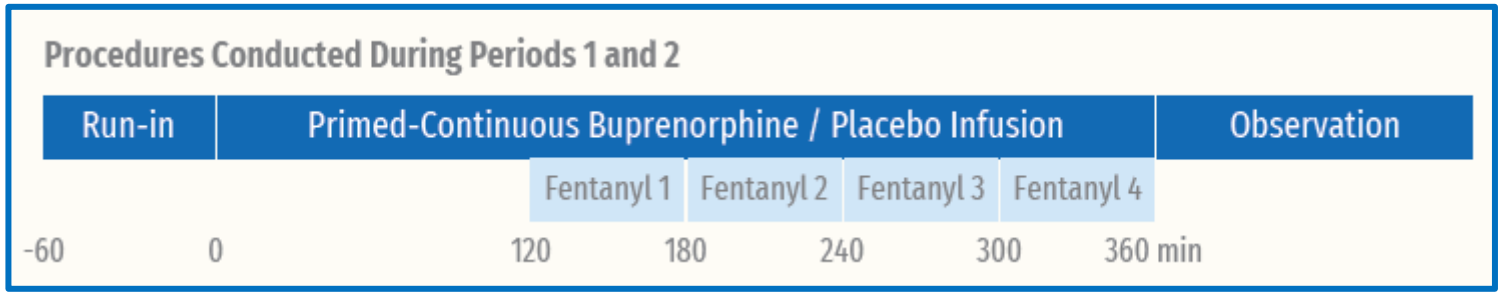
- **Examine the effects of sustained BUP concentrations on respiratory depression inducec by intravenous (IV) fentanyl injection**

Methods (1)

- **Eight opioid-tolerant patients using >90 mg daily oral morphine** equivalent were enrolled in an open-label, placebo-controlled, 2-period crossover study
- **Patients received placebo (PLC)/fentanyl on Day 1 and BUP/fentanyl on Day 3**
- **Minute ventilation (MV)** was measured at isohypercapnia (baseline MV about 20 L/min)
- **BUP infusion targeted plasma concentrations of 1 (low dose), 2 (middle dose) or 5 ng/mL (high dose) for 6 hours**

Methods (2)

- Following initiation of PLC or BUP infusion, IV fentanyl boluses of 250, 350, 500 and 700 mcg/70 kg were administered at 2, 3, 4, and 5 hours, respectively



- 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

Patient Demographic and Clinical Characteristics

Table 1. Patient Demographic and Clinical Characteristics					
BUP 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

Results (1)

- **The study showed that fentanyl boluses decreased MV, and that buprenorphne administration prevented apnoea events in most patients.**
- During the PLC period, abrupt declines in MV were seen following each fentanyl bolus
- **BUP infusion (especially at concentrations > 2 and 5 ng/mL) may act as a competitive inhibitor of fentanyl boluses at doses up to 700 mcg/70 kg, thereby reducing the magnitude of fentanyl-induced respiratory depression**

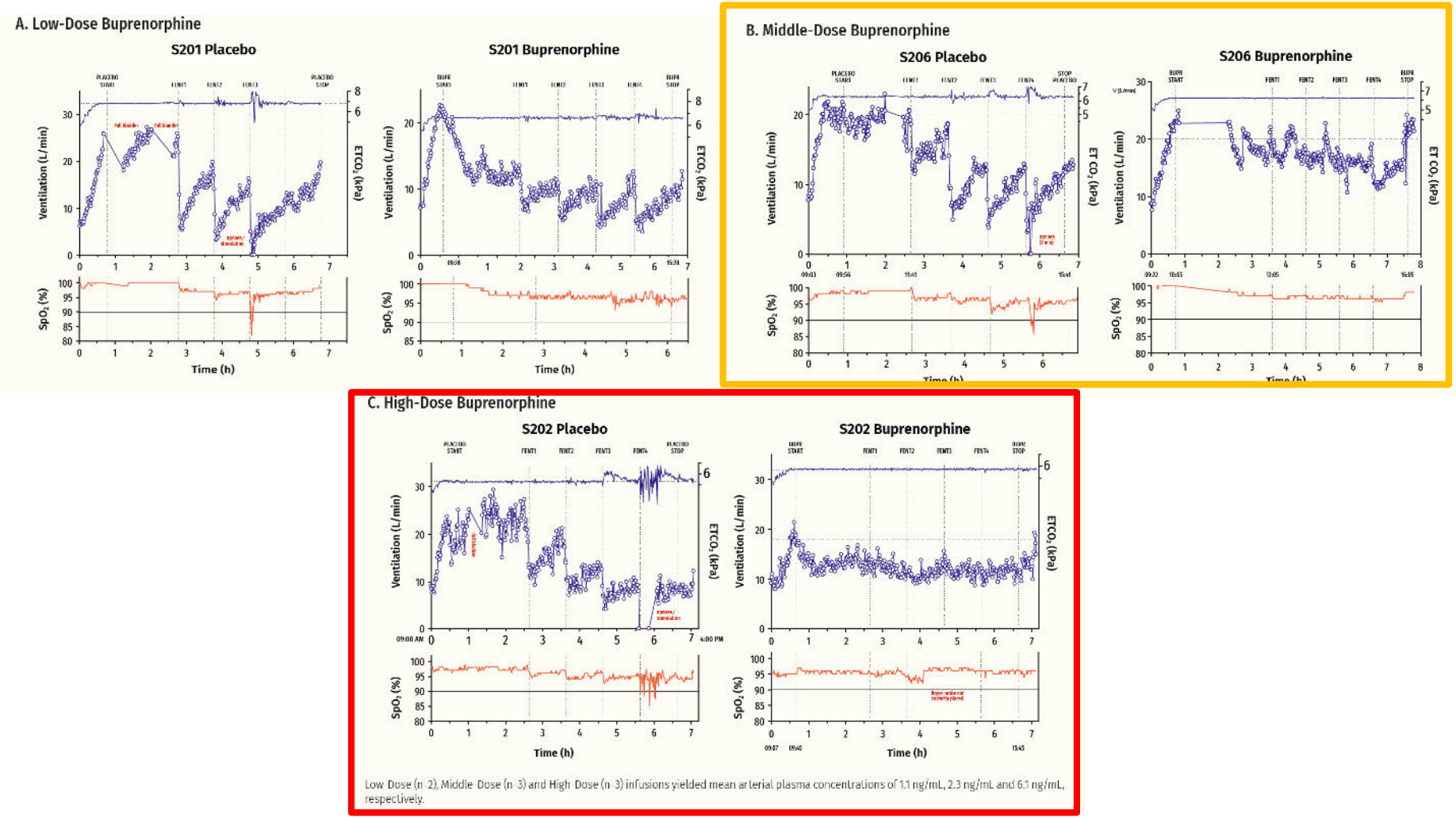
Results (2)

Table 2. Effects of Buprenorphine Doses on Fentanyl Boluses

Subject	BUP Dose	# Boluses	Notes
201	Placebo	3	Apnoea after 3rd bolus. Intermittent for 5 minutes with verbal stimulation. ↓ O2 sat.
	Low	4	No apnoea events.
205	Placebo	2	Prolonged apnoea after 2nd bolus. Lasted ~10 minutes and required verbal stimulation. ↓ O2 sat.
	Low	4	Apnoea after 3rd bolus. No verbal stimulation. Intermittent apnoea after 4th bolus but no verbal stimulation required and O2 sat stable.
206	Placebo	4	Apnoea after 4th bolus for 2 minutes with verbal stimulation required. ↓ O2 sat.
	Middle	4	No apnoea events.
208	Placebo	4	Prolonged apnoea after 4th bolus. Lasted 12 minutes with verbal stimulation required. ↓ O2 sat.
	Middle	4	No apnoea events.
1207	Placebo	4	No apnoea events.
	Middle	4	No apnoea events.
202	Placebo	4	Prolonged apnoea after 4th bolus. Lasted 25 minutes with verbal stimulation required. ↓ O2 sat.
	High	4	No apnoea events.
203	Placebo	2	Apnoea after 2nd bolus. Two events with verbal stimulation.
	High	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	4	No apnoea events.

Results (3)

End-Tidal CO2, Minute Ventilation and Oxygen Saturation (SpO2) of the First Participant Who Received Low-Dose (A), Middle-Dose (B) and High-Dose (C) Buprenorphine With Fentanyl Boluses



Conclusions

- These data suggest that buprenorphine may act as a competitive inhibitor of fentanyl bolus 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

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