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HIGH SUSTAINED THERAPEUTIC BUPRENORPHINE PLASMA LEVELS REDUCE RESPIRATORY DEPRESSION INDUCED BY IV FENTANYL

Felice Alfonso Nava,[1] presenting on behalf of Katharina Wiest[2], M. Hyke Algera[3], Laurence Moss[4], Monique van Velzen[3], Geert Jan Groeneveld[3,4], Jules Heuberger[4], Albert Dahan[3], Frank Gray[5], Stephanie Strafford[5], Robert Dobbins[5]

[1]Penitentiary Medicine and Drug Abuse Unit, Public Health Service Padua, Italy; [2]CODA, Inc., Portland, OR, USA; [3]Leiden University Medical Center, Leiden, NLD; [4]Centre for Human Drug Research, Leiden, NLD; [5]Indivior Inc., North Chesterfield, VA, USA

Background

The number of Italian drug overdose deaths is underestimated,[1] although according to EMCDDA, in 2017, the special register (Police Forces and Prefectures) reported an increase of 10% in the number of drug-induced deaths in Italy.[2] It is also alarming to learn of the first death in Italy attributed to the use of a novel synthetic opioid (U-47700).[2] In the US, the number of drug overdose deaths exceeded 70,000 in 2017, partially driven by an increase in deaths involving potent synthetic opioids such as fentanyl/fentanyl analogs.[3] 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 a reduced risk of overdose and death,[4] but they may be vulnerable due to the exposure to fentanyl via unprescribed drug use.[5] Buprenorphine (BUP), a partial agonist at the mu-opioid receptor (MOR), is used for MAT of OUD. BUP has high affinity for the MOR; prior studies indicate that plasma concentrations of BUP ≥2 ng/mL achieve 70%-80% brain MOR occupancy and block the subjective drug-liking effect of full opioid agonists such as hydromorphone.[6] As a partial agonist, BUP 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%-60%.[7] The hypothesis is that sustained plasma concentrations of BUP ≥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:

Examine the effects of sustained BUP concentrations on respiratory depression induced by intravenous (IV) fentanyl.

Methods

Eight opioid-tolerant patients using >90 mg daily oral morphine equivalents 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. MV was measured at isohypercapnia (baseline MV ~20 L/min) through a facemask connected to a pneumotachograph.[6] Once ventilation stabilised, pulsed-continuous infusions of PLC or BUP were initiated. BUP infusion targeted plasma concentrations of 1 (low dose), 2 (middle dose) or 5 ng/mL (high dose) for 6 hours, consistent with concentrations achieved with RBP-6000, an extended-release BUP delivered via subcutaneous injection.[8] Following initiation of BUP or PLC 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

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

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.

apnoeic events (lasting ≥20 seconds), need for ventilatory stimulation, and changes in oxygen saturation. 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.

Results

Demographic and clinical characteristics of the patients are shown in Table 1.

The study showed that fentanyl boluses decreased MV, and that buprenorphine administration prevented apnoea events in most patients. During the PLC period, abrupt declines in MV were seen following each fentanyl bolus, and 6 of 8 patients (75%) experienced 1 or more apnoeic events requiring verbal stimulation to maintain adequate MV. IV fentanyl dose escalation was stopped early after the 2nd (n=2) or 3rd bolus (n=2) in 4 subjects because of prolonged apnoea or changes in oxygen saturation (Table 2).

In contrast, during the BUP period, each patient completed 4 fentanyl boluses and only 1 experienced apnoeic episodes after the 3rd and 4th boluses. With BUP, none of the patients required verbal stimulation and oxygen saturation did not drop below 90%. For the low-dose BUP infusion targeting 1 ng/mL, declines in MV were evident after fentanyl boluses and the 1 patient with apnoeic events during BUP infusion was in this group. For the high-dose BUP infusion targeting 5 ng/mL, marked changes in MV or repeated apnoeic events did not occur after the fentanyl infusions.

CONCLUSIONS: These data suggest BUP acts as a competitive inhibitor of fentanyl boluses at doses up to 700 mcg/70 kg, thereby reducing the magnitude of fentanyl-induced respiratory depression, especially at BUP 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 in sustaining plasma concentrations against fentanyl-induced respiratory depression warrants additional investigation.

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