Benefit of Buprenorphine Buccal Film Versus Oral Oxycodone Hydrochloride on Respiration: A Phase 1 Placebo-Controlled Trial

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Introduction

Background

- Hypoxia caused by opioid-induced respiratory depression is the primary cause of death related to opioid overdose[1]
- Respiratory depression is caused, in part, by inhibition of respiratory drive (ie, the ability of neuronal respiratory centers to control and regulate ventilation)[2]
- Buprenorphine is a partial μ-opioid receptor agonist that, unlike full μ-opioid receptor agonists (eg, morphine, oxycodone, fentanyl), has been shown to exhibit a ceiling effect for respiratory depression when administered intravenously[3,4]
- Partial agonism refers to receptor-level activity and not analgesic efficacy, as buprenorphine has analgesic efficacy comparable to that of full μ-opioid receptor agonists[5]
  - This partial agonism at the μ-opioid receptor, together with antagonism at the κ and δ opioid receptors and agonism at the nociceptin receptor (formerly known as opioid receptor-like 1 or ORL-1), may play a role in limiting common opioid-related adverse events (AEs) such as respiratory depression

Purpose

- This study was designed to compare the effects of buprenorphine buccal film (BBF; BELBUCA®) and oral oxycodone (immediate release) on respiratory drive to differentiate the impact of a partial μ-opioid receptor agonist from that of a full μ-opioid receptor agonist

Methods

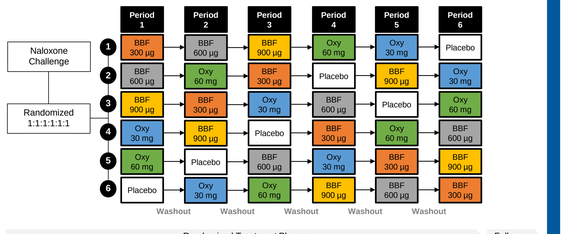
Subjects

- Subjects were healthy men and women who self-identified as recreational opioid users and were not dependent on opioids (confirmed via a Naloxone Challenge Test at day −1)

Study Design

- Effects on respiratory drive were assessed using a randomized, double-blind, double-dummy, 6-treatment, 6-period, placebo-controlled crossover design
- Treatments were BBF 300, 600, and 900 μg; oral oxycodone 30 and 60 mg; and placebo
- Each subject received every treatment once, following a computer-generated randomization treatment sequence (**Figure 1**)
  - All treatments were separated by a minimum 7-day washout period to avoid any potential carryover effects
- This study design was chosen to minimize variability by allowing each subject to serve as their own control

Figure 1. Study Design



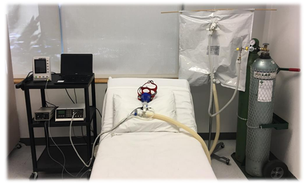
Abbreviations: BBF, buprenorphine buccal film; oxy, oxycodone.

Methods (cont'd)

Assessments

- Respiratory drive was evaluated by measuring the ventilatory response to hypercapnia (VRH) through assessment of the maximum decrease in minute ventilation (maximum effect; E_{max}) after administration of each study drug (primary endpoint)
  - The VRH test was performed with the subjects comfortably seated or semi-supine in a hospital bed and breathing through a face mask (**Figure 2**)
  - Assessment of VRH was performed once predose and at 0.5, 1, 2, 3, and 4 hours postdose
  - At each time point, subjects were allowed a period of acclimation to room air to establish a regular breathing pattern; this was immediately followed by breathing of a hypercapnic gas mixture (7% CO_2, 21% O_2, 72% N_2) for a 5-minute capture period, unless the subject reached an end-tidal CO_2 of 60 mm Hg for 3 consecutive breaths—in which case the procedure was terminated
- Throughout the study, from the first dose up to 7 ±2 days after the last study dose was administered, patients were monitored for AEs, which were recorded

Figure 2. Ventilatory Response to Hypercapnia: Experimental Setting



Statistical Analyses

- Statistical analyses were performed using a linear mixed-effects model with treatment, period, and sequence as fixed effects and subject nested within sequence as a random effect
- E_{max} was defined as the maximum effect for each subject after each study medication was administered
- Least squares (LS) mean differences between each treatment were calculated, along with differences in LS means with 95% confidence intervals (CIs) and *P* values
- A similar model was used to assess the difference between each treatment and placebo at each post-baseline time point (where the model also included a fixed effect for time point)

Results

Table 1. Subject Disposition and Demographics

Disposition			
Subjects, no.			
Screened	40		
Enrolled	19		
Partial completers[a]	16		
Completers	15		
Demographics			
Category	**Enrolled**	**Partial completers**	**Completers**
Men, no. (%)	18 (94.7)	15 (93.8)	14 (93.3)
Age, mean (SD), y	33.1 (4.5)	32.8 (4.3)	32.9 (4.4)
Race, no. (%)			
White	14 (73.7)	13 (81.3)	12 (80.0)
Black or African American	1 (5.3)	1 (6.3)	1 (6.7)
Asian	1 (5.3)	1 (6.3)	1 (6.7)
American Indian or Alaska Native	3 (15.8)	1 (6.3)	1 (6.7)
Weight, mean (SD), kg	78.6 (15.8)	79.3 (16.9)	80.6 (16.7)
Height, mean (SD), cm	177.1 (8.4)	177.0 (9.1)	177.4 (9.3)
Body mass index, mean (SD), kg/m²	24.9 (3.7)	25.1 (3.9)	25.4 (3.8)

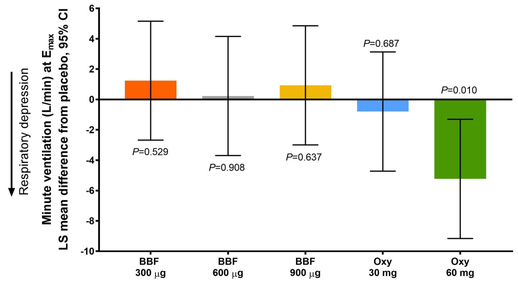
[a]Subjects who completed at least 2 study treatment periods.

Results (cont'd)

Ventilatory Response to Hypercapnia

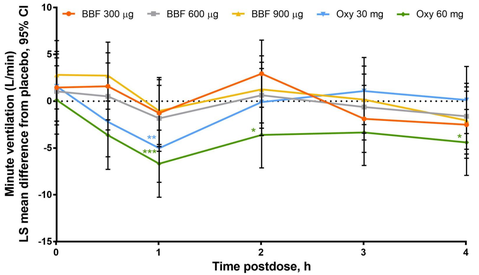
- There were no significant differences between placebo and any of the BBF doses for minute ventilation at E_{max} (L/minute) (**Figure 3**). In contrast, oxycodone 60 mg led to a significantly greater decrease in minute ventilation at E_{max} than did placebo (**Figure 3**). Oxycodone 30 mg produced a significantly greater decrease in mean minute ventilation than did placebo at 1 hour postdose, and oxycodone 60 mg led to significantly greater decreases than did placebo at 1, 2, and 4 hours postdose (**Figure 4**). Mean minute ventilation was similar for placebo and BBF for all doses and time points (**Figure 4**)

Figure 3. Effect of Each Treatment on Respiratory Drive (Study Completers, n=15)



Abbreviations: BBF, buprenorphine buccal film; CI, confidence interval; E_{max}, maximum effect; LS, least-squares; oxy, oxycodone.

Figure 4. Mean Minute Ventilation Over Time (Partial Completers, n=16)



*P<0.05; **P<0.01; ***P<0.001.
Abbreviations: BBF, buprenorphine buccal film; oxy, oxycodone; SE, standard error.

Safety

- No deaths or serious AEs were reported in this study
- The most common treatment-emergent AEs are shown in **Table 2**
- Only 1 subject discontinued owing to an AE—idioventricular rhythm—which was considered likely related to the study drug (BBF 600 μg)

Results (cont'd)

Table 2. Summary of Safety

	BBF 300 μg (n=15)	BBF 600 μg (n=17)	BBF 900 μg (n=17)	Oxy 30 mg (n=15)	Oxy 60 mg (n=16)	Placebo (n=16)
No. of TEAEs	10	28	30	19	45	2
Subjects with ≥1 TEAE	8 (53.3)	12 (70.6)	12 (70.6)	9 (60.0)	14 (87.5)	2 (12.5)
Discontinuation owing to an AE	0	1 (5.9)	0	0	0	0
Most common TEAEs, no. (%)						
Gastrointestinal disorders						
Nausea	0	4 (23.5)	4 (23.5)	2 (13.3)	5 (31.3)	0
Vomiting	1 (6.7)	1 (5.9)	4 (23.5)	2 (13.3)	6 (37.5)	0
Nervous system disorders and psychiatric disorders						
Somnolence	0	4 (23.5)	4 (23.5)	3 (20.0)	7 (43.8)	1 (6.3)
Euphoric mood	3 (20.0)	3 (17.6)	4 (23.5)	4 (26.7)	4 (25.0)	0
Dizziness	1 (6.7)	4 (23.5)	2 (11.8)	1 (6.7)	2 (12.5)	0
Headache	2 (13.3)	1 (5.9)	1 (5.9)	0	1 (6.3)	0
Irritability	0	1 (5.9)	1 (5.9)	0	0	0
Skin and subcutaneous tissue disorders						
Pruritis	0	1 (5.9)	4 (23.5)	4 (26.7)	9 (56.3)	0
Hyperhidrosis	1 (6.7)	1 (5.9)	0	0	2 (12.5)	1 (6.3)

Abbreviations: AE, adverse event; BBF, buprenorphine buccal film; oxy, oxycodone; TEAE, treatment-emergent adverse event.

Conclusions

- In this study of healthy recreational opioid users who were not dependent on opioids, compared with placebo, BBF did not significantly reduce respiratory drive at any dose (300, 600, or 900 μg)
- Administration of oxycodone 30 and 60 mg resulted in a significant dose-dependent decrease in respiratory drive
- The tolerability profiles of both drugs were similar
- No AEs related to respiratory depression have been reported in previous clinical studies of BBF[6-8]
- Data from this study show that BBF is well tolerated, and results from previous studies[3,4] suggest that BBF provides effective analgesia with a potentially lower risk of respiratory depression than a full μ-opioid receptor agonist for patients with chronic pain

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Author Disclosures

- In the previous 3 years, **LW** has received consultation, advisory board, and travel fees from Charleston Laboratories, Depomed, Egalet, Insys Therapeutics, Mallinckrodt Pharmaceuticals, Pfizer, Teva, and Trevena; consultation and travel fees from Alcobra, Bonti, Cassava Sciences, Daiichi Sankyo, Elysium, Indivior, KemPharm, Pernix, and Shionogi; advisory board and travel fees from BioDelivery Sciences International, Inc., Ensysce Biosciences, and Inspirion Pharmaceuticals; travel fees from Cara Therapeutics; and consultation fees from Jefferies, Merck, Trevi, Vallon, and Vector Pharma. **JC** has no conflicts of interest. **TS** is an employee of BioDelivery Sciences International, Inc.

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