A Phase I Placebo-Controlled Trial Comparing the Effects of Buprenorphine Buccal Film and Oral Oxycodone Hydrochloride on Respiratory Drive

Lynn Webster, MD[1]; Jacqueline Cater, PhD[1]; Thomas Smith, MD[2]

[1]PRA Health Sciences, San Diego, CA, USA; [2]BioDelivery Sciences International, Inc., Raleigh, NC, USA

Acknowledgment and Funding

This study was funded by BioDelivery Sciences International, Inc. Professional writing and editorial support was provided by MedLogix Communications, LLC, Itasca, Illinois, under the direction of the authors and was funded by BioDelivery Sciences International, Inc.

Introduction

- Buprenorphine buccal film (BELBUCA®) is approved by the US Food and Drug Administration for use in patients with chronic pain severe enough to require daily, around-the-clock, long-term opioid treatment and for whom alternative treatment options are inadequate[1]
- Buprenorphine is a partial μ-opioid receptor agonist that, unlike full μ-opioid receptor agonists, has been shown to have a ceiling effect on respiratory depression[2,3]
- This placebo-controlled study compared the effects of buprenorphine buccal film and oral oxycodone hydrochloride (a full μ-opioid receptor agonist) on respiratory drive, as measured by the ventilatory response to hypercapnia (VRH) after drug administration

Methods

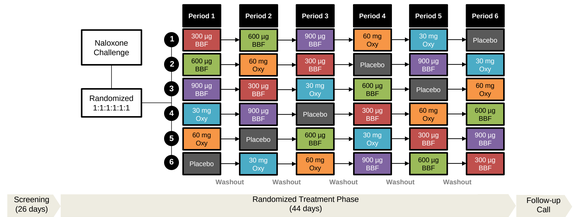
Subjects

- Subjects were healthy men and women self-identifying as recreational drug users and were determined not to be physically dependent on opioids via naloxone challenge

Study Design

- Effect on respiratory drive was assessed using a randomized, double-blind, double-dummy, 6-treatment, 6-period, placebo-controlled crossover design
- Treatments were 300, 600, and 900 μg buprenorphine buccal film; 30 and 60 mg oral oxycodone (immediate-release); and placebo (each separated by a 7-day washout period), as demonstrated in **Figure 1**
- Each subject received every treatment once (allowing subjects to act as their own control) in an order determined by a computer-generated randomization scheme based on the Williams design (whereby each treatment follows every other treatment at least once)

Figure 1. Study Design



Abbreviations: BBF, buprenorphine buccal film; Oxy, oxycodone hydrochloride.

Selection of Doses in the Study

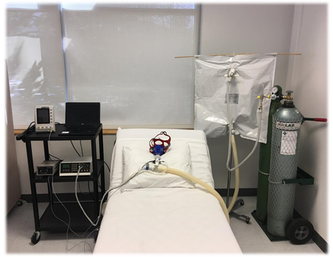
- The doses selected for this study were based on an estimate of equivalent doses of buprenorphine buccal film and oxycodone required to produce a similar analgesic effect
- It is estimated that 30 to 60 mg oxycodone has analgesic effects similar to those of 300 μg to 900 μg buprenorphine buccal film

Methods (cont'd)

Ventilatory Response to Hypercapnia

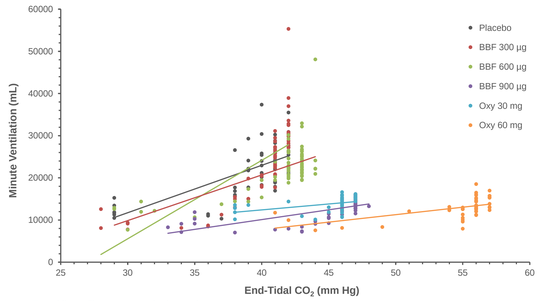
- Respiratory drive was evaluated by measuring VRH through assessment of the maximum decrease in minute ventilation (E_{max}) after administration of each study drug
- The VRH test was performed with the subjects in a hospital bed at a 45° recumbent position and breathing through a face mask (**Figure 2**)

Figure 2. Ventilatory Response to Hypercapnia: Experimental Setting



- The VRH assessment 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
- The different effects of oxycodone and buprenorphine buccal film on respiratory drive are shown in the data from a representative study subject in **Figure 3**

Figure 3. Minute Ventilation as a Function of End-Tidal CO_2 at 2 Hours Postdose for Each Treatment (Single Subject)



Note: Trend lines (linear regression) are shown.
Abbreviations: BBF, buprenorphine buccal film; Oxy, oxycodone hydrochloride.

Methods (cont'd)

Statistical Analyses

- Statistical analyses were performed using a mixed-effects model with treatment, period, and sequence as fixed effects and subject nested within sequence as a random effect
- Mean minute ventilation at E_{max} for each treatment was calculated; least squares (LS) mean difference, 95% CI, and *P* values were calculated for each treatment comparison

Results

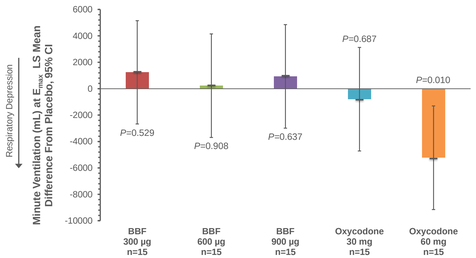
Demographics/Disposition

- A total of 57 subjects were screened, and 19 enrolled; 15 subjects completed the study
- Demographics of enrolled subjects: 18 men, 1 woman; age range, 27 to 42 years; 73.7% white

Primary Measure

- The LS mean difference from placebo in minute ventilation (at E_{max}) for each of the treatments is presented in **Figure 4**
- Oxycodone 60 mg caused significantly greater respiratory depression than placebo did (*P*=0.010)
- No statistically significant differences in respiratory depression (versus placebo) were seen for any of the buprenorphine buccal film doses or for the oxycodone 30-mg dose
- Minute ventilation at E_{max} with oxycodone 60 mg was statistically lower than with all dose strengths of buprenorphine buccal film (300 μg, *P*=0.002; 600 μg, *P*=0.007; 900 μg, *P*=0.003)
- The treatment effect on respiratory drive can also be observed when mean minute ventilation is graphed over time (**Figure 5**)

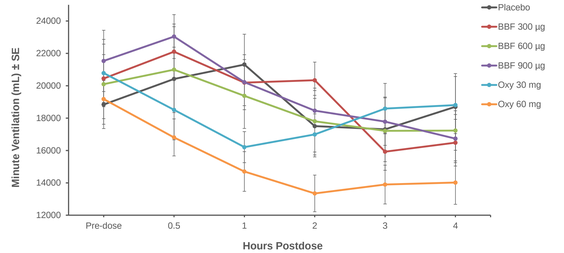
Figure 4. Effect of Each Drug Treatment on Respiratory Drive as Measured by Minute Ventilation LS Mean Difference From Placebo at E_{max}



Abbreviations: BBF, buprenorphine buccal film; E_{max}, maximum decrease in minute ventilation; LS, least squares.

Results (cont'd)

Figure 5. Effect of Each Drug Treatment on Respiratory Drive: Mean Minute Ventilation Over Time



Abbreviations: BBF, buprenorphine buccal film; Oxy, oxycodone hydrochloride; SE, standard error.

Conclusions

- Buprenorphine buccal film did not significantly reduce respiratory drive in healthy volunteers at any dose, including the maximum available prescription dose of 900 μg
- Administration of oxycodone resulted in a dose-dependent decrease in respiratory drive; the reduction in respiratory drive with oxycodone 60 mg was statistically significant, relative to placebo
- No statistically significant differences in respiratory depression (versus placebo) were seen for any dose of buprenorphine buccal film or for oxycodone 30 mg
- These data suggest the risk of respiratory depression with buprenorphine buccal film may be less than that of a full μ-opioid receptor agonist

References

1. Belbuca. Prescribing information. BioDelivery Sciences International, Inc.; 2019.
2. Dahan A, et al. *Br J Anaesth*. 2006;96(5):627-632.
3. Khanna IK and Pillarisetti S. *J Pain Res*. 2015;8:859-870.

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.

Presented at the International Conference on Opioids (ICOO) 2020 Annual Meeting • Virtual • August 2020