Buprenorphine Buccal Film and Oral Oxycodone Hydrochloride: Effects on Pupillometry in a Phase 1 Placebo-Controlled Trial

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Introduction

Background

- The opioid crisis and danger associated with the use of opioids have led to increased scrutiny of prescriptions for chronic pain management
  - Of particular concern is the abuse liability of opioids, which can lead to accidental overdose and potentially death
- Most opioid-related deaths are caused by respiratory depression[1,2]
- Buprenorphine is a partial μ-opioid receptor agonist analgesic[3] that has been shown to exhibit a ceiling effect on respiratory depression, unlike full μ-opioid receptor agonists[4,5]

Purpose

- Buprenorphine is considered to have a lower abuse potential than full μ-opioid receptor agonists and is therefore classified as a Schedule III drug[6]
- However, buprenorphine may induce euphoria in subjects who are not physically dependent on opioids and may be positively reinforcing[7]
- Since previous opioid studies have demonstrated a relationship between drug "liking" and pupil diameter,[8,9] pupillometry was used to assess the effects of buprenorphine buccal film (BBF; BELBUCA®) and oxycodone hydrochloride (a full μ-opioid receptor agonist) on pupil diameter
- This analysis was part of a larger phase 1 placebo-controlled study comparing the effects of BBF and oxycodone on respiratory drive
  - The primary outcome of the study evaluated the maximum decrease in minute ventilation (E_{max}) after the administration of each study drug via the ventilatory response to hypercapnia (VRH) and showed that, relative to placebo, oxycodone decreased respiratory drive in a dose-dependent fashion, whereas BBF did not impact respiratory drive at any of the doses tested

Objective

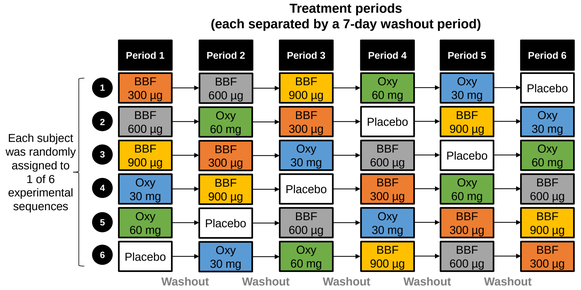
- We hypothesized that both BBF and oxycodone would have pupillary-constricting effects, with oxycodone having more prominent effects

Methods

Study Design

- The effect of each treatment on respiratory drive and pupil diameter was assessed using a double-blind, double-dummy, 6-treatment, 6-period, placebo-controlled, randomized crossover design (**Figure 1**)
  - Subjects were healthy individuals who self-identified as recreational opioid users, which was confirmed with a Naloxone Challenge Test
- Study treatments were placebo; BBF 300 μg, 600 μg, and 900 μg ; and oxycodone 30 mg and 60 mg
  - Each treatment was separated by a 7-day washout period to avoid any potential carryover effects

Figure 1. Study Design



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

Methods (cont'd)

Assessments

- Respiratory drive was evaluated by testing the VRH, which was performed once pre-dose and at 0.5, 1, 2, 3, and 4 hours post-dose
- During VRH testing, pupil diameter was determined with standard pupillometry at the following time points: pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, and 4 hours post-dose

Statistical Analyses

- Statistical analyses were performed using a mixed-effects model with treatment, period, and sequence as fixed effects, and time point and treatment by time point interaction as repeated fixed effects

Results

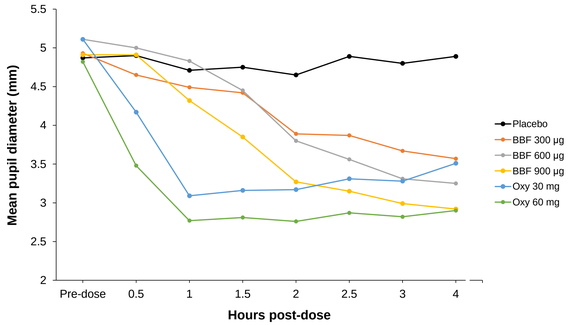
Subject Demographics and Disposition

- A total of 19 subjects were enrolled, and 15 subjects completed the study (16 subjects completed at least 2 treatments)
- Of the 19 subjects enrolled, there were 18 men and 1 woman, ranging in age from 27 to 41 years
- Most (73.7%) of the subjects were white

Pupillometry Outcomes

- For pupillometry, statistically significant miosis was slower to develop with BBF than with oxycodone
  - The initial onset of statistically significant miosis (relative to placebo) occurred at 2 hours, 1.5 hours, and 1 hour after dosing with BBF 300 μg, 600 μg, and 900 μg, respectively; and at 0.5 hours after dosing with oxycodone 30 mg or 60 mg (**Figure 2**)
- Miosis observed with BBF 300 μg was significantly less than that seen with oxycodone 30 mg (at all time points except 4 hours post-dose) and oxycodone 60 mg (at all time points; **Figure 3A**)
- Compared with both oxycodone doses (30 mg and 60 mg), administration of BBF 600 μg resulted in significantly less miosis for up to 2 hours post-dose (**Figure 3B**)
- Similarly, BBF 900 μg led to significantly less miosis than either oxycodone dose did for up to 1.5 hours post-dose (**Figure 3C**)

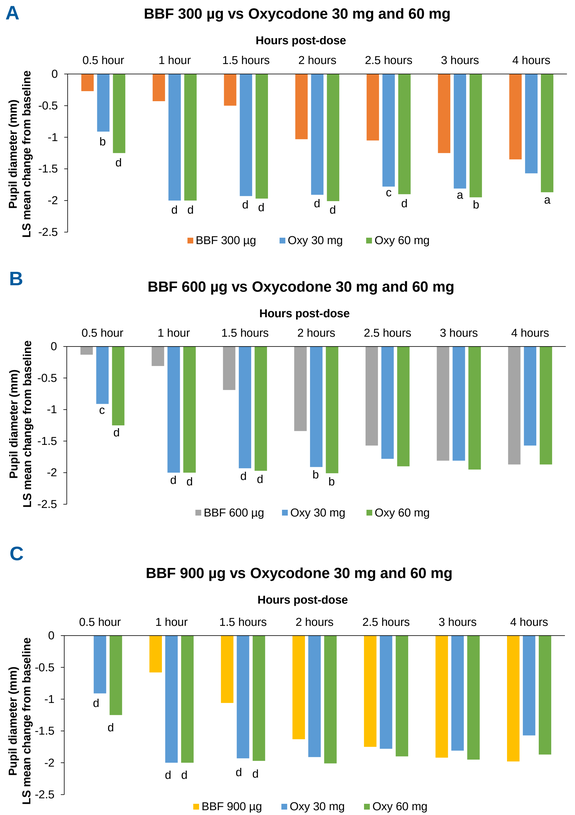
Figure 2. Mean Pupil Diameter in Response to BBF and Oxycodone Administration (n=15)



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

Results (cont'd)

Figure 3. Effects of BBF 300 μg (A), 600 μg (B), and 900 μg (C) vs Oxycodone 30 mg and 60 mg on Pupil Diameter (N=16)



[a]P<0.05, [b]P<0.01, [c]P<0.001, [d]P<0.0001 (*P* values represent differences in LS means between BBF and oxycodone).
Abbreviations: BBF, buprenorphine buccal film; LS, least squares; oxy, oxycodone.

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 μg, 600 μg, or 900 μg)
- Administration of oxycodone 30 mg and 60 mg resulted in a significant dose-dependent decrease in respiratory drive
- The decrease in pupil diameter typically associated with opioid administration occurred earlier after oxycodone administration than after BBF
- Since previous studies have shown a relationship between pupil constriction and drug liking, the delayed miosis found with BBF, relative to that seen with oxycodone, may be indicative of a lower risk of drug liking and abuse potential, at least in the time period immediately following drug administration
- This is also in agreement with the abuse quotient (C_{max}/T_{max}) for BBF (300 μg: 0.17), which is much lower than published estimates for oral oxycodone (30 mg: ~15.1)[10]
- Together, these results may translate to a decreased risk of drug liking and lower abuse potential for BBF compared with full μ-opioid receptor agonists such as oxycodone

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Author Disclosures

- In the last 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, Daiichi Sankyo, Elysium Health, Indivior, KemPharm, Pain Therapeutics, Pernix Therapeutics, 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 Therapeutics, Vallon Pharmaceuticals, and Vector Pharma. **JC** declares no conflicts of interest. **TS** is an employee of BioDelivery Sciences International, Inc.

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