The Pharmacodynamics and Pharmacokinetics of Buprenorphine Buccal Film Versus Oral Oxycodone Hydrochloride: Results of a Phase 1 Placebo-Controlled Trial

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Introduction

Background

- Buprenorphine is a Schedule III atypical opioid that functions as a partial agonist with high binding affinity at the mu-opioid receptor, an antagonist with high binding affinity at the delta- and kappa-opioid receptors, and an agonist with low binding affinity at the nociceptin receptor[1]
- Unlike full mu-opioid receptor agonists (eg, oxycodone), the unique pharmacodynamic and pharmacokinetic properties of buprenorphine contribute to its ceiling effect on respiratory depression[1,2]
- A recent phase 1 placebo-controlled study compared the pharmacologic properties of buprenorphine buccal film (BBF; BELBUCA®, BioDelivery Sciences International, Inc.) with those of the full mu-opioid receptor agonist oxycodone hydrochloride (ClinicalTrials.gov, NCT03996694)[3]

Objective

- The purpose of this study was to assess the pharmacodynamic and pharmacokinetic properties of BBF compared with those of oxycodone

Methods

Study Design

- This was a randomized, double-blind, double-dummy, 6-period, 6-treatment, placebo-controlled, crossover study that compared the effects of BBF (300 µg, 600 µg, or 900 µg) with those of oral immediate-release (IR) oxycodone hydrochloride (30 mg or 60 mg) and matching placebo on respiratory drive in recreational opioid users (**Figure 1**)
- Each treatment was separated by a 7-day washout period to avoid any unintentional carryover effects
- All subjects self-identified as recreational opioid users, which was confirmed prior to randomization with a Naloxone Challenge Test

Pharmacodynamic Assessments

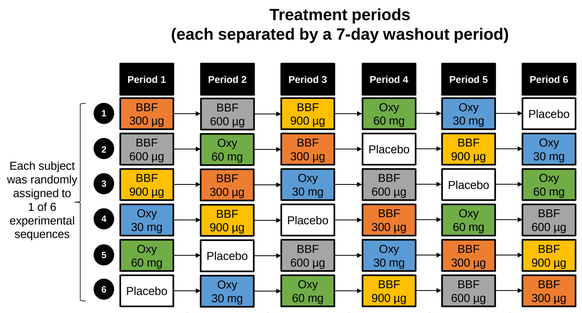
- Pharmacodynamic measures of respiratory drive included the maximum decrease in minute ventilation (primary endpoint) as well as minute ventilation and peak expiratory flow rates over time, which were all measured during a ventilatory response to hypercapnia test

Methods (cont'd)

Pharmacokinetic Assessments

- Maximum observed plasma concentration (C_{max}), time to attain maximum observed plasma concentration (T_{max}), area under the plasma concentration versus time curve from 0 to the last measurable concentration ($AUC_{0\text{-}last}$), and the abuse quotient (AQ; the ratio of C_{max} to T_{max}) were evaluated using blood samples collected pre-dose and at 0.5, 1, 2, 3, 4, and 6 hours post-dose
- Parameters were calculated using non-compartmental methods

Figure 1. Study Design



After subjects completed and passed the screening phase and Naloxone Challenge Test, they were eligible to enter the treatment phase, which was a double-blind, double-dummy, 6-treatment, 6-period, placebo-controlled, randomized, crossover design with each treatment separated by an approximate 7-day washout period.
Abbreviations: BBF, buprenorphine buccal film; oxy, oxycodone.

Results

Subject Demographics

- A total of 19 subjects were enrolled, and 15 (78.9%) completed the study
- Most subjects who completed the study were white males and not of Hispanic or Latino ethnicity (**Table 1**)

Results (cont'd)

Table 1. Summary of Demographics

Category	Completer Population (n=15)
Sex, no. (%)	
Female	1 (6.7)
Male	14 (93.3)
Race, no. (%)	
White	12 (80.0)
Black or African American	1 (6.7)
Asian	1 (6.7)
American Indian or Alaska Native	1 (6.7)
Ethnicity, no. (%)	
Hispanic or Latino	3 (20.0)
Not Hispanic or Latino	12 (80.0)
Age, mean (SD), y	32.9 (4.4)
BMI, mean (SD), kg/m²	25.4 (3.8)

The completer population consisted of all randomized subjects who completed all 6 treatment periods in the treatment phase with a valid maximum decrease in minute ventilation measurement in each completed treatment period.
Abbreviations: BMI, body mass index; SD, standard deviation.

Pharmacodynamic Outcomes

- BBF did not significantly impact any of the pharmacodynamic measures of respiratory drive, including the maximum decrease in minute ventilation (primary endpoint) as well as changes in minute ventilation and peak expiratory flow rates over time, whereas oxycodone decreased each of these parameters relative to placebo

Pharmacokinetic Outcomes

- The C_{max} of BBF and IR oxycodone increased proportionally with dose (**Table 2**)
- IR oxycodone had a faster onset than BBF, as observed with T_{max} (**Table 2**)
- $AUC_{0\text{-}last}$ was numerically higher for oxycodone, but increased proportionally with dose for both study drugs (**Table 2**)
- The AQ for BBF was low and similar between all doses, whereas IR oxycodone had a high AQ that increased more prominently with increasing dose (**Table 2**)

Results (cont'd)

Table 2. Pharmacokinetic Parameters

Parameter	BBF			IR Oxycodone	
	300 µg (n=15)	600 µg (n=17)	900 µg (n=17)	30 mg (n=15)	60 mg (n=16)
C_{max}, mean (SD), ng/mL,	0.4 (0.2)	0.8 (0.9)	1.1 (0.4)	65.8 (19.1)	132 (46.2)
T_{max}, median (min, max), h	2.2 (2.1, 3.2)	3.1 (1.1, 6.0)	2.2 (2.1, 6.0)	1.2 (0.6, 3.2)	1.2 (0.7, 6.0)
$AUC_{0\text{-}last}$, mean (SD), h*ng/mL,	1.8 (1.2)	2.9 (2.5)	4.0 (1.0)	216 (49.4)	435 (141)
AQ, mean (SD), C_{max}/T_{max}	0.2 (0.1)	0.3 (0.2)	0.4 (0.1)	67.4 (39.2)	110 (75.3)

Abbreviations: AQ, abuse quotient; $AUC_{0\text{-}last}$, area under the plasma concentration versus time curve from 0 to the last measurable concentration; BBF, buprenorphine buccal film; C_{max}, maximum observed plasma concentration; h, hours; IR, immediate-release; max, maximum; min, minimum; SD, standard deviation; T_{max}, time to attain maximum observed plasma concentration.

Conclusions

- BBF resulted in a slower absorption and lower AQ than IR oral oxycodone
- Higher AQ is associated with greater drug liking and abuse potential[4]
- Medication selection of atypical opioids with a lower risk of drug liking and abuse potential, such as BBF, should be considered during the current opioid crisis
- These data further support the tolerability of BBF over full mu-opioid receptor agonists for the treatment of chronic pain

References

1. Gudin J and Fudin J. *Pain Ther*. 2020;9(1):41-54.
2. US Department of Health and Human Services. Pain management best practices inter-agency task force report: updates, gaps, inconsistencies, and recommendations. May 9, 2019. Accessed July 11, 2020. https://www.hhs.gov/ash/advisory-committees/pain/reports/index.html.
3. Single dose crossover study to compare the respiratory drive after administration of BELBUCA, oxycodone and placebo. ClinicalTrials.gov identifier: NCT03996694. https://clinicaltrials.gov/ct2/show/NCT03996694. Updated November 18, 2019. Accessed August 12, 2020.
4. Webster LR, et al. *Pain Res Manag*. 2018:7276021.

Author Disclosures

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