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ORIGINAL RESEARCH

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

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ABSTRACT

Introduction: 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. Buprenorphine buccal film (BBF) 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. This study was conducted to compare the effects of BBF and immediate-release oral oxycodone hydrochloride administration on respiratory drive, as measured by the ventilatory response to hypercapnia (VRH) after drug administration.

Methods: Subjects ($N = 19$) were men and women, ages 27–41 years, self-identifying as recreational opioid users who were not physically dependent on opioids as determined via a Naloxone Challenge Test. Respiratory drive was evaluated by measuring VRH through the assessment of the maximum decrease in minute ventilation (E_{max}) after administration of each treatment. The treatments utilized in this study included 300, 600, and 900 μg BBF; 30 and 60 mg orally administered oxycodone; and placebo (each separated by a 7-day washout period). Effects on respiratory drive were assessed using a double-blind, double-dummy, six-treatment, six-period, placebo-controlled, randomized crossover design. Statistical analyses were performed using a linear mixed-effects model.

Results: The least squares mean differences in minute volume E_{max} (L/min, versus placebo) were as follows: 300 μg BBF (+ 1.24, $P = 0.529$), 600 μg BBF (+ 0.23, $P = 0.908$), 900 μg BBF (+ 0.93, $P = 0.637$), 30 mg oxycodone (− 0.79, $P = 0.687$), and 60 mg oxycodone (− 5.23, $P = 0.010$).

Conclusions: BBF did not significantly reduce respiratory drive at any dose compared with placebo, including at the maximum available prescription dose of 900 μg. Administration of oxycodone resulted in a significant dose-dependent decrease in respiratory drive. These data suggest that BBF may be a safer treatment option than full μ-opioid receptor agonists for patients with chronic pain.

Trial Registration: ClinicalTrials.gov identifier, NCT03996694.

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Keywords: Buprenorphine; Buprenorphine buccal film; Hypercapnia; Oxycodone hydrochloride; Pain; Respiratory depression; Respiratory drive

Key Summary Points

Why carry out this study?

Respiratory depression is a leading cause of death due to opioid overdose and is a serious public health concern. We tested the effect of buprenorphine buccal film compared with oxycodone to distinguish the impact of a partial versus a full μ-opioid receptor agonist on respiratory drive

What was learned from the study?

Buprenorphine buccal film did not significantly reduce respiratory drive at any dose compared with placebo

Administration of oxycodone resulted in a significant dose-dependent decrease in respiratory drive

Buprenorphine buccal film may be a safer treatment option than full μ-opioid receptor agonists for patients with chronic pain

INTRODUCTION

Drug-induced respiratory depression is a serious public health concern. In 2015, there were approximately 450,000 drug-related deaths reported globally, and approximately 118,000 deaths were associated with opioid use disorder [1]. The primary cause of death related to opioid overdose is hypoxia caused by opioid-induced respiratory depression [2]. Interaction of opioids with μ-opioid receptors located throughout the central nervous system, including those in the respiratory centers of the brainstem, can cause a reduction in respiratory drive [3]. In addition, opioid treatment can suppress peripheral chemoreceptors, thereby blunting the response to hypoxemia and hypercapnia [3]. The combined suppressive effects of these processes may lead to respiratory depression (the medical outcome that occurs when inadequate ventilation of the lungs decreases the rate of gas exchange) and potential death [3–5].

Buprenorphine is a partial μ-opioid receptor agonist that, unlike full μ-opioid receptor agonists (such as morphine, oxycodone, and fentanyl), has been shown to have a ceiling effect on respiratory depression in studies in which it was administered intravenously [6–8]. Buprenorphine has a lower abuse potential than most other opioids [9] and is therefore classified under the Controlled Substances Act as a Schedule III drug (rather than a Schedule II drug, such as oxycodone) [10].

Buprenorphine buccal film (BBF) has been 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 [11]. The safety and efficacy of BBF for the treatment of chronic pain have been proven in clinical trials; BBF also has comparable analgesic efficacy to Schedule II opioids, while exhibiting a more favorable safety and tolerability profile [12, 13]. In addition, BBF may be preferable compared with other formulations of buprenorphine owing to greater bioavailability and tolerability [13].

Purpose

This randomized, double-blind, placebo-controlled, double-dummy crossover study was conducted to compare the effects of similar analgesic dose ranges of BBF and immediate-release oral oxycodone hydrochloride administration on respiratory drive, as measured by the ventilatory response to hypercapnia (VRH) following drug administration.

METHODS

Subjects

Subjects were healthy individuals self-identifying as recreational opioid users who were determined to not be physically dependent on opioids via a Naloxone Challenge Test. This patient population was recruited to avoid exposing opioid-naive subjects to opioid medications.

A total of 19 subjects were enrolled, and 15 subjects completed the study. 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. The partial completer population consisted of subjects who completed at least two of the study's treatment periods, and the safety population consisted of subjects who have received at least one dose of a study drug.

Study Design

The effect of each treatment on respiratory drive was assessed using a double-blind, double-dummy, six-treatment, six-period, placebo-controlled, randomized crossover design. Treatments included 300, 600, and 900 μg BBF; 30 and 60 mg orally administered oxycodone hydrochloride (immediate release); and matching placebo. Each drug treatment was combined with oral or buccal placebo, as appropriate (double-dummy design). All treatments were separated by a 7-day washout period to avoid any potential carryover effects. Each subject received every treatment once (allowing for subjects to act as their own control) using a computer-generated randomization scheme based on the Williams design (whereby every treatment follows every other treatment at least once; Fig. 1). Each of the treatment sequences presented in Fig. 1 was used for at least two subjects.

Study Schedule and Procedures

The study schedule and procedures are presented in Fig. 2. Screening began no more than 28 days before the first dose of study drug. After completing the informed consent process, subjects underwent the following study-specific screening procedures: physical examination, blood and urine laboratory testing, review of medical and medication history, and a 12-lead electrocardiogram. Subjects also underwent the VRH procedure to determine tolerability and demonstrate adequate VRH. Subjects were checked into the clinic on day −1, pending a negative urine drug screen test. Subjects then underwent a Naloxone Challenge Test (prior to the first treatment only) to exclude the possibility of physical dependence on opioids.

Treatment and assessments with VRH were performed on day 1. Before each dose of study drug, subjects fasted overnight for at least 10 h; fasting continued for 4 h after dosing. Subjects first received the capsule (over-encapsulated oxycodone or placebo), followed by the application of a buccal film (BBF or placebo). A limited number of staff administered the buccal film, were considered unblinded, and were restricted from study conduct except for study drug administration. Subjects were given a physical examination on day 2, adverse events (AEs) were collected, and then subjects were discharged from the clinic. A follow-up call was completed approximately 7 ± 2 days after the final study dose.

Dose Selection

Doses for this study were selected in ranges that are expected to produce similar analgesic effect. The dose range of oxycodone was selected because 30 mg is a high therapeutic dose, and 60 mg may be a dose for acute pain in subjects with opioid tolerance. As there is no known morphine milligram equivalent for BBF [14], it is not known whether 30 mg oxycodone is roughly equivalent in efficacy to 300 μg or 450 μg BBF. However, the range of 300–900 μg BBF is believed to encompass an equivalent range of effectiveness as 30–60 mg oxycodone.

Ventilatory Response to Hypercapnia

The primary endpoint of the study was the evaluation of VRH through assessment of the

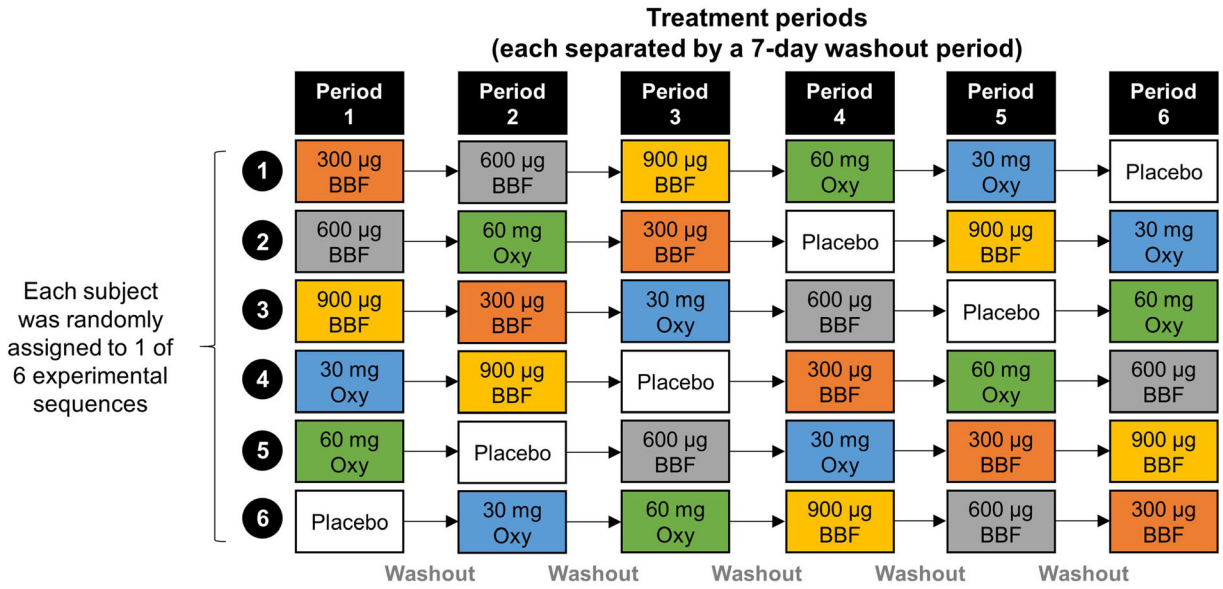

Fig. 1 Subjects were randomly assigned to 1 of 6 computer-generated treatment randomization sequences. *BBF* buprenorphine buccal film, *Oxy* oxycodone

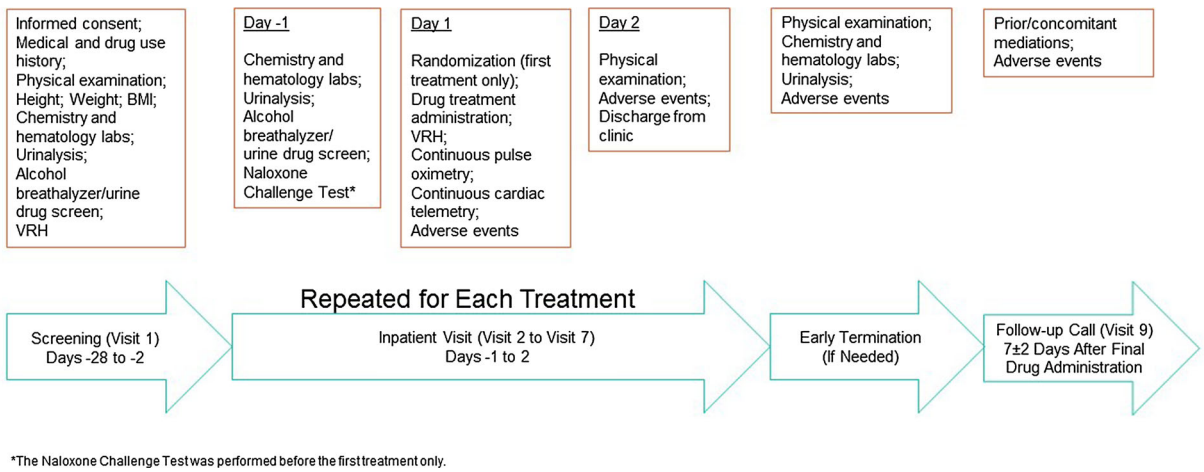

Fig. 2 Study design and procedures. Blood pressure, heart rate, respiration rate, temperature, O_2 saturation, and prior/concomitant medications were collected at all clinic visits; 12-lead ECG was performed at all clinic visits except day 1. *BMI* body mass index, *ECG* electrocardiogram, *VRH* ventilatory response to hypercapnia

maximum decrease in minute ventilation (E_{max}); this allowed for the determination of the effects of each treatment on respiratory drive. The measurement of VRH is a more sensitive way to assess respiratory drive than by simply measuring the partial pressure of CO_2 ($PaCO_2$), O_2 saturation (SpO_2), or minute ventilation alone. Typically, these measures are slow to respond to changes in respiratory drive and individually do not provide adequate or timely indication of respiratory depression [15]. However, the normal increase in minute ventilation resulting from an increase in inspired CO_2 is blunted by the introduction of μ-opioid receptor agonists, which inhibit the response of respiratory centers in the medulla [3]. This can be

measured as a change in minute ventilation. Hypercapnia acts as a stress test for the respiratory system, and VRH measures the capacity of the body to compensate under stress (elevated $PaCO_2$) by altering respiratory drive.

The VRH test was performed with the subjects breathing through a tightly sealed facemask in a hospital bed at a 45° recumbent position (Fig. 3). Pharmacodynamic measurements (expired volume [mL/min]), respiratory rate [breaths/min], and tidal volume [mL], were collected using a pneumotachometer (Hans Rudolph, Inc: Shawnee, Kansas) with acquisition software RSS 100HR. End tidal CO_2 ($ETCO_2$) was collected using a DRE Echo CO_2 capnography monitor (DRE Medical: Louisville, Kentucky).

The VRH assessment was performed once pre-dose and at 0.5, 1, 2, 3, and 4 h post dose. At each timepoint subjects were allowed an acclimation period of room air to establish a regular breathing pattern, followed by introduction of a hypercapnic gas mixture (7% CO_2, 21% O_2, 72% N_2) for a 5-min capture period, unless the subject reached an end-tidal CO_2 of 60 mmHg for three consecutive breaths, in which case the procedure was terminated.

Safety

All AEs and serious AEs (SAEs) encountered during the clinical study were reported in detail from the time the first dose was administered, throughout the clinical conduct, and up to 7 ± 2 days after the last study dose. Prior and concomitant medications were continuously monitored after informed consent was received through the follow-up visit. AEs were followed until they returned to the baseline status or were stabilized, and all clinically significant findings were reported as AEs.

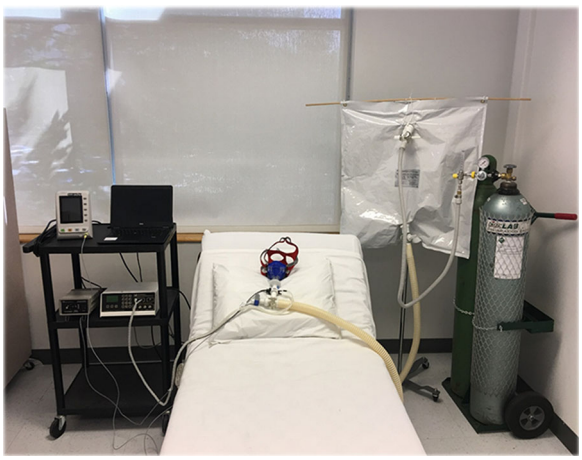

Fig. 3 Ventilatory response to hypercapnia: experimental setting

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 for E_{max} parameters (where E_{max} was computed as the maximum value per subject after study drug administration for each treatment). Mean minute ventilation at E_{max} for each treatment was derived from least squares (LS) means from the statistical model. LS mean differences, 95% confidence intervals, and P values were calculated for each treatment comparison relative to placebo. A similar model was used to assess the difference between each treatment versus placebo at each post-baseline timepoint (where the model also included a fixed-effect term for timepoint).

Ethics

The authors have received approval from an institutional review board (Midlands Independent Review Board, Lenexa, KS). This study was conducted in accordance with the principles and requirements of the Declaration of Helsinki and International Council for Harmonization E6 Guidelines for good clinical practice (European Medicines Agency/Committee for Medicinal Products for Human Use).

All subjects were informed verbally and in writing regarding the objectives, procedures, and risks of study participation. The subjects signed the informed consent form that contained information about the objectives of the study, the procedures followed during the study, and the risks and restrictions of the study, with special reference to possible side

effects of the medication and potential interactions. This study is registered on ClinicalTrials.gov (NCT03996694).

RESULTS

Treatment Effect on Minute Ventilation

The primary endpoint of this study was the LS mean difference from placebo in minute ventilation at E_{max}. Only oxycodone 60 mg significantly decreased E_{max} minute ventilation compared with placebo ($P = 0.010$; Fig. 4, Table 1). There were no statistically significant differences in minute ventilation for any of the BBF doses or oxycodone 30 mg compared with placebo at E_{max}. Minute ventilation at E_{max} for oxycodone 60 mg was significantly lower compared with all dose strengths of BBF (300 µg, $P = 0.002$; 600 µg, $P = 0.007$; 900 µg, $P = 0.003$). The impact of each treatment on respiratory drive can also be observed when mean minute ventilation is graphed over time (Fig. 5). Oxycodone 60 mg exhibited statistically significant decreases (LS mean difference [95% CI] relative to placebo) in minute ventilation at 1 h (− 6.67 [− 10.25, − 3.09] L/min, $P < 0.001$), 2 h (− 3.60 [− 7.12, − 0.07] L/min, $P = 0.045$), and 4 h (− 4.40 [− 7.92, − 0.88] L/min, $P = 0.014$) post dose. Oxycodone 30 mg exhibited a statistically significant decrease (LS mean difference [95% CI] relative to placebo) in minute volume at 1 h post dose (− 5.01 [− 8.66, − 1.36] L/min, $P = 0.007$). Mean minute ventilation for BBF was not statistically different from placebo at any dose for any timepoint.

The different effects of oxycodone and BBF on respiratory drive are also evident when mean minute ventilation is graphed versus $ETCO_2$ (see Appendix I, Fig. S1 in the electronic supplementary material for an example from one subject). Oxycodone 60 mg depressed respiratory drive, resulting in a decrease in minute ventilation and a concomitant increase in $ETCO_2$.

Safety

A summary of treatment-emergent AEs (TEAEs) for the safety population (defined as all enrolled

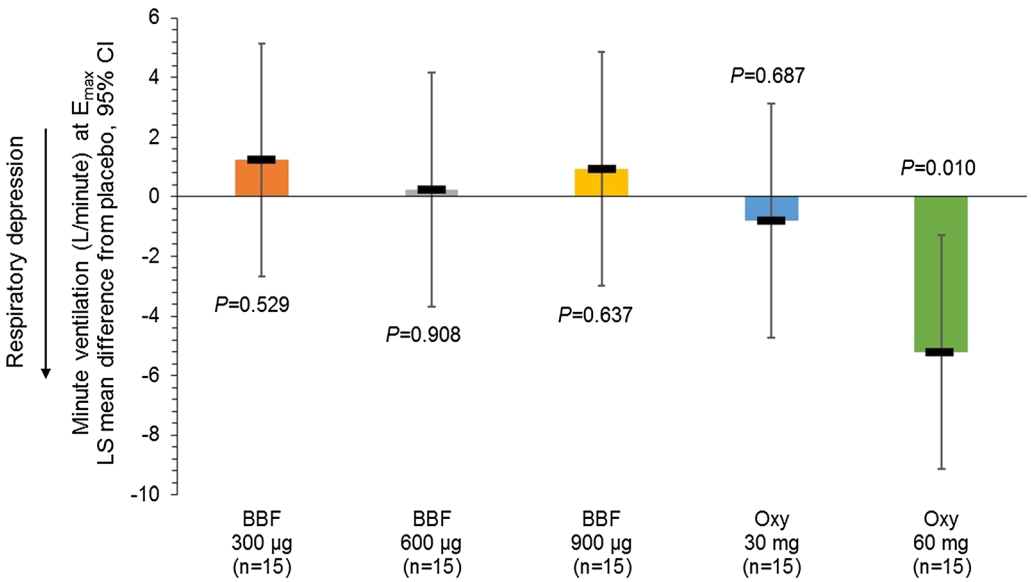

Fig. 4 Effect of each drug treatment on respiratory drive as measured by minute ventilation LS mean difference from placebo (± 95% CI) at E_{max}. In the completer population ($N = 15$), only oxycodone 60 mg significantly reduced minute ventilation at E_{max}. Horizontal black bars represent the means. *BBF* buprenorphine buccal film, E_{max} maximum decrease in minute ventilation, *LS* least squares

Table 1 Summary of least squares mean differences in minute volume at E_{max} for all treatment comparisons

Test	References (mg)	Least squares mean difference (test − reference)						
		Estimate	Standard error	Degrees of freedom	*t*	95% CI	*P* value	Effect size[a]
Oxycodone 30 mg	Placebo	− 0.79	1.96	65	− 0.40	(− 4.72, 3.13)	0.687	0.10
Oxycodone 60 mg	Placebo	− 5.23	1.96	65	− 2.66	(− 9.15, − 1.31)	0.010	0.69
BBF 300 µg	Placebo	1.24	1.96	65	0.63	(− 2.67, 5.15)	0.529	0.16
BBF 600 µg	Placebo	0.23	1.96	65	0.12	(− 3.70, 4.15)	0.908	0.03
BBF 900 µg	Placebo	0.93	1.96	65	0.47	(− 2.99, 4.85)	0.637	0.12
BBF 300 µg	Oxycodone 30	2.03	1.96	65	1.04	(− 1.89, 5.96)	0.304	0.27
BBF 300 µg	Oxycodone 60	6.47	1.96	65	3.29	(2.55, 10.39)	0.002	0.85
BBF 600 µg	Oxycodone 30	1.02	1.96	65	0.52	(− 2.89, 4.94)	0.604	0.13
BBF 600 µg	Oxycodone 60	5.46	1.96	65	2.78	(1.53, 9.38)	0.007	0.72
BBF 900 µg	Oxycodone 30	1.73	1.96	65	0.88	(− 2.20, 5.65)	0.383	0.23
BBF 900 µg	Oxycodone 60	6.16	1.96	65	3.14	(2.25, 10.07)	0.003	0.81

BBF buprenorphine buccal film

[a] Effect size was calculated as the mean difference for each pairwise comparison (test − reference least squares mean) divided by the standard deviation of the difference. The standard deviation of the difference is calculated as the square root of the mean square error from the crossover model multiplied by the square root of 2 ($\sqrt{MSE} \times \sqrt{2}$)

subjects receiving at least one dose of a study drug, $N = 19$) is presented in Table 2. There were no deaths or SAEs. One subject discontinued as a result of an AE that was judged likely to be related to the study drug (BBF 600 µg, moderate intermittent idioventricular rhythm). More AEs were usually reported when subjects received higher doses of both medications. The most common TEAEs for BBF and oxycodone were nausea, vomiting, somnolence, euphoric mood, dizziness, and pruritus.

DISCUSSION

Respiratory Depression

There is no standard definition of respiratory depression. In general, it is a reduction in ventilation leading to a failure to maintain normal pulmonary exchange of CO_2 and O_2. With respiratory depression, there is an inadequate response to hypercapnia or hypoxia resulting in increased CO_2 and/or decreased O_2 blood levels [16]. The relationship between $PaCO_2$ and ventilation is shown in Fig. 6. The National Heart,

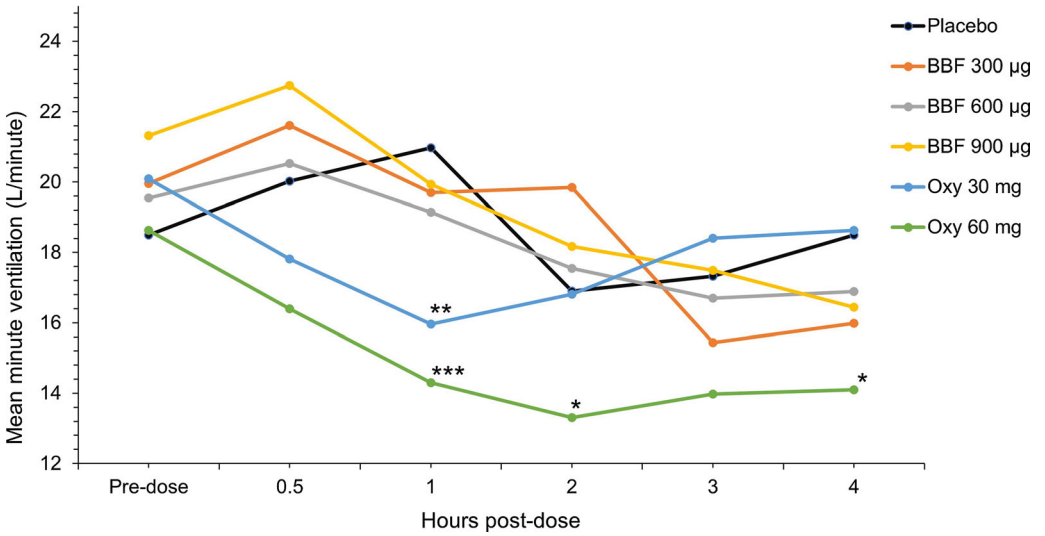

Fig. 5 Effect of each drug treatment on respiratory drive: mean minute ventilation over time. In the partial completer population ($N = 16$), mean minute ventilation for BBF was not significantly different from placebo at any timepoint. *BBF* buprenorphine buccal film, *Oxy* oxycodone. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$

Lung, and Blood Institute Acute Respiratory Distress Syndrome Network suggests a cutoff of 40% of normal baseline minute ventilation to indicate inadequate ventilation. Some studies use a minute ventilation volume of less than 40% predicted to indicate an "unsafe" level of respiratory depression [17]. Opioid-induced respiratory depression follows a relatively consistent pattern: a progressive rise in the $PaCO_2$ (and $ETCO_2$) and a fall in peripheral capillary SpO_2 over the course of minutes to hours [15]. This highlights a potential issue with current methods for accurately identifying respiratory depression in the clinical setting. Individual measurements of $PaCO_2$, SpO_2, and respiratory rate can remain relatively normal even as respiratory depression gets progressively worse [15]. In this study, VRH was utilized to assess decreases in respiratory drive under stressed conditions. VRH challenges the respiratory system and reveals potentially unsafe decreases in respiratory drive resulting from exposure to clinical doses of opioids.

In a clinical setting, opioids are useful analgesics, but most are known to reduce respiratory drive in a dose-dependent manner. They reduce the responsiveness of respiratory centers to increased CO_2 such that minute ventilation increases that would normally be triggered by hypercapnia are depressed [4]. This reduction in respiratory drive may increase the probability of respiratory depression and potential death in cases of opioid overdose [4]. In this study, administration of oxycodone resulted in a dose-dependent decrease in respiratory drive. The reduction in respiratory drive with oxycodone 60 mg (relative to placebo) was statistically significant ($P = 0.010$), and the reduction in respiratory drive with oxycodone 30 mg was statistically significant at 1 h post dose ($P = 0.007$). In comparison, none of the BBF doses significantly reduced respiratory drive, even at the maximum prescribing dose.

In previous clinical studies, BBF has been shown to be an effective analgesic, with no reported AEs related to respiratory depression [12, 19, 20]. In addition, unlike other Schedule II full μ-opioid receptor agonists, previous experimental studies have demonstrated a ceiling effect on respiratory depression with intravenous buprenorphine administration [6, 7]. This is likely due to buprenorphine having a unique mechanism of action consisting of partial agonism at the μ-opioid receptor, antagonism at the κ- and δ-opioid receptors, and agonism at opioid-receptor like 1, potentially

Table 2 Summary of treatment-emergent adverse events (safety population)

	BBF 300 µg (*N* = 15) *N* (%)	**BBF 600 µg (*N* = 17) *N* (%)**	**BBF 900 µg (*N* = 17) *N* (%)**	**Oxy 30 mg (*N* = 15) *N* (%)**	**Oxy 60 mg (*N* = 16) *N* (%)**	**Placebo (*N* = 16) *N* (%)**
Number of TEAEs	10	28	30	19	45	2
Subjects with at least one TEAE	8 (53.3)	12 (70.6)	12 (70.6)	9 (60.0)	14 (87.5)	2 (12.5)
Discontinuation due to an AE	0	1 (5.9)	0	0	0	0
Most common TEAEs[a]						
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						
Pruritus	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)

AE adverse event, *BBF* buprenorphine buccal film, *Oxy* oxycodone, *TEAE* treatment-emergent adverse event
[a] TEAEs experienced by ≥ 2 subjects are listed

limiting classic opioid-related AEs such as respiratory depression [21]. The results presented here extend these findings to the buccal formulation of buprenorphine when used in a clinical setting. Other factors that might have contributed to the observed effects include route of administration, dose, and study population.

Safety

This was a small, well-controlled study with only 19 subjects in the safety population. There were no SAEs or deaths. Overall, the percentage of subjects who experienced an AE was similar across treatments, but several TEAEs were numerically higher for oxycodone 60 mg compared with all BBF doses, including vomiting, somnolence, and pruritus. However, larger clinical studies are needed to provide a broader safety profile of the medications tested, beyond the effects of BBF and oral oxycodone administration on respiratory drive observed in this study.

Limitations

Although this was a small phase I study, the data were collected under tightly controlled conditions (inpatient, with a standard

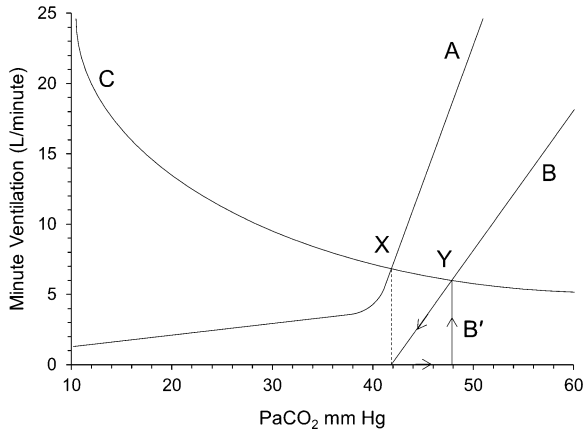

Fig. 6 Relationship between ventilation and $PaCO_2$. Curve A represents the normal CO_2 response of an awake individual. Line B represents the CO_2 response following administration of a sedative or anesthetic medication (sufficient decrease in $PaCO_2$ can result in apnea). Once apnea develops, $PaCO_2$ must increase to approximately the resting value before ventilation restarts (line B′, a hysteresis loop). Curve C represents the carbon dioxide excretion hyperbola. Assuming constant CO_2 production in the body, increasing ventilation will decrease $PaCO_2$, whereas decreasing ventilation tends to increase $PaCO_2$. In the awake state, point X defines the resting $PaCO_2$ and ventilation, whereas point Y represents the values of $PaCO_2$ and ventilation during sedation or anesthesia. *$PaCO_2$* partial pressure of CO_2 Figure reproduced with permission from Jeffrey B. Gross; When You Breathe IN You Inspire, When You DON'T Breathe, You … Expire: New Insights Regarding Opioid-induced Ventilatory Depression. Anesthesiology 2003;99(4):767–770 [18]

methodology), and subjects acted as their own control such that every subject received each dose of each medication and placebo. The subjects who were selected for recruitment into this study were self-reported recreational opioid users, partly because it could be safely assumed that they would be able to tolerate opioid administration. It is known that tolerance to respiratory depression does develop in individuals taking opioids [22], but the subjects in the present study were shown to not be physically dependent on opioids, as determined by a Naloxone Challenge Test. In addition, any possible effects of tolerance on opioid-related respiratory depression would have had no effect on the comparison between treatments because each subject acted as his or her own control.

It should be noted that these subjects were relatively young, healthy, non-obese, and without serious comorbid conditions. Thus, they may have been less susceptible to any potential effects on respiratory drive than elderly patients or patients with serious comorbid conditions who may be taking these drugs to relieve chronic pain. Also, the subjects selected for this study were not taking multiple drugs (other than for TEAEs) and were also fully alert/not sedated. It is likely that many patients taking opioids for chronic pain may have underlying comorbid conditions that require multiple medications, which potentially increases the likelihood of opioid-induced respiratory depression, especially during sleep.

CONCLUSIONS

In our study consisting of healthy individuals, administration of BBF (even at the highest available dose of 900 μg) did not result in a significant decrease in respiratory drive compared with placebo. However, administration of oxycodone significantly decreased respiratory drive in a dose-dependent fashion, compared with placebo. These data indicate that the risk of respiratory depression using BBF may be less than that of a full μ-opioid receptor agonist and suggest that BBF may be a safer treatment option for patients with chronic pain.

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Prior Presentation. The results presented in this article were presented at the American Academy of Pain Medicine (AAPM) annual meeting held in National Harbor, MD, on February 26 – March 1, 2020.

Disclosures. In the previous 3 years, Dr. Lynn Webster has received consultation, advisory board, and travel fees from Charleston Labs, Depomed, Egalet, Insys Therapeutics, Mallinckrodt Pharmaceuticals, Pfizer, Teva, and Trevena; consultation and travel fees from Alcobra, Bonti, Daiichi Sankyo, Elysium, Indivior, KemPharm, Pain Therapeutics, 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. Dr. Thomas Smith is an employee of BioDelivery Sciences International, Inc. Dr. Erik Hansen and Dr. Jacqueline Cater have nothing to disclose. Dr. Erik Hansen's present affiliation is with KalVista Pharmaceuticals, Inc., Cambridge, MA.

Compliance with Ethics Guidelines. The authors have received approval from an institutional review board (Midlands Independent Review Board, Lenexa, KS). This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. All subjects provided informed consent to participate in this study. This study is registered on ClinicalTrials.gov (NCT03996694).

Data Availability. All data generated or analyzed during this study are included in this published article/as supplementary information files.

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