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

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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.
- 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.

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, placebo-controlled, crossover design.
- Treatments were 300, 600, and 900 μg buprenorphine buccal film; 30 and 60 mg oral oxycodone hydrochloride; and placebo (each separated by a 7-day washout period), as demonstrated in Figure 1.
- Each subject received every treatment in a 1:1:1:1:1:1 order, 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).

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
- 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% CO2, 21% O2, 72% N2) for a 6-minute cycle.
- 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.

Minute Ventilation as a Function of End-Tidal CO2 at 2 Hours Postdose for Each Treatment (Single Subject)

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 Emax 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 (E1-max) for each of the treatments is presented in Figure 4.
- Oxycodone 60 mg caused significantly greater respiratory depression than placebo (P=0.005).
- 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 Emax 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 effect on respiratory drive can also be observed when mean minute ventilation is graphed over time (Figure 5).

Results (cont’d)

Conclusions
- Buprenorphine buccal film did not significantly reduce respiratory depression 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 20 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

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