Pharmacokinetic and Pupillometry Outcomes from a Phase 1 Placebo-controlled Trial to Compare the Effects of Buprenorphine Buccal Film and Oral Oxycodone Hydrochloride

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Introduction

• The opioid crisis has led to increased concern about the safety of opioids administered for chronic pain, especially regarding abuse and respiratory depression associated with death.

• As a partial opioid receptor agonist, buprenorphine has unique properties that distinguish it from full µ opioid receptor agonists.

• Buprenorphine is classified as a Schedule III drug because it has a lower abuse potential than full µ opioid receptor agonists.

• Buprenorphine buccal film (BELBUCA®) is approved by the US Food and Drug Administration for use in patients with pain severe enough to require daily, around-the-clock, long-term opioid treatment and for whom alternate treatment options are inadequate.

• In this phase 1 study, evaluation of the primary endpoint revealed immediate-release oxycodone administration led to a significant, dose-dependent decrease in respiratory drive, whereas BELBUCA did not (ClinicalTrials.gov Identifier: NCT03996694).

• The pharmacokinetic and pupillometry outcomes presented here were chosen because of their relevance for respiratory safety and potential risk for abuse.

• As expected, time to Cmax was higher for immediate-release oxycodone than BBF.

• Significant miosis occurred faster for immediate-release oxycodone than BBF.

Methods

Population and Treatments
• The study included healthy individuals who self-identified as recreational opioid users and who were not dependent on opioids as confirmed by a Naloxone Challenge Test on day –1.

• Study treatments (Figure 1):
  – Placebo
  – 30 µg, 100 µg, and 300 µg BBF
  – 60 mg and 60 mg oral immediate-release oxycodone

Study Design
• For the 2 drugs, the choice was based on calculations for equipotency.

• In a randomized, double-blind, double-dummy, 6-period, 6-period, placebo-controlled crossover design, 17 study participants were performed between treatments (Figure 1).

• This study design was chosen to minimize variability by allowing each subject to serve as their own control.

• An institutional review board approved the study protocol.

Assessments
• Respiratory drive was evaluated by ventilatory response to hypercapnia.

• Blood samples were collected for pharmacokinetic analysis.

• Pupil diameter was measured with standardized pupillometry via the NeuroOptics VPH-200 pupillometer.

• An institutional review board approved the study protocol.

Results

• A total of 19 subjects were enrolled; 15 subjects completed the study (Table 1).

Table 1. Subject Demographics and Disposition

<table>
<thead>
<tr>
<th>Subjects, No.</th>
<th>Enrolled</th>
<th>Partial completers*</th>
<th>Completers</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>33.4 (4.8)</td>
<td>32.3 (4.8)</td>
<td>32.9 (4.4)</td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>16 (97.7)</td>
<td>15 (96.7)</td>
<td>14 (92.9)</td>
</tr>
<tr>
<td>Race, No. (%)</td>
<td>18 (94.7)</td>
<td>14 (86.7)</td>
<td>13 (86.7)</td>
</tr>
<tr>
<td>White</td>
<td>14 (77.8)</td>
<td>13 (83.3)</td>
<td>12 (80.0)</td>
</tr>
<tr>
<td>Black or African Americans</td>
<td>2 (11.1)</td>
<td>2 (12.5)</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td>Asian</td>
<td>2 (11.1)</td>
<td>1 (6.3)</td>
<td>1 (6.3)</td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>2 (11.1)</td>
<td>1 (6.3)</td>
<td>1 (6.3)</td>
</tr>
<tr>
<td>Weight, mean (SD), kg</td>
<td>76.5 (15.9)</td>
<td>79.3 (16.2)</td>
<td>80.6 (16.7)</td>
</tr>
<tr>
<td>Height, mean (SD), cm</td>
<td>171.4 (8.7)</td>
<td>174.3 (8.7)</td>
<td>174.3 (8.7)</td>
</tr>
<tr>
<td>BMI, mean (SD), kg/m²</td>
<td>24.9 (3.7)</td>
<td>25.1 (3.3)</td>
<td>25.3 (3.6)</td>
</tr>
</tbody>
</table>

*Subjects who completed ≥ 80% of study treatment.

• Mean AQ (Cmax) ranged from 0.4 to 3.2 for BBF and 6.7 to 11.0 for immediate-release oxycodone (Table 2).

Table 2. Plasma Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BBF (n=17)</th>
<th>Oral IR oxycodone (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax, ng/mL</td>
<td>3.4 (0.2)</td>
<td>6.5 (1.9)</td>
</tr>
<tr>
<td>Tmax, median (min, max)</td>
<td>2.2 (1.1, 2.3)</td>
<td>2.2 (1.1, 2.3)</td>
</tr>
<tr>
<td>AUC, Cmax, (ng × min)/mL</td>
<td>0.0 (3.9)</td>
<td>0.0 (3.9)</td>
</tr>
</tbody>
</table>

*Analyses were performed using a linear mixed-effects model with treatment, period, and sequence as fixed effects and time point as a random effect.

• Significant miosis was observed later after BBF administration, compared with immediate-release oxycodone (Figure 2).

Conclusions

• The secondary outcomes of this study showed that pharmacokinetics of immediate-release oxycodone and BBF differed significantly in recreational opioid users.

• Cmax was highest, Tmax was faster, and AUC was higher for immediate-release oxycodone than for estimated equianalgesic doses of BBF.

• Significant miosis occurred faster for immediate-release oxycodone than BBF.

• Results from this study suggest that a single dose of BBF may have lower risks of drug liking and abuse compared with a single dose of the full µ-receptor agonist, immediate-release oxycodone.

References


Author Disclosures

All authors disclose no conflict of interest.

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