INTRODUCTION

CR845, a new therapeutic agent, is being investigated for its potential as a kappa opioid receptor agonist (KORA). It exhibits analgesic effectiveness in clinical studies of acute and chronic pain.

Although the analgesic activity of CR845 has been recognized for more than 10 years, its development has been hampered due to central nervous system (CNS) mediated adverse events, in particular dysphoria and hallucinations.

CR845’s intrahippocampal injection study indicates its entry into the brain, and thus CR845 should be devoid of the centrally mediated adverse effects observed with other opioids.

Preclinical and clinical studies were undertaken to determine whether CR845 would transform the drug’s potential for abuse in humans. We investigated whether CR845 would generalize to the discriminative cue elicited in rats by (-)-pentazocine, a mixed kappa/delta-opioid receptor agonist and mu partial agonist.

The ability of CR845 to serve as a positive reinforcer was also evaluated in rats that had been trained to self-administer a dose of heroin.

The results supported the conclusion that CR845 was not a sigma agonist. The positive discriminative stimulus effects observed for CR845 were not consistent with a sigma agonist effect.

METHODS

30 female Sprague-Dawley rats were trained to discriminate between saline and solutions containing Butorphanol (1 mg/kg iv), CR845 (15 mcg/kg iv), or (-)-pentazocine (25 mg/kg iv). CR845 was administered in the peak phase of the discriminative stimulus (drug cue).

RESULTS

Clinical

44 recreational polydrug users (18 to 55 years old) who were experienced in the use of drugs of abuse were enrolled in a 4-way crossover study assessing the abuse potential of CR845.

Preclinical

30 female Sprague-Dawley rats were trained to discriminate between saline and solutions containing Butorphanol (1 mg/kg iv), CR845 (15 mcg/kg iv), or (-)-pentazocine (25 mg/kg iv).

CONCLUSIONS

All together, these studies did not identify a significant potential of CR845 for drug-seeking behavior relative to the CNS active mixed kappa/mu comparator, (-)-pentazocine. This study was funded by Cara Therapeutics, Inc.

In agreement with these findings, pentazocine showed old pharmacological activity (ie, pupillary constricted), whereas CR845, like placebo, produced no evidence of pupil constriction (Figure 6).

Table 3. Summary Results in MITT Population

| CR845 15 mcg/kg (n=40) | Placebo (n=41) | p Value
|-------------------------|----------------|--------|
| CR845 50 mg/kg (n=40) | Placebo (n=41) | p Value
| CR845 100 mg/kg (n=40) | Placebo (n=41) | p Value
| CR845 150 mg/kg (n=40) | Placebo (n=41) | p Value
| CR845 200 mg/kg (n=40) | Placebo (n=41) | p Value

* = p ≤ 0.0001 compared with placebo.

For the highest dose tested in the drug-discrimination test (0.5 mg/kg iv), the maximal plasma concentration (Cmax) of CR845 was 1127 ± 61.1 ng/mL.

The plasma exposure to CR845 produced by the various doses of the drug tested in the model ranged between 2.0% and 200% of the Cmax at the highest dose tested clinically (0.04 mg/kg).

The plasma concentration of CR845 at 8 hours after the last dose was 1750 ± 390.4 ng/mL.

The drug-discrimination test was conducted in a group of 37 rats that had previously been trained to self-administer (-)-pentazocine (1 mg/kg iv) and displayed a stable pattern of responding.

Figure 1. Dose-Response Function for Drug-Likability: Discriminative Stimulus Elicited by (-)-Pentazocine and CR845

Figure 2. Effect of Intravenous Administration of (-)-Pentazocine, Butorphanol, and CR845 in Rats Trained to Discriminate Between 1 mg/kg of Butorphanol (Control) or 15 mcg/kg CR845 (n=6 rats/group).

Figure 3. Dose-Response Function for Drug-Likability: Discriminative Stimulus Elicited by (-)-Pentazocine and CR845

Figure 4. Pentazocine Has Significantly Higher Drug-Liking Than Either Dose of CR845

Figure 5. Drug Liking vs. Scores

Figure 6. Effect of Treatment on Pupil Diameter in MITT Population

Table 1. Maximal Plasma CR845 Concentrations (Cmax) in the Drug Discrimination Experiment in Lister Hooded Rats

| CR845 Dose (mg/kg/infusion iv) | Cmax (ng/mL) | Mean±SEM | p Value
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<tr>
<td>CR845 0.04</td>
<td>1760 ± 113.6</td>
<td>2.0% Cmax</td>
<td>0.01</td>
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<tr>
<td>CR845 0.125</td>
<td>2487 ± 159.5</td>
<td>100% Cmax</td>
<td>&lt;0.001</td>
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| CR845 0.250 | 200% Cmax | 0.125 mg/kg/infusion iv CR845 produced by the various doses of the drug tested in the model ranged between 2.0% and 200% of the Cmax at the highest dose tested clinically (0.04 mg/kg). The plasma concentration of CR845 at 8 hours after the last dose was 1750 ± 390.4 ng/mL.

Table 2. Mean Number of Infusions per 2-hour Test Session Obtained during the Last 2 Days of Drug-Discrimination Testing

| CR845 Dose (mg/kg/infusion iv) | Mean Number of Infusions/session | p Value
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<tbody>
<tr>
<td>CR845 0.04</td>
<td>25.7 ± 3.3</td>
<td>0.01</td>
</tr>
<tr>
<td>CR845 0.125</td>
<td>18.3 ± 2.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CR845 0.250</td>
<td>14.5 ± 2.0</td>
<td>&lt;0.0001</td>
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ACKNOWLEDGEMENTS

The authors thank in particular the MITT population patients and all partners and investigators for their contributions to this study. This study was funded by Cara Therapeutics, Inc.

DISCLOSURES

The authors report no conflicts of interest.

Presented at PAINWeek 2016; September 6–10, 2016, Las Vegas, NV.