Respiratory Effects of IV CR845 - A Peripherally Acting, Selective Kappa Opioid Receptor Agonist

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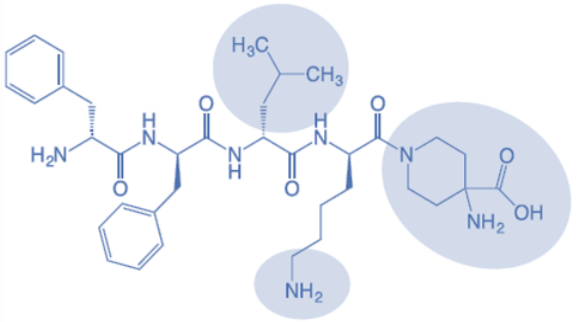
Opioid Analgesics and Respiratory Depression

- Mu opioid receptor agonists are commonly used to treat post-surgical and other acute pain: morphine, hydrocodone, fentanyl, etc.
- Mu opioid agonists are often abused due to centrally-mediated euphoria
- Opioid-induced respiratory depression is the leading cause of death following overdose[1]
- Kappa opioid receptor agonists have analgesic properties[2,3]
  - Centrally-mediated dysphoria has limited their development[3]

1-White, J.M. and Irvine, R.J. Addiction. 1999; 94: 961-72
2-Kivell, B. and Prisinzano, T.E. Psychopharmacology (Berl.). 2010; 210: 109-19
3-Vanderah, T.W. et al. Eur. J. Pharmacol. 2008; 583: 62-72

CR845 (difelikefalin)

- **Peripherally restricted, highly selective kappa opioid receptor agonist**
  - Peptidic structure restricts entry into the CNS[1]
  - Minimizes potential for adverse events mediated by central opioid receptors



- **In development for treatment of pain and pruritus[2,3]**

- **3 double-blind, placebo-controlled clinical trials of treatment of post-operative pain[2,4,5]**
  - Statistically significant analgesic response compared to placebo
  - No changes in arterial oxygen saturation were observed using pulse oximetry
  - Pulse-oximetry does not measure ventilation and may be limited in recognizing early signs of respiratory depression

1- Vanderah, T.W. et al. Eur. J. Pharmacol. 2008; 583: 62-72; 2- Stauffer, J.W. et al. PAINWEEK, Las Vegas,NV, September 8-12, 2015; 3- Spencer, R.H. et al. American Society of Nephrology Kidney Week 2015 Annual Meeting, San Diego, CA, November 5-8, 2015; 4-Menzaghi, F. et al. International Association for the Study of Pain, Montreal, Canada; 5- Stauffer, J.W. et al. CR845 American Society of Anesthesiologists Annual Meeting, San Diego, CA, 2015

CR845 and Respiratory Depression – Study Design

- Single-center, double-blind, randomized, placebo controlled, 3-way crossover study

- Healthy adult non-smoking volunteers
  - Key exclusion criteria included: self-reported substance abuse in prior 2 years, opioid use in past 30 days, history of pulmonary or cardiac disease or dysfunction, history of sleep disorder breathing

- Treatments – All administered as intravenous bolus
  - A: Placebo
  - B: CR845 1 µg/kg
  - C: CR845 5 µg/kg

- Subjects randomized to 1 of 3 treatment sequences
  - ABC
  - BCA
  - BAC

CR845 and Respiratory Depression – Study Design (cont.)

- **Measurements**
  - Respiratory rate
  - End tidal CO_2 ($ETCO_2$, mmHg)
  - Peripheral capillary oxygen saturation (SpO_2, %), measured by pulse oximetry

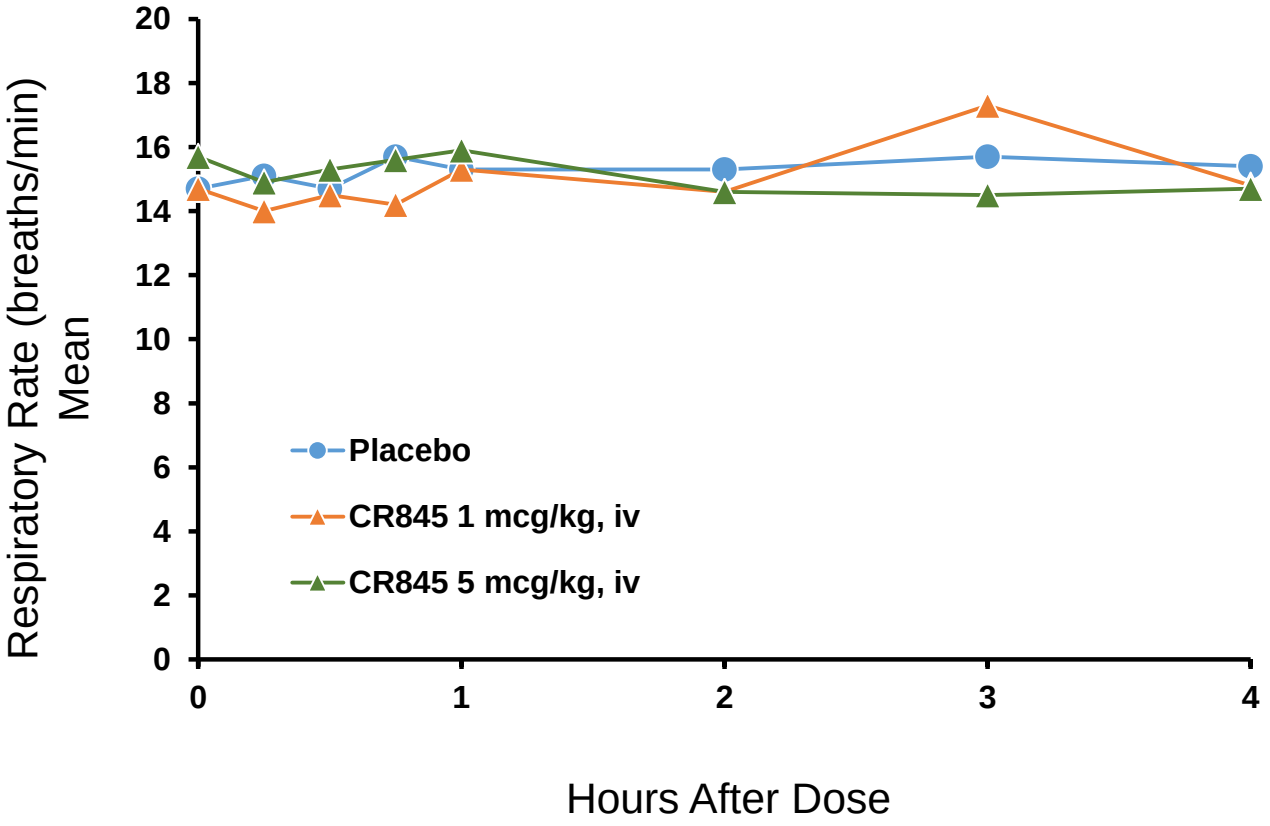
- **Definition of Respiratory Depression Events**
  - Increased $ETCO_2$ of ≥10 mmHg compared to baseline or to a level >50 mmHg (sustained for at least 30 sec)
  - Reduction in SpO_2 to <92% (sustained for at least 30 sec)
  - Reduction in respiratory rate to <10 breaths per minute or by 30% compared with baseline (sustained for at least 30 sec)

Subject Demographics

Parameter	
Subjects (n)	15
Male	11
Female	4
Race (n)	
White	6
African American	6
Asian	3
Age (years)[a]	38.3 ± 7.8
Body weight (kg)[a]	77.7 ± 8.9
BMI (kg/m2)[a]	25.6 ± 2.4

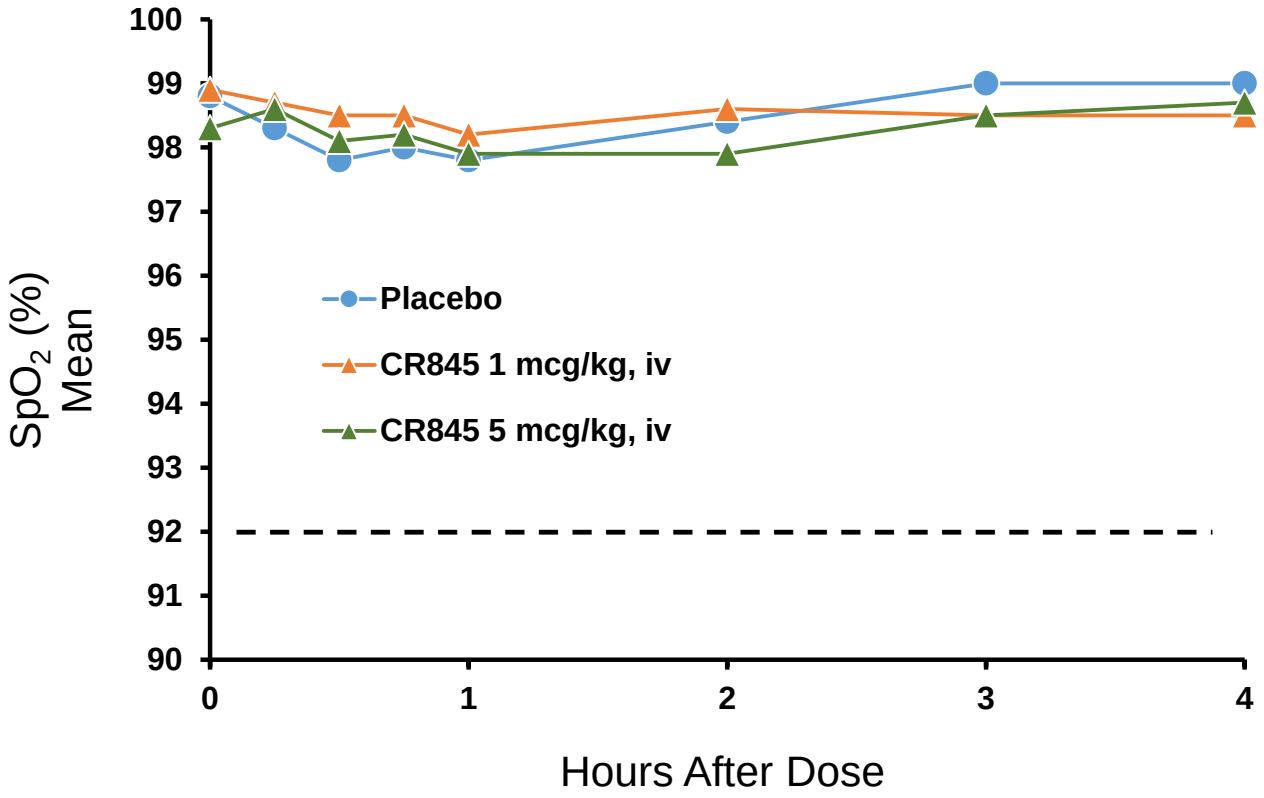
[a] mean ± SD

Observed Respiratory Rate



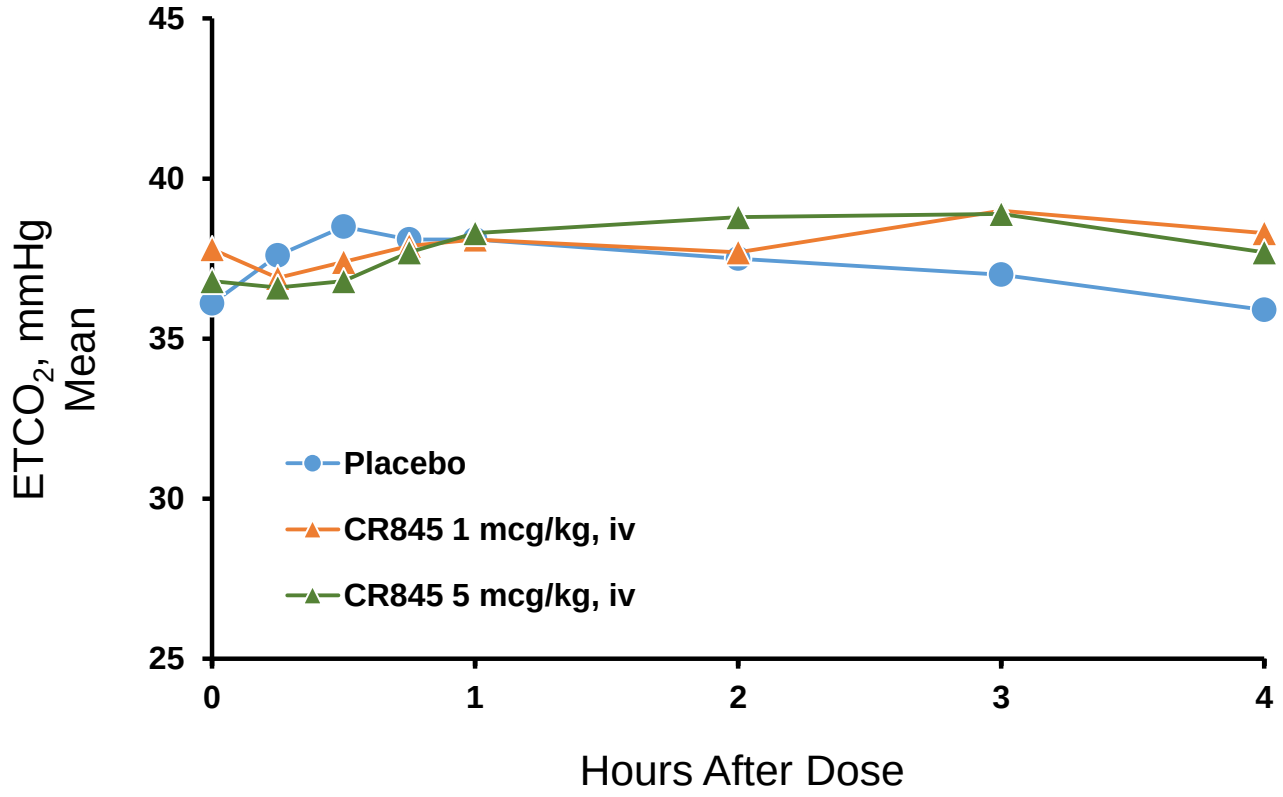
- **No incidence of a respiratory rate <10 breaths per minute or to a level 30% below baseline rate sustained for 30 seconds was seen in any subject**

Observed Oxygen Saturation (SpO_2)



- **No incidence of reduction in SpO_2 to below 92% for 30 sec duration was seen in any subject**

Observed End Tidal CO_2



- **No incidence of increased ETCO2 ≥10 mmHg from baseline or to a level >50 mmHg sustained for ≥30 seconds was seen in any subject**

Safety: Treatment-related Adverse Events Reported in ≥10% of Subjects

Treatment-related Adverse Event (TRAE)	Placebo N=15	CR845 1 mcg/kg N=15	CR845 5 mcg/kg N=15
Any TRAE	3 (20%)	12 (80%)	12 (80%)
Paraesthesia	1 (7%)	5 (33%)	9 (60%)
Hypoaesthesia	0	3 (20%)	5 (33%)
Dysgeusia	0	2 (13%)	1 (7%)
Headache	1 (7%)	2 (13%)	0
Gastrointestinal Disorders	1 (7%)	2 (13%)	1 (7%)
Dizziness	0	0	2 (13%)
Somnolence	1 (7%)	3 (20%)	2 (13%)
Discomfort	0	0	2 (13%)

Conclusions

- No evidence of respiratory depression was observed in any subject during treatment with either dose of CR845 in healthy subjects

- CR845 was well tolerated and no unanticipated Treatment Related Adverse Events were observed