NKTR-181, a novel mu opioid analgesic with inherently low abuse potential and efficacy in multiple preclinical models of pain

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NEKTAR

INTRODUCTION

- NKTR-181 is a novel mu opioid receptor agonist designed for a reduced rate of entry into the central nervous system (CNS) that is currently in Phase 3 clinical studies for treatment of chronic low back pain. The reduced rate of brain entry of NKTR-181 is an inherent characteristic of the molecule, and has been shown to reduce central side-effects as well as abuse potential (demonstrated in preclinical and Phase 1 human abuse liability studies), while retaining strong analgesic efficacy in preclinical studies of acute visceral pain.

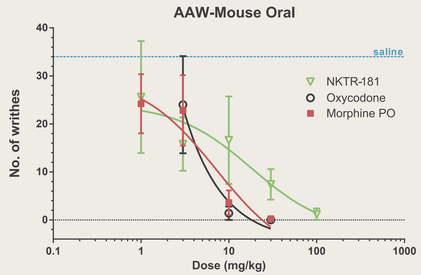

Figure 1. Acetic acid writhing in the mouse. Data represent mean ±SEM number of writhes 30min following oral administration of test compound.

- Here we demonstrate analgesic efficacy of NKTR-181 in additional preclinical models of pain, including acute thermal nociception, persistent pain and inflammatory pain.

METHODS

Hot Plate Latency: Compound was administered orally and hot plate response (latency to lick hindpaw or jump following placement on a 55ºC hot plate) was evaluated at 0.5, 1, 2, 4 or 6 hrs post-dose. Male CD-1 mice or Male Sprague Dawley rats were evaluated.

Formalin Paw Test: Compound was administered orally 5 min prior to formalin injection in the hindpaw. Paw flinches were measured using the Automated Nociception Analyzer for 60 min post-formalin. Cumulative number of flinches was measured between 0-9 min defined as Phase 1 and 10-60 min for Phase 2. Formalin-induced paw licking was measured as cumulative time spent licking the hindpaw 30 minutes following oral administration of compound. Male Sprague Dawley rats were evaluated.

Thermal Nociception Test: Compound was administered orally 30 min prior to Carrageenan (Cg). Thermal nociception (latency of paw withdrawal) was evaluated at baseline (prior to Cg), and 0.5, 1, 2 and 4 hrs post-Cg. Male Sprague Dawley rats were evaluated.

RESULTS

NKTR-181 Demonstrates Full Analgesic Efficacy in a Centrally-Mediated Pain Model

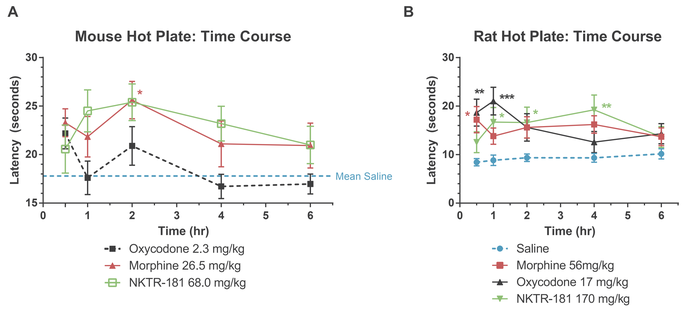

Figure 2. Hot Plate latency time course effect of NKTR-181, morphine, oxycodone or saline following oral administration of a single concentration (50% effective dose) in the mouse (A) and rat (B). Time course was evaluated following a single dose and latency tested at 0.5, 1, 2, 4 and 6 hr post-dose. Data represent mean ± SEM (n = 10). Two-way ANOVA, Dunnett's post-test with respect to saline, *p<0.05.

NKTR-181				
	10 mg/kg	30 mg/kg	100 mg/kg	300 mg/kg
Mouse	37	12	68*	79*
Rat	11	7	38*	32*
Oxycodone				
	1 mg/kg	3 mg/kg	10 mg/kg	30 mg/kg
Mouse	48	46	70*	89*
Rat	- 10	5	16*	81*
Morphine				
	10 mg/kg	30 mg/kg	56 mg/kg	100 mg/kg
Mouse	30	41	67*	100*
Rat	6	21*	ND	22*

Table 1. Hot plate latency dose-response of NKTR-181, morphine, oxycodone or saline at 30 min following oral administration in mice or rats. Data are normalized to percent maximal effect, with saline equal to 0% and 30 seconds as 100%. (n = 10) Statistical significance is determined using One-way ANOVA, Dunnett's post-test with respect to saline, *p<0.05. ND - not determined

Previously demonstrated reduced abuse liability in rats (self-administration and drug discrimination)

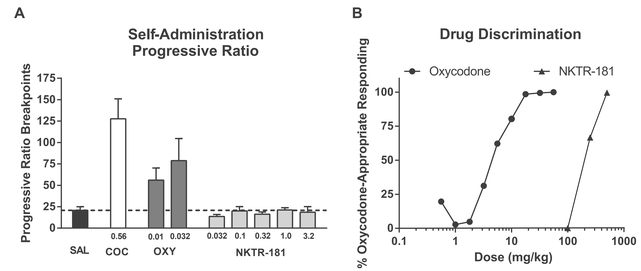

Figure 6. Self-administration reinforcing behavior evaluated with progressive ratio breakpoint and drug discrimination of NKTR-181. A) Progressive Ratio displays behavior comparable to saline. Doses of infusion are as indicated in mg/kg/infusion. Data represent means ±SEM. B) Drug discrimination following oral administration of NKTR-181 after stimulus training to recognize oxycodone. Data represent mean percent oxycodone appropriate response (n = 6). Male Sprague Dawley rats were evaluated.

NKTR-181 Demonstrates Analgesia in Persistent Pain Models

Analgesic efficacy is observed in both Acute and Persistent Phases of the Formalin Paw Model

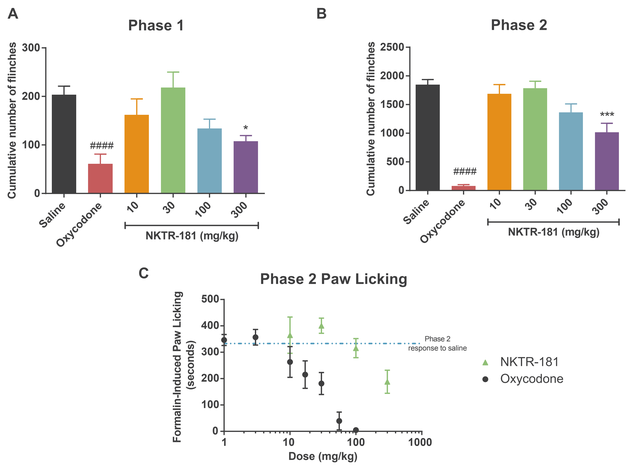

Figure 3. Formalin-induced paw flinches following oral administration of NKTR-181 at 10, 30, 100, 300 mg/kg dose. Single dose of oxycodone (100 mg/kg) used as reference comparator. Cumulative flinches in Phase 1 (A) and Phase 2 (B) data represent mean ± SEM (n = 10). Statistical significance is determined using One-way ANOVA, Dunnett's post-test with respect to saline, *p<0.05, ***p<0.001. Unpaired t-test used to compare oxycodone to saline, ####p<0.0001. C) Dose response curves demonstrating reduction of formalin paw-induced paw licking in the rat 30 minutes following oral administration of NKTR-181 or Oxycodone in the rat. Data represent mean ± SEM.

NKTR-181 Demonstrates Comparable Analgesic Efficacy in Inflammatory Pain Model

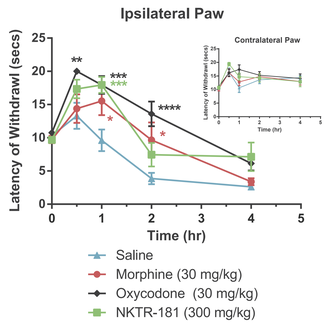

Figure 4. Thermal nociception post-Cg induced inflammation time course following oral administration of NKTR-181, morphine, oxycodone or saline. Doses evaluated were determined as 50% effective dose at 30 min post-dose. Inset is contralateral paw. Data represent mean ± SEM (n = 8). Two-way ANOVA, Dunnett's post-test with respect to saline, *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

CONCLUSIONS

- NKTR-181 exhibits strong analgesic efficacy in multiple preclinical models of pain, comparable to morphine and oxycodone.
- Reducing rate of CNS entry with NKTR-181 does not reduce central mechanisms of analgesic response in preclinical models.
- NKTR-181 previously shown to have reduced abuse liability in preclinical studies.
- Data support NKTR-181 could be the first opioid analgesic that can adequately treat chronic pain without adding to the epidemic of opioid abuse.

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