NKTR-181, a Novel Polymer Conjugated Opioid Agonist, Demonstrates Reduced Toxicity and CNS Side Effects Relative to Oxycodone

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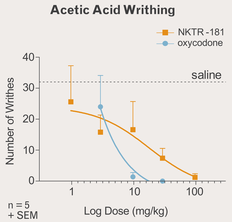
Introduction

- Opioid analgesics represent the mainstay of pain therapeutics, but carry with them severe CNS side effects, including abuse liability, respiratory depression and sedation. NKTR-181 uses Nektar's polymer conjugation technology to create a novel mu-opioid agonist that displays a very low rate of brain uptake compared with oxycodone. NKTR-181 has been shown to have low abuse liability but comparable analgesic properties to marketed opioids in preclinical pharmacology models (1).
- In the current studies, we investigated the toxicity of NKTR-181 relative to oxycodone hydrochloride in Sprague-Dawley rats in order to assess the relative toxicity and neurobehavioral changes produced by the two compounds.

NKTR-181 Shows Analgesic Activity in a Preclinical Model of Pain[1]



Mice, oral administration, tested 30 mins post-dose

- NKTR-181 produces full suppression of acetic acid writhing
- Maximal efficacy achieved at 100 mg/kg p.o.
- Potency is maximal 1-2 hr after oral dosing
- Activity sustained for up to 8 hours after oral dosing

Methods

Study 1: Female Sprague-Dawley rats (n = 3/group) were administered a single oral gavage dose (100, 200, 500, 700 mg/kg) of oxycodone or NKTR-181 and monitored for changes in clinical condition for up to 24 hr post-dose. Clinical observations were recorded at least hourly for 8 hr following dosing and at 12 and 24 hours post-dose. Doses were chosen based on published LD50 values for oxycodone.

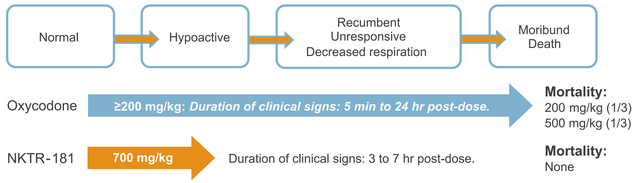
Study 2: Female Sprague-Dawley rats (n = 3/group) were administered 5 daily doses of oxycodone (100 mg/kg) or NKTR-181 (200, 500, 1000 mg/kg) by oral gavage. Animals were monitored for changes in clinical signs, body weight, and food consumption. Animals were euthanized the day after the final dose, a necropsy performed, and samples collected for histopathological assessment. Plasma samples were collected on Day 1 for TK analysis.

References

1. Fishburn, C.S. et al., NKTR-181: A Novel Opioid With Slowed Brain Entry Shows Low Abuse Liability and Reduced CNS Side Effects. Frontiers in Research Symposium, 2010.

Results

A single oral dose of NKTR-181 resulted in fewer CNS side effects and no mortality compared with equivalent doses of oxycodone



Progression of clinical signs in female Sprague-Dawley rats (n = 3) administered a single oral gavage dose of oxycodone or NKTR-181 and monitored for changes in clinical condition for up to 24 hr post-dose. Doses of oxycodone ≥200 mg/kg produced mortality and/or decreased respiration and sedation. Only the highest dose of NKTR-181 produced hypoactivity and no mortality or respiratory changes were observed. Detailed clinical changes are observed in the table below.

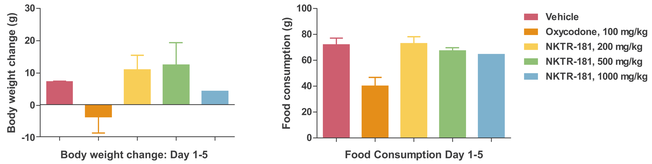
Dose (mg/kg)	Oxycodone			NKTR-181		
	Clinical Signs	Time Observed	#animals affected	Clinical Signs	Time Observed	#animals affected
100*	Hypoactivity	15-24 hr	3/3	No Findings	--	--
200	Mortality Hypoactive Hunched posture Hematuria	3 hr 5-12 hr 4-24 hr 24 hr	1/3 3/3 2/3 2/3	No Findings	--	--
500	Mortality Decreased respiration Unresponsive Recumbent Hypoactive Hematuria	12 hr 30 min 0.5 – 1hr 4-5 hr 5 min – 7 hr 24 hr	1/3 3/3 3/3 3/3 3/3 2/3	No Findings	--	--
700	Tachypnea, muscle rigidity Decreased respiration Unresponsive or reduced responsiveness Recumbent Hypoactive Hematuria Poor hydration, rough hair coat	5 min 2 hr 30 min – 7 hr 3-24 hr 7-24 hr 24 hr 24 hr	3/3 3/3 3/3 3/3 3/3 1/3 3/3	Hypoactivity Piloerection	5-7 hr 3-4 hr	3/3 3/3

Repeat-dose administration of NKTR-181 results in fewer CNS side effects relative to oxycodone

Oxycodone 100 mg/kg	NKTR-181		
	200 mg/kg	500 mg/kg	1000 mg/kg
Hypoactivity (3/3) Recumbent (1/3) Abnormal behavior (2/3)* Paw chewing (1/3) Increased reactivity (2/3) Increased heart rate (3/3) Increased muscle tone (1/3) Red urine (1/3)	No significant findings	Increased activity (2/3) Paw chewing (2/3)	Mortality (1/3) Hypoactivity (3/3) Altered reactivity (3/3) Increased muscle tone (1/3) Paw chewing (1/3)

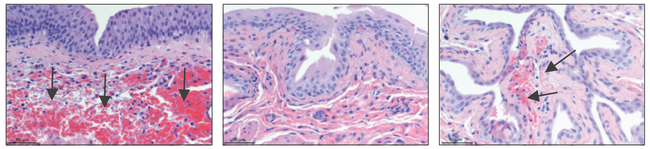
Female Sprague-Dawley rats (n = 3/group) were administered 5 daily doses of oxycodone (100 mg/kg) or NKTR-181 (200, 500, 1000 mg/kg) by oral gavage and monitored daily for changes in clinical signs. Numbers in parenthesis indicate the number of affected animals.

NKTR-181 produces minimal effects on body weight with repeated dose administration



Rats given 100 mg/kg of oxycodone had a minimal (5%) decrease in body weight and a moderate (44%) decrease in food consumption by Study Day 5 compared to control animals. No changes in body weight occurred in rats dosed with NKTR-181, although rats given 1000 mg/kg NKTR-181 had a minimal (10%) decrease in food consumption by Study Day 5. Body weight change on Day 5 was calculated based on pre-dose (Day 1) body weights. Food consumption based on pre-dose feeder weights versus Day 5 feeder weights.

NKTR-181 produces fewer adverse urinary bladder changes compared with oxycodone



Oxycodone 100 mg/kg: Hemorrhage present — NKTR-181 500mg/kg: No changes observed — NKTR-181 1000 mg/kg: Minimal hemorrhage

Urinary Bladder Gross & Microscopic Findings	Oxycodone 100 mg/kg	NKTR-181		
		200 mg/kg	500 mg/kg	1000 mg/kg
Distention	2/3	0/3	0/3	1/3
Hemorrhage	2/3(+ to ++)	NA	--	1 (+)
Necrosis	2/3 (+)	NA	--	--

Distended urinary bladders were noted at necropsy in 2/3 rats given 100 mg/kg oxycodone and 1/3 rats given 1000 mg/kg NKTR-181 (see table). Representative micrographs of urinary bladders are shown. Bladder distention correlated with histological changes of submucosal hemorrhage (arrows, left and right panel) and/or single cell necrosis in the bladder epithelium (not shown). No evidence of submucosal hemorrhage was detected in urinary bladder tissue from animals given 500 mg/kg NKTR-181 (center panel). Size bars represent 50 µm. Key: # animals affected (severity). + = minimal ++ = slight, +++ = moderate. NA = Not applicable; tissue not examined.

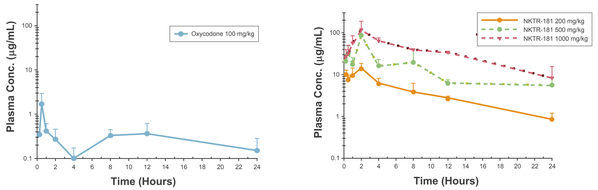
Neurobehavioral Assessment of NKTR-181 Demonstrates No Adverse CNS side effects

NKTR-181 Dose (mg/kg)	Abnormal Observations in Modified Irwin Assay			
	Home Cage	Hand Held	Open Field	Elicited Behaviors
0 (Vehicle)	0/2	0/9	0/8	0/15
50	0/2	0/9	0/8	1/15 [a]
150	0/2	0/9	0/8	2/15 [a, b]
500	0/2	0/9	0/8	3/15 [a,c]

Evaluation of neurological effects was based on observations collected pre-dose and approximately 0.5, 2, 4, 8, and 24 hours post-dose in a modified Irwin battery in male rats given NKTR-181 orally (n = 6/group). Observers were uninformed of each animal's dose level. Data is presented as # of abnormal observations /total # of parameters measured for each type of observation.

* 2-3% increase in mean body temperature noted relative to controls 4 hrs post-dose (0.7-0.9°C↑)
[a] Abnormal approach response noted in 4/6 animals at 2 hrs post-dose and 5/6 animals 4 hrs post-dose.
[c] Abnormal approach response in 6/6 animals at 2 and 4 hrs post-dose. Reduced hind limb grip strength noted at all time points (21% ↓ relative to controls based on grand covariate-adjusted mean).

NKTR-181 plasma exposure is greater than oxycodone on a dose-normalized basis



Compound	Dose (mg/kg)	Tmax (hr)	Cmax (µg/mL)	T1/2 (hr)	$AUC_{0\text{-}last}$ (hr·µg/mL)	Dose normalized AUC
Oxycodone	100	0.5	1.7	12.7	6.88	0.07
NKTR-181	200	2.0	14.3	7.6	96.4	0.48
	500	2.0	86.3	6.9	370.2	0.74
	1000	2.0	118.9	6.9	916.6	0.92

Blood samples were collected from rats administered 100 mg/kg of oxycodone or 200, 500, or 1000 mg/kg of NKTR-181 (n=3/group/timepoint) at 0.25, 0.5, 1, 2, 4, 8, 12, and 24 hrs post-dose. Plasma samples were analyzed for oxycodone or NKTR-181 using a LC-MS/MS method. The linear range for oxycodone was 0.001-1 µg/mL; for NKTR-181 the range was 0.02-10.0 µg/mL.

Conclusions

- NKTR-181 exhibits minimal side effects, including respiratory depression and sedation, compared with equivalent doses of oxycodone.
- The no observed adverse effect level (NOAEL) of 500 mg/kg was identified for NKTR-181 after 5 days of repeated dosing. At 100 mg/kg, oxycodone produced significant CNS changes, body weight loss, and adverse urinary bladder changes; therefore, this dose exceeded the NOAEL.
- NKTR-181 demonstrates improved tolerability over oxycodone while producing potent analgesia in mouse models.

Poster 775-901, Society for Toxicology 50th Annual Meeting & ToxExpo, 6-10 March 2011, Washington, DC
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