NKTR-181: A Novel Opioid Analgesic That Exhibits Reduced Abuse Potential and Maintains Full Analgesic Activity Following Repeat Dosing in Preclinical Rodent Models

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Conclusions

- NKTR-181 is a novel opioid analgesic compound engineered to have a slowed rate of brain uptake compared with oxycodone.
- NKTR-181 displays markedly lower abuse liability than oxycodone in self-administration and drug discrimination studies.
- NKTR-181 maintains full analgesic efficacy following repeated oral dosing in a preclinical model of pain.
- The low abuse liability of NKTR-181, coupled with effective analgesic activity that is maintained following repeated oral dosing in preclinical models suggest this compound could represent a potent, low abuse opioid for the treatment of chronic pain.

Introduction

The potential for abuse of opioid analgesics is believed to be related to rapid entry into the CNS (1,2). Attempts to change this dynamic to reduce abuse potential center around formulations that seek to make it more difficult to accelerate the delivery of a currently used opioid to the CNS. NKTR-181 is not a formulation based approach, NKTR-181 is a novel opioid, the properties of which are derived from the molecular structure of the compound. The physiochemical properties of NKTR-181 cause the drug to enter the brain more slowly while maintaining opioid receptor affinity.

In these studies, NKTR-181 demonstrates low abuse liability in rat models of self-administration and drug discrimination, as well as sustained analgesic effects in a mouse model of visceral pain following repeated dosing.

Methods

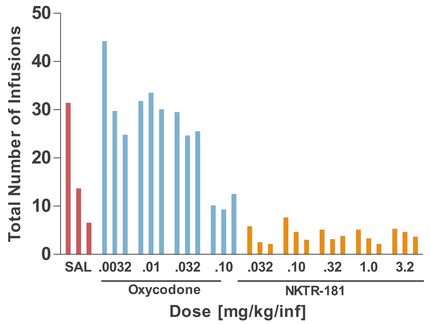
Abuse Liability Models: Self-administration studies were performed on cocaine-trained rats using intravenous NKTR-181, cocaine or saline [n = 6 for oxycodone and NKTR-181; Cocaine n = 38]. In the substitution test, a lever test protocol was used in 1h sessions on three consecutive days, with reinforcement defined as < 20% variability over the three sessions. In the progressive ratio test, the number of lever presses required to deliver a defined dose was increased until animals no longer worked for reward. Drug Discrimination studies were performed in rats trained to discriminate between oxycodone and vehicle. Animals then received oxycodone or NKTR-181 to determine if either produced a response similar to oxycodone or saline.

Repeat Dosing Analgesia Model: Analgesia was determined using the acetic acid writhing model in mice. Male CD-1 mice [n = 10 per group] received oral doses of NKTR-181 or vehicle once daily for up to 10 days. On Days 1 or 10, mice received intraperitoneal 0.5% acetic acid 30 min postdose, and writhes were counted over a 20-min period.

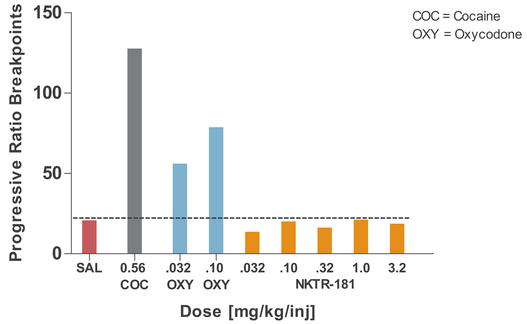
Results

NKTR-181 Displays Low Abuse Liability in Self Administration Studies in Rats

NKTR-181 Shows 100-fold lower abuse liability than oxycodone in self-administration studies in rats



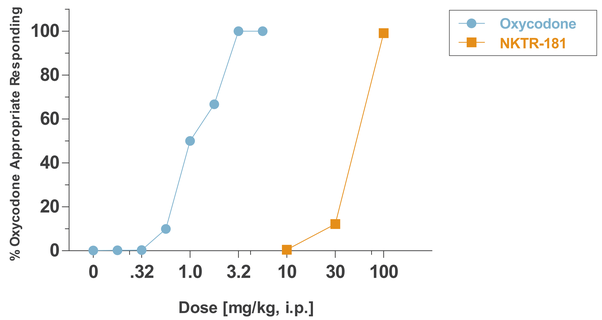
NKTR-181 shows no difference from saline over a 100-fold range of doses in self-administration studies



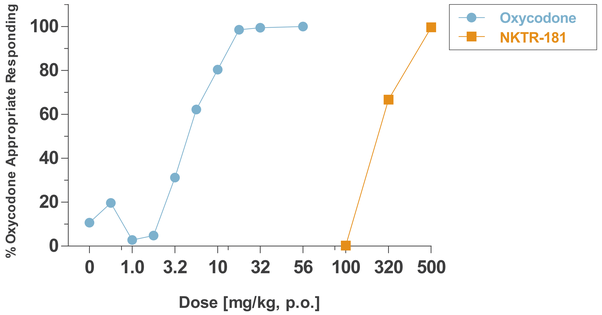
Self-administration studies were performed in rats as described in Methods, on animals treated with NKTR-181, oxycodone [OXY], cocaine (COC) or saline [SAL] at the indicated unit doses. NKTR-181 produced a response similar to that in saline-treated animals, with lever pressing rates typical of sampling behavior. Bars represent group means [n = 6 OXY and NKTR-181; N = 38 for COC].

NKTR-181 Displays Low Abuse Liability in Drug Discrimination Studies in Rats

Significant decrease in abuse liability for NKTR-181 compared to oxycodone following parenteral (ip) administration

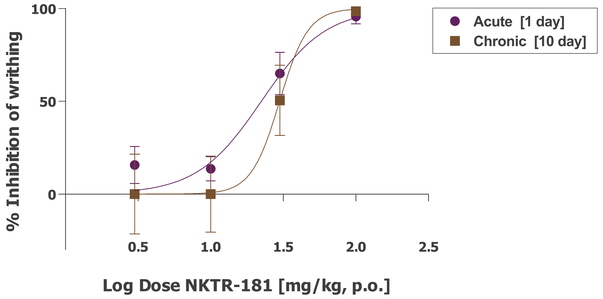


Significant decrease in abuse liability for NKTR-181 compared to oxycodone following oral administration



Drug discrimination studies were performed in rats trained to discriminate between oxycodone and vehicle. Animals then received oxycodone or NKTR-181 [N = 6] to determine if either produced a response similar to oxycodone or saline at the indicated unit doses. The "minimum discriminable dose" [MDD; the dose that produced >80% oxycodone appropriate responding] was determined for both oxycodone and NKTR-181 following either intraperitoneal [i.p.] or oral, p.o.] dosing. The MDD for both i.p. [3.2 versus 100 mg/kg] and orally administered NKTR-181 [17.8 versus 500 mg/kg] showed equivalent shifts in the dose-response function [an approximate 30-fold shift in potency].

Sustained Analgesic Activity in a Preclinical Model of Pain with Repeated Oral Dosing of NKTR-181



Acetic Acid Writhing studies were performed in mice, 30 min after either acute [single dose] or chronic [10 days] daily injections of NKTR-181 or vehicle. Data shown represent the Mean [+/- SEM values] for % Inhibition of writhing relative to the vehicle writhing response [e.g., 0% = same writhing response as vehicle treated animals, 100% = complete inhibition of writhing response].

References

1: Pharmacol Biochem Behav. 2007; 86:45-54. 32 J Pharmacol Exp Ther. 2001; 299 :1056-65. 3: IDrugs. 2010 ;13:139-41.

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