NKTR-181, a Novel Opioid Analgesic with Slow Entry into the CNS and Markedly Reduced CNS Side Effects

NEKTAR

C. Simone Fishburn, Ph.D.[1], Jack Bergman, Ph.D. [2], Hema Gursahani, Ph.D. [1], Juergen Pfeiffer, M.S [1]., Irene Choi, Ph.D [1]., Jennifer Riggs-Sauthier, Ph.D. [1], Stephen D. Harrison, Ph.D. [1], Stephen K. Doberstein, Ph.D. [1] and Timothy A. Riley, Ph.D. [1]

[1]Research, Nektar Therapeutics, San Carlos, California, United States, and [2]Department of Psychiatry, Harvard Medical School, Boston, Massachusetts, United States.

Abstract

INTRODUCTION: The abuse properties of opioid drugs are believed to relate to their rapid entry into the CNS (1,2). Conjugation of a small PEG polymer to drugs has been clinically demonstrated to reduce CNS entry of the compound PEG-naloxol (NKTR-118) (3). NKTR-181 is a new opioid analgesic containing a small PEG side chain that reduces entry into the CNS in a controlled manner, while remaining orally available. We used models of brain uptake rates in rats, self-administration in primates and analgesia in mice to determine whether NKTR-181 reduces abuse liability while retaining anti-nociceptive properties.

METHODS: Slowed entry to the CNS was demonstrated in rats using *in situ* brain perfusion to compare brain uptake rates of oxycodone, morphine and NKTR-181. Compounds (10 uM) were perfused into the left carotid artery of anesthetized rats for 30 seconds, and were extracted and quantitated using LC-MS/MS following excision of the left brain hemisphere (n=3). Brain uptake rates were measured from the unidirectional transfer constant, Kin, (mL/g/min). Abuse liability was determined using self-administration in squirrel monkeys trained to choose between delivery of IV drug or food under FR30 schedules of reinforcement. Animals (n=4) were treated with doses from 0.003 – 0.03 (oxycodone, morphine) or 0.1 – 3.2 (NKTR-181) mg/kg/injection, and percent injection lever responses (%ILR) were calculated to measure reinforcing. Analgesia was determined using the acetic acid writhing model in mice. Animals (n=5) were treated orally with saline or compounds (0.1 – 100 mg/kg range) 30 min prior to intraperitoneal injection of 0.5 % acetic acid, and writhes were counted over a 20 minute period.

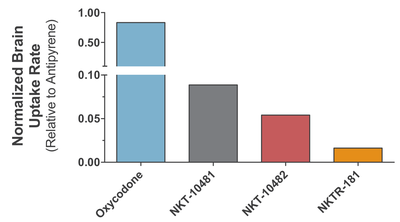
RESULTS: NKTR-181 has a significantly slower rate of entry to the CNS demonstrated by a brain uptake rate of under 0.001 mL/g/min, compared with 0.148 ± 0.024 mL/g/min for oxycodone and 0.002 ± 0.001 mL/mg/min for morphine. This slower CNS entry was paralleled by a marked reduction in the reinforcing properties of the drug. Whereas oxycodone and morphine demonstrated reinforcing behavior in all 4 animals at 0.03 mg/kg/injection and 0.1 mg/kg/injection respectively (100% ILR), similar doses of NKTR-181 produced exclusively food lever responses. At the highest dose of NKTR-181 tested, 3.2 mg/kg/injection, two animals exhibited reinforcing effects (50% ± 29% ILR). Despite the slowed entry to the brain and reduced reinforcing effects, NKTR-181 displays high analgesic potency in preventing writhing following injection of acetic acid into mice. In this model, NKTR-181 demonstrated an ED_{50} of about 20 mg/kg following oral delivery, while the EDs_{50} for oxycodone and morphine were 4.5 mg/kg and 7.2 mg/kg, respectively. Maximal analgesia was achieved at 100 mg/kg for NKTR-181 compared with 30 mg/kg for oxycodone and morphine.

CONCLUSIONS: NKTR-181 is a novel opioid analgesic with significantly slowed entry to the CNS and a marked reduction in self-administration in primates, a key indicator of abuse liability for drugs.

Results

NKTR-181 Demonstrates Significantly Slower CNS Uptake than Oxycodone

NKTR-181 displays a greater than 95% reduction in the uptake rate into the CNS compared with oxycodone, when evaluated in *in situ* brain perfusion studies in rats.

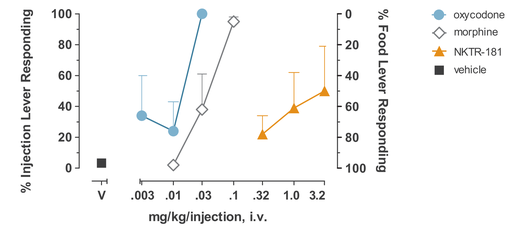


The brain uptake rates of the polymer conjugates were evaluated using *in situ* brain perfusion studies in rats, as described in the Methods section. Mean uptake rates (n=3) were normalized to the uptake rate of the highly permeant compound antipyrene for comparison.

NKTR-181 was selected from a range of conjugates based in its reduction of over 95% in the update rate into the CNS compared with that of oxycodone. This correlates well with the 90% lower rate of CNS entry for NKTR-181 compared with oxycodone, determined by *in vivo* PK studies (4).

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

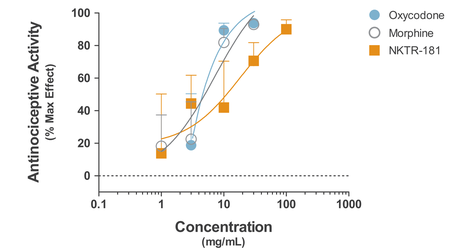
In self-administration studies in non-human primates, NKTR-181 displays significantly lower reinforcing behavior than oxycodone and morphine.



NKTR-181, oxycodone and morphine were tested in self-administration studies in squirrel monkeys, as described in the Methods section. Data shown represent the mean + SEM (n=4). Oxycodone and morphine produced 100% injection lever responses in all 4 subjects at 0.03 and 0.1 mg/kg/injection respectively. By contrast, at 3.2 mg/kg/injection, the highest dose of NKTR-181 tested, only 2 of the 4 subjects showed reinforcing behavior (50 ± 19% injection lever responding).

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

NKTR-181 shows comparable efficacy to oxycodone and morphine in the acetic acid writhing model in mice.



Acetic Acid Writhing studies were performed in mice, 30 minutes after oral dosing of NKTR-181, oxycodone or morphine, as described in the Methods section. Data shown represent mean + SEM values (n=5). NKTR-181, oxycodone and morphine produced ED_{50} values in this study of approximately 20 mg/kg, 4.5 mg/kg and 7.2 mg/kg respectively.

Introduction

The abuse properties of opioid analgesics are believed to relate to their rapid entry into the CNS (1,2). Most attempts at altering the rate of CNS penetration, or at creating low abuse opioids, center around formulation approaches which aim to alter the delivery of the drug. Here, we have used our polymer conjugation technology to incorporate a small PEG side-chain and create a novel molecule whose physicochemical properties cause the drug to enter the brain slowly, while retaining opioid receptor affinity. Conjugation of a small PEG polymer to drugs has been clinically demonstrated to underlie the restricted CNS entry of the compound PEG-naloxol (NKTR-118) (3).

In this study we demonstrate, using preclinical models, that NKTR-181 displays a very low rate of brain uptake compared with oxycodone, and that this correlates with decreased abuse potential but comparable analgesic properties to marketed opioids.

Methods

In situ brain perfusion: Slowed entry to the CNS was demonstrated in rats using *in situ* brain perfusion to compare brain uptake rates of oxycodone and NKTR-181. Compounds (10 uM) were perfused into the left carotid artery of anesthetized rats for 30 seconds, and were extracted and quantitated using LC-MS/MS following excision of the left brain hemisphere (n=3). Brain uptake rates were measured from the unidirectional transfer constant, Kin, (mL/g/min).

Self-administration in non-human primates: Abuse potential was determined using self-administration in squirrel monkeys trained to choose between delivery of IV drug or food under FR30 schedules of reinforcement. Animals (n=4) were treated with doses from 0.003 – 0.03 (oxycodone, morphine) or 0.1 – 3.2 (NKTR-181) mg/kg/injection, and percent injection lever responses (%ILR) were calculated to measure self-administration behavior.

Acetic acid writhing model in mice: Analgesia was determined using the acetic acid writhing model in mice. Animals (n=5) were treated orally with saline or compounds (0.1 – 100 mg/kg range) 30 min prior to intraperitoneal injection of 0.5 % acetic acid, and writhes were counted over a 20 minute period.

References

1: Pharmacol Biochem Behav. 2007; 86:45-54. 2: J Pharmacol Exp Ther. 2001; 299 :1056-65. 3: IDrugs. 2010 ;13:139-41. 4: Fishburn CS, Wong et al. NKTR-181 A Novel Opioid With Slowed Brain Entry Shows Low Abuse Liability and Reduced CNS Side Effects. Poster presented at Frontiers in Research Symposium - Pain 2010: From bench to bedside, October 14-16. 2010, San Diego CA, USA.

Conclusion

- NKTR-181 is a novel opioid analgesic compound engineered to have a slowed rate of brain uptake compared with oxycodone while producing effective analgesia in standard preclinical models of pain.
- NKTR-181 displays markedly lower abuse potential than oxycodone and morphine in self-administration studies in non-human primates.
- The low abuse liability of NKTR-181, coupled with its effective analgesic activity in preclinical models, suggest this compound could represent a potent, low abuse opioid for the treatment of pain.

Abstract #A509, American Society of Anesthesiologists (ASA) Annual Meeting: Anesthesiology 2010, 16-20 October 2010, San Diego, CA
To download a copy of this poster, please visit http://www.nektar.com

Acknowledgment:
In situ brain perfusion studies were performed at Absorption Systems (Exton, PA).