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

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NKTR-181 is a novel 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 μM) were perfused through 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/g/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% ± 10% 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 ED50 of about 20 mg/kg following oral delivery, while the ED50 for oxycodone was 4.5 mg/kg and 7.2 mg/kg respectively.

The brain uptake rates of the polymer conjugates were evaluated using in situ brain perfusion studies in rats, as described in the Methods section. Data shown represent mean ± SEM values (n=5). 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 0.09 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).

Conclusions

1. 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.
2. NKTR-181 displays markedly lower abuse potential than oxycodone and morphine in self-administration studies in non-human primates.
3. 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.

References