NKTR-181: A novel opioid analgesic with slowed CNS entry shows reduced abuse liability and CNS side effects

Nektar Therapeutics, San Carlos, CA

Introduction

• Abuse liability and CNS side effects such as sedation, respiratory depression and ‘opioid fog’ limit the use of opioids in treating pain.
• Separation of the analgesic properties of opioids from their abuse potential and CNS side effects is hampered by their rapid entry to the brain and the resulting high peak concentrations in brain tissue.
• To slow the rate of transfer across the blood-brain barrier (BBB) and avoid these CNS side effects, we have applied our polymer conjugation technology to generate a novel opioid analgesic, NKTR-181.
• This molecule has been engineered to stabilize a polymer side chain and is designed to reduce brain penetration while enabling oral absorption and retaining activity at opioid receptors.

Methods

• Brain uptake rate (μg/μl perfusion in rats)

  The rate of brain uptake of test compounds was measured using an in situ brain perfusion method in Sprague-Dawley rats. The left common carotid artery was cannulated and test compounds diluted in Kreb’s Ringer buffer were perfused for 30 seconds. The left brain hemisphere was excised, homogenized and the concentrations of test articles were measured using LC-MS/MS. The unidirectional brain permeability, Kin, was calculated as Kin = [Cbr/Cpf]/t, where Cbr and Cpf represent the concentration of compound in brain and perfusate respectively and t is the perfusion time.

• Brain to plasma ratios

  Oxycodone (1 mg/kg) and NKTR-181 (10 mg/kg) were administered orally to rats; these different concentrations were used to avoid toxicity (oxycodone) and enable detection (NKTR-181). Subsequent studies demonstrated linear PK for NKTR-181. At specified time points following dosing, animals were euthanized, exsanguinated and concentrations of test articles in brain and plasma samples were measured using LC-MS/MS.

• Oral bioavailability in mice

  Oxycodone and NKTR-181 were administered to mice orally at 5 mg/kg, or intravenously at 1 mg/kg. Plasma samples were taken at specified time points following dosing and test articles were measured using LC-MS/MS.

• Self-administration studies

  Self-administration studies were performed on cocaine-trained rats, involving intravenous bolus injections of test article or vehicle (saline) at the specified unit doses. In the progressive ratio test, the number of lever presses required to deliver a unit dose of the indicated value was progressively increased until the breakpoint was reached at which the animal discontinued pressing and no longer would work for reward.

• Acetic acid writhing studies and Straub Tail Response

  For acetic acid writhing studies, CD-1 mice were treated orally with test article, and 30 minutes later were injected intraperitoneally with 0.2% acetic acid (0.1 mL/10 g body weight). After 5 minutes, writhes were counted over a 20 minute period. For the Straub tail response, mice were treated with test articles orally and the Straub tail response was monitored for up to 2 hours. Data shown represent the response 30 minutes post-dose, but are representative for NKTR-181 at all time points measured.

Results

NKTR-181 Shows Dramatically Slower Brain Uptake Than Oxycodone

NKTR-181 was selected from a range of opioid-polymer conjugates with dramatically slower brain uptake than oxycodone as measured by in situ brain perfusion studies in rats.

NKTR-181 Displays Markedly Different Distribution Between Brain and Plasma Compared with Oxycodone

NKTR-181 shows a low brain:plasma ratio at all time points tested following oral dosing in rats.

NKTR-181 Displays Very Low Abuse Liability in Preclinical Studies

NKTR-181 displays very low abuse potential in self-administration studies in rats using progressive ratio tests.

Conclusions

• NKTR-181 represents a novel opioid analgesic with low abuse potential and reduced CNS side effects compared with commonly used opioids.
• NKTR-181 displays slowed entry to the brain and increased plasma exposure following oral administration, when compared with oxycodone in rats and mice.
• NKTR-181 exhibits full efficacy in the acetic acid writhing model in mice, and shows a marked reduction in CNS-based activity compared with oxycodone and morphine at equal analgesic doses.