Nalbuphine attenuates itch in the substance P-induced itch model

Abstract

Nalbuphine is a mixed agonist/antagonist opioid agent. The effect of nalbuphine on substance P (SP)-induced itch in mice was evaluated and compared with results obtained in human skin. Nalbuphine reduces substance P-induced itch in mice to a similar extent as the standard antipruritic agent, clobetasol.

Opioid Hypothesis

Substance P receptors are the main itch receptor at the level of peripheral nerves in the skin. Their expression is altered in itch conditions.

Study Design

Scratching behavior study design following methods previously described for the substance P receptor agonist, (Buckley, 1996).

Conduct of Experiment

Scratching time course following pre-treatment with Nalbuphine (30 mg/kg SC) 90 minutes prior to SubP challenge

Mouse Study Conclusions

• SubP itch model was successfully established.

Nalbuphine Antipruritic Properties: Two Independent pharmacological mechanisms?

• Nalbuphine’s antipruritic efficacy in the intradermal SubP administration mouse model with nalbuphine as an active control, suggests nalbuphine can be effective in the treatment of peripherally mediated pruritic conditions such as hyperalgesia, dermatitis, and atopic dermatitis.

• Thus, nalbuphine’s ability to work both centrally and peripherally on itch, potentially makes it a good therapy for various pruritic conditions.

Next Steps

Nalbuphine is a mixed agonist/antagonist agent with potential antipruritic activity in peripheral neuropathic conditions as well as in central pruritus. Further studies are required to identify the mechanisms of action of nalbuphine in different pruritus conditions.

would nalbuphine be effective in treating peripheral mediated itch?

Substance-P ICH Mouse Model

Substance-P-induced itching behavior in a standard naïve ICH model widely used in preclinical studies.

Scoring of Scratching

Effect of Nalbuphine on SubP Scratching in mice

Mean number of scratches at 60 minutes following 10μg administration of vehicle (PBS, 0.05 mL) or SubP (250 nM/0.05 mL in PBS) with or without nalbuphine (30 mg/kg SC, 90 minutes prior to SubP challenge)

Substance-P and μ-receptor agonist-induced percutaneous itching is used in non-human primates.

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Opioid Receptors Implicated in Itch Sensation

- Specialized neural pathways involving the sensation of itch may vary due to the contribution of itch receptors.

- Pain and itch sensation may result from neurophysiological interactions between different areas of the brain.

- Substance P (SP) activates the peripheral itch receptor, neurokinin 1 (NK1).

- Nalbuphine tested at doses with no effect on spontaneous scratching following subcutaneous pre-challenge.

- Nalbuphine administered intramuscularly is an effective agent in treatment of morphine natural products.

μ-antagonist and μ-agonist

- Binding and functional activity studies in mice reveal a β- and a α- opioid receptor expression in human peripheral blood (HPB) cells lines, and the cloned human opioid receptors expressed in Chinese Hamster Ovary (CHO) cells.

- μ-agonist activation with high affinity associated with cAMP accumulation and μ morphine receptor mediated increase.

- μ-antagonist activation is associated with cAMP inhibition or decrease.

- Nalbuphine is a potent opioid agonist in mice with a high binding affinity and μ-receptor distribution.

Conduct of Experiment

Day -1
- Male C57BL/6 mice (~20-25g) were shaved at the injection sites
- Animals randomized to treatment groups (5
n=8/group over 1
week).
- Monitor by video & record scratching to right injection site for 30-60 min post-challenge

Scoring of Scratching

- Two independent scorers review videos.
- Scorers blinded to dosing scheme.
- Scorers recorded scratching time course following intradermal administration of SubP (250 nM/0.05 mL in PBS) or vehicle only (PBS, 0.05 mL).

- Nalbuphine does not affect locomotor activity of mice as measured by total distance traveled.

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