

## **6beta-naltrexol preferentially antagonizes opioid effects on gastrointestinal transit compared to antinociception in mice.**

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**AIMS:** The current studies were designed to compare the in vivo potencies of the opioid antagonists 6beta-naltrexol and naltrexone in blocking the effects of the opioid agonist hydrocodone following intravenous (i.v.) or oral (p.o.) administration. **MAIN METHODS:** Adult male CD-1 mice were used for all experiments. The 55 degrees C tail-flick assay was used to assess the CNS antinociceptive activity of hydrocodone, and a charcoal meal gastrointestinal transit assay was used to assess the peripheral effects of hydrocodone. Graded antagonist dose-response curves for i.v. and p.o. 6beta-naltrexol and naltrexone were generated to determine ID(50) antagonist potency estimates against fixed doses of hydrocodone.

**KEY FINDINGS:** Both antagonists produced dose-related blockade of hydrocodone-induced antinociception and inhibition of gastrointestinal transit. Naltrexone was between 5- and 13-fold more potent than 6beta-naltrexol in blocking a CNS effect of hydrocodone, whereas the drugs were nearly equipotent in blocking inhibition of gastrointestinal transit. Co-administration studies indicated an approximate 10-fold greater potency of 6beta-naltrexol for antagonism of hydrocodone-induced inhibition of gastrointestinal transit versus antinociception, whereas naltrexone blocked both effects with near equal potency. 6beta-naltrexol produced a longer duration of antagonist blockade and had a slower time to peak effect compared to naltrexone.

**SIGNIFICANCE:** The pharmacology of 6beta-naltrexol differentiates it from currently available opioid antagonists. This includes an intermediate selectivity for peripheral versus central opioid receptors, a long duration of action, and neutral antagonist qualities in opioid exposed systems. These properties render it a drug candidate for a co-formulation product with opioid analgesics to reduce peripheral opioid side effects and limit abuse potential.