

[2003 Fall A4] Morphine prolongs analgesic effects of ketamine in models of visceral nociception

Ness T, Uzzel T

University of Alabama at Birmingham, Birmingham, AL, USA

Introduction: Opioids and N-methyl-D-Aspartate (NMDA) receptor antagonists have been demonstrated to produce analgesia in humans and anti-nociceptive effects in animal models of somatic pain. Interaction effects of the two drug classes have been noted with a potentiation of analgesic effects most commonly noted. Recently we have demonstrated analgesic effects of these same drugs in models of visceral nociception. The present study sought to determine if an interaction effect was apparent between the analgesic effects of the archetype opioid - morphine - and a common clinically employed NMDA receptor antagonist - ketamine.

Methods: All studies approved by the local IACUC and were performed in halothane-anesthetized, mechanically-ventilated male and female Sprague-Dawley rats. Two different visceral stimuli were employed: colorectal distension (CRD - 80 mm Hg, 20s duration, 8 cm balloon placed into the colon via the anus) and urinary bladder distension (UBD - 60 mm Hg, 20 s duration, 22 gauge angiocatheter placed transurethrally). Stimuli were presented at 4 minute intervals after the establishment of reliable and reproducible responses. Measured endpoints included cardiovascular (CV) responses measured using an arterial cannula (carotid or femoral), visceromotor (VM) responses measured using electromyographic electrodes placed in the superior oblique musculature and neuronal responses measured as extracellular recordings of neurons excited by visceral stimulus which are located in the caudal ventrolateral medulla CVLM). Sequential, cumulative doses of ketamine (0.1-1 mg/kg i.v.) were administered in the presence and absence of pretreatment with morphine (0.5 mg/kg i.v. - 30 minutes prior to additional testing)

Results: Ketamine, at these doses, produced transient inhibitory effects of CV, VM and CVLM neuronal responses. Morphine, at this dose had no major inhibitory effects 30 minutes after administration, but resulted in a prolongation of the inhibitory effects of ketamine.

Conclusions: Systemic ketamine, at the doses employed and by itself had limited effects on responses to visceral stimulation, but in the presence morphine had stronger inhibitory effects. This was demonstrated in separate visceral pain models using two differing visceral stimuli and three different endpoints. This suggests the benefit of combining these two drug classes when treating clinical visceral pain.

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