Title: ANALGESIA AND VENTILATORY CHARACTERISTICS OF EPIDURAL SPIRADOLINE -- A SPECIFIC KAPPA AGONIST

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Introduction. Administration of epidural and intrathecal narcotics is an effective approach to the treatment of pain. However, observations of delayed, potentially lifethreatening respiratory depression and other side effects have limited the utility of this treatment modality.[1] Recent identification of subpopulations of opioid receptors with separation of opioid effects has stimulated the development of specific opioid agonists. Spiradoline mesylate (U-62,0066E) is a potent, selective Kappa agonist. This structurally unique opioid is known to have analgesic properties but should not produce the morphine, mu, receptor effects. Therefore, it may be an effective analgesic without producing the undesirable respiratory depressant, and addiction liability with morphine-like opioids. The purpose of this study was to determine the analgesic and the ventilatory effects of epidurally administered spiradoline.

Methods. Three female "Western" sheep (weighing 30-35 kg) were studied. Under general anesthesia with ketamine, 10 mg/kg IV, xylazine, 0.20 mg/kg IM, and isoflurane (0-2.5%) a tracheostomy was performed with placement of a #10 Shiley cuffed tracheostomy cannula. The external jugular vein was percutaneously cannulated with an 8", 16 g catheter for plasma sampling. A 19 g nylon epidural catheter was surgically placed 5 cm into the epidural space at the $L_{3-4}$ interspace. Identical catheters were placed into the subarachnoid space after a modified partial laminectomy at $L_{5-6}$ and $C_{3-4}$ for CSF sampling. Doses of 15, 45, 90, 120, and 180 µg/kg of spiradoline were administered epidurally in a blinded manner. For nociceptive testing, we applied an incrementally increased electrical stimulus (Grass peripheral nerve stimulator Model SM6, Freq. 10Hz, pulse 10 m/sec) to bipolar cutaneous Ag/AgCl electrodes placed 5 and 10 cm lateral to the dorsal midline at $L_4$ and $C_7$ dermatomes. Impulse amplitude present at the time of first appearance of avoidance movement in the animal was measured in AC mAMPs with a Keithley multimeter Model 169 at 0, 0.5, 1, 1.5, 2, 3, 4, 5, and 6 hr and the results seen were calculated as a percent change from control. Statistical analysis was by ANOVA, with multiple group comparisons. Ventilatory response to $CO_2$ was determined every 60 min for 6 hr after drug administration by having the animal rebreath in a 5L circuit charged with 5% $CO_2$ and 95% $O_2$. The effects seen following drug administration were compared to a predrug control evaluation. End tidal $CO_2$ was measured with a Hewlett-Packard capnometer and continually recorded on a strip chart recorder. Tidal volumes were determined with a Boehringer respirometer and minute ventilation (VE) was calculated at 15 sec intervals. Linear regression of VE on $TECO_2$ for each curve yielded a slope ($VE/TECO_2$). Venous $CO_2$ ($PVCO_2$) was measured hourly with a Corning #178 blood gas analyzer. Results of $PVCO_2$ and $VE/TECO_2$ were compared over time to control with ANOVA. Animals were observed for side effects.

Results. Significant analgesia was noted at all doses except for 15 µg/kg. Onset of analgesia occurred within 30 min and peak effect was observed at 60-90 min in all groups. The duration of action varied with the dose; 2 hr at 45 µg/kg to 4 hr with 120 and 180 µg/kg (Figure 1). The $CO_2$ response curves were observed to be linear with correlation coefficients ranging from 0.92-0.99. There was no evidence of respiratory depression by $PVCO_2$ or $VE/TECO_2$ for doses up to 120 µg/kg. There was a suggestion of respiratory depression in one animal receiving 180 µg/kg. All animals displayed a dose-dependent sedative effect that was correlated temporally with the analgesic effects. One animal receiving 180 µg/kg displayed evidence of marked pruritis.

Discussion. The results of this study suggest that spiradoline, a selective Kappa agonist, is an efficacious analgesic when administered epidurally. No evidence of respiratory depression occurred in doses up to 120 µg/kg given epidurally. These results suggest that spiradoline does not interact significantly with mu receptors, mediator of opioid-induced respiratory depression. Further studies of this specific agonist are continuing.

References.

1. Yaksh TL: Spinal opiate analgesia: Characteristics and principles of action. Pain 11:293-346, 1981

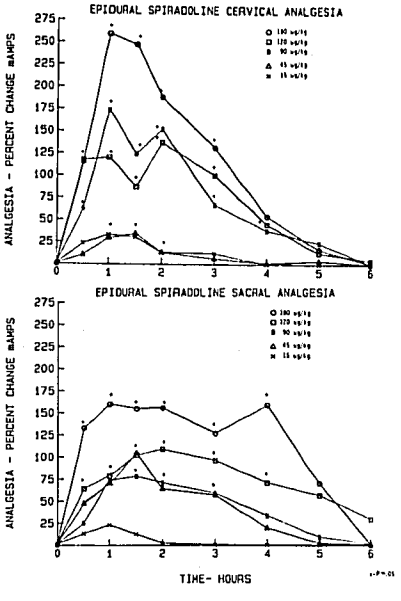


Fig. 1. Analgesic response measured as percent increase in mAmp stimulus compared to control in cervical and sacral dermatomes.

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