ANTINOCICEPTION AND CO2-RESPONSE FOLLOWING SPINAL AND SYSTEMIC DEXMEDETOMIDINE IN DOGS.

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Introduction: Dexmedetomidine (DEX), a novel α_2 agonist, produces a hypnotic action and anesthetic-sparing effect in rats and dogs following systemic administration. These effects are suggested to be supraspinal. Spinal administration of an α_2 agonist also induces a spinal analgesic effect. In the present study we examined the antinociceptive, CO2-response and neurobehavioural effects of DEX intravenously (IV), cisternally (ICV), intrathecally (IT) and epidurally (EP) administered in dogs. The purpose of this study was to determine whether DEX can produce a spinal/supraspinal antinociceptive effect with minor respiratory effects.

Methods: The study was approved by the Institutional Animal Care Committee. Beagles (15±1 kg.) were prepared with a chronic tracheostomy and trained to be intubated awake and to rebreath in a closed system (modified Read rebreathing system). The nociceptive response was quantitated by measuring the response latency of a thermally-evoked skin twitch. Following the IV studies, the IT, EP and ICV catheters were implanted during a single combined surgical procedure. The administered doses were 1, 3 and 10 µg/kg IV; 0.5, 1.5 and 5 µg ICV; 1, 3 and 10 µg IT; 5, 15 and 50 µg EP (n= 5, each dose and route). The α_2 antagonist atipamezole (0.3 mg/kg IV) was used as an antagonist. Studies were performed with at least 5 days interval. The change in slope of the CO_2-response curve was converted to percent change of the baseline ($\%\Delta V_e/CO_2$). Statistical analysis was performed with the two-tailed t-test .

Results: A dose-dependent antinociceptive effect was observed for all the different routes with spinal administration showing a stronger effect than systemic. The dogs given IV DEX showed a significant and dose-related hypnotic effect and a decrease in heart rate. Only 10 µg/kg IV induced a significant reduction in CO_2-response. All the effects were antagonized by atipamezole.

Discussion: Dexmedetomidine produced a spinal/supraspinal antinociceptive effect which was dose-dependent and atipamezole reversible. High intravenous doses resulted in a hypnotic state and a significant reduction in heart rate and response to increasing CO_2. However, these effects may result from the sedative actions of DEX and may not be a direct α_2 effect on respiratory centers.

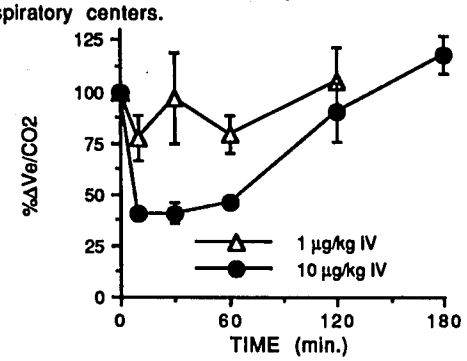

Figure shows percent change of the slope of the CO_2-response curve versus time for 1 and 10 µg/kg IV.

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TITLE: INVOLVEMENT OF SPINAL OPIOID RECEPTORS IN MIDAZOLAM INDUCED ANTINOCICEPTION

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Midazolam (Mi) is a benzodiazepine with a rapid and short elimination half-life after i.m. injection. It is used as a sedative and anesthetic drug for premedication in outpatient anesthesia and as an adjunct to anesthesia. We have earlier reported that intrathecal injection of low doses of Mi (10 µg) potentiated morphine (Mo) induced antinociception in the rat.[1] We have now further extended these studies and investigated the effect of Mi on the binding of opiates to the rat spinal opioid receptors (SOR).

The binding of radioactive opiates to SOR was investigated in vitro by a radio-receptor assay system described by us in detail recently.[2] Briefly, rat spinal cord was homogenized in 20mM Hepes buffer pH 7.5 (100 mg wet wt/ml). The homogenate was centrifuged and the pellet containing SOR was incubated at 37°C for 40 min to degrade endogenous opioid peptides bound to SOR. After washing, the pellet was suspended in the buffer (1 ml buffer for about 10 mg of original tissue). Assays, using 1 ml of membrane suspensions, was performed by using [^{3}H]-naloxone. Effect of Mo on the specific binding of [^{3}H]-naloxone to SOR was studied in absence and presence of Mi. After the incubation at 25°C, the suspensions were filtered on Whitman GF/B filters, and filters counted for radioactivity in the presence of liquid scintillation mixture. Student's t-test was used for statistical analysis.

Morphine inhibited the specific binding of [^{3}H]-naloxone to SOR in a dose dependent manner. Midazolam when used alone did not affect the binding of [^{3}H]-naloxone. However, when Mi and Mo were used together, they decreased the binding of [^{3}H]-naloxone more than that observed with Mo alone. These results suggest that at low doses Mi favors the displacement of [^{3}H]-naloxone from SOR by Mo. We believe that Mi alters the conformation of SOR in such a manner that SOR show more affinity for opiate agonists (Mo) and less affinity for opiate antagonists (naloxone). These results also explain the reported synergistic effect of Mi and Mo in producing antinociception at low doses.[1]

REFERENCES:
1. Anesthesiology 71(3A), 1989.
2. Neuropharmacology 27:1145-1149, 1988.