TITLE: BENZODIAZIPINE ANTAGONIST, RO-15-1788, ANTAGONIZES CARDIOVASCULAR DEPRESSANT EFFECT OF LORAZEPAM

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A specific benzodiazepine antagonist, RO-15-1788(RO) has been shown to reverse benzodiazepine induced sedation, presumably at the site of benzodiazepine receptors in the CNS.[1] The aim of the present study was to investigate whether RO and other possible anti-benzodiazepine agents reverse benzodiazepine induced cardiovascular depression,

Ten New Zealand White rabbits weighting 2.5 to 3.3 kg, were anesthetized with α-chloralose, tracheotomized and mechanically ventilated. The left renal sympathetic nerves were isolated retroperitoneally through a left flank incision, and a bipolar silver electrode was placed on the sympathetic nerves for recording renal sympathetic nerve activity (RSNA). Mean arterial pressure (MAP) was monitored through a femoral artery. After a steady state was achieved lorazepam 0.05 mg/kg was administered, and 5min later, either RO, 0.3 mg/kg, physostigmine,0.14 mg/kg, or aminophylline, 10mg/kg was administered while measuring MAP, ECG and RSNA.

Lorazepam 0.05 mg/kg decreased MAP to 83.2±3.3%(mean±SE, n=7) and RSNA to 61.4±9.3%. (Figs.1 and 2) Immediately after RO administration both MAP and RSNA returned toward the baseline values (Figs.1 and 2). RO did not increase RSNA in those cases where RSNA remained unchanged. Aminophylline and physostigmine failed to restore MAP and RSNA, which had been decreased by lorazepam.

It is known that benzodiazepines not only can induce sedation but can also cause depression of the cardiovascular system. It is believed that the reduction of RSNA was due to the depressant effect of lorazepam on the medullarry cardiovascular center, and the reduction of MAP resulted, at least in part, from decreased overall sympathetic nerve activity. Although physostigmine and aminophylline may be able to reverse benzodiazepine induced sedation[2,3] they failed to reverse benzodiazepine induced cardiovascular depression in this study. Therefore, this may suggest that these drugs do not affect the benzodiazpine receptors. In conclusion, it was found in this study that the benzodiazepine antagonist, RO-15-1788 reverses lorazepam inducedcardiovascular depression in addition to reversal of sedation.

Referrences:
1. ANESTHESIOLOGY 63:61-64.1985
2. Anesth Analg 63:900-2,1984
3. Ann Int Med 91:53-55, 1979

Fig.1

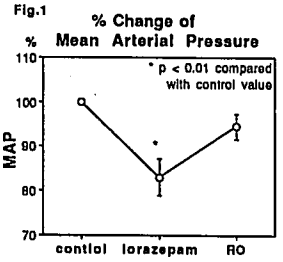
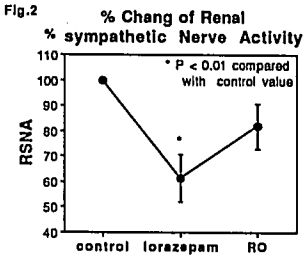


Fig.2



Statistical analysis : ANOVA followed by the Newman-Keuls' test

A620

Title : ORAL DEXMEDETOMIDINE BLUNTS THE HEMODYNAMIC RESPONSE TO EMERGENCE FROM ENFLURANE ANESTHESIA IN DOGS

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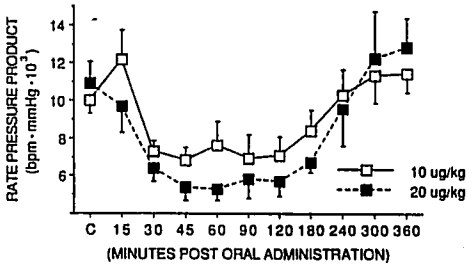
Alpha$_2$ adrenoreceptor agonists produce sedation, analgesia and reduce the dose requirements for anesthetics without respiratory depression. Dexmedetomidine (D) is a selective alpha$_2$ agonist but causes transient hypertension when administered IV. The purpose of this investigation was to evaluate the duration and hemodynamic effects of orally administered D in chronically instrumented dogs in the conscious state, during enflurane anesthesia, and following emergence from enflurane anesthesia.

Dogs were instrumented for measurement of aortic pressure, coronary blood flow velocity (CBF), cardiac output, left ventricular pressure, dP/dt and regional contractility. Four experimental groups (N = 9 each) were completed. In groups 1 and 2, D (10 or 20 μg/kg) was administered orally and hemodynamics, arterial blood gas tensions (ABG) and plasma catecholamine levels (PCL) were monitored for 6 hr. Groups 3 and 4 were given D (20 μg/kg p.o.) or placebo, respectively, and hemodynamics, ABG and PCL were monitored 1 hr later in the conscious state, after 30 min of enflurane anesthesia (1.0 MAC) and 2 and 7 minutes after extubation. All data were analyzed by SAS software GLM followed by Bonferroni's t-test with significance at $p<0.05$ (*).

Oral administration of 10 or 20 μg/kg of D was associated with sedation, decreased heart rate (HR), rate-pressure product (RPP) (figure) and PCL. The peak effect occurred by 30 min and lasted approximately 3 hr. No hypertensive effect, decrease in CBF or respiratory depression was observed. Administration of 20 μg/kg of D before enflurane



anesthesia was also associated with a reduction in HR, RPP (table) and PCL without change in CBF, contractile function or ABG prior to or upon emergence.

RPP (BPM·mmHg·10^3)	Conscious Control	1 hr Post D	Enflurane	Post Extubation 2 min	Post Extubation 7 min
Placebo	13.2	13.1	10.2	20.2	21.9
D	12.0	6.1*	7.9*	7.1*	7.2*

The results of this investigation indicate that oral administration of D produces sedation and decreased HR, RPP, and PCL without reduction in CBF and segment function or depression of respiration. Oral D diminishes the hemodynamic response to emergence from enflurane anesthesia in chronically instrumented dogs. The lack of an initial pressor response, sedation without respiratory depression and favorable hemodynamic actions suggest that oral D may have potential as a premedication for general anesthesia.