

TITLE: DIFFERENTIAL EFFECTS OF AMRINONE ON PULMONARY RESPONSES TO HISTAMINE
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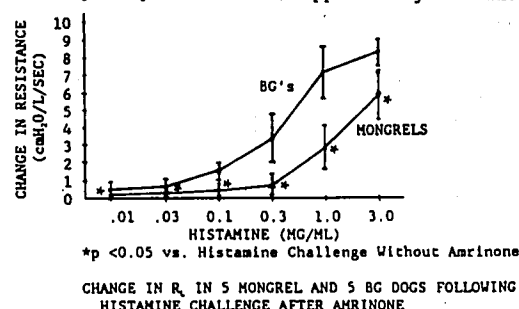
Phosphodiesterase (PDE) inhibitors (e.g. theophylline) have been commonly used as bronchodilators in asthmatics. Yet the interest in new PDE inhibitors recently approved for use as inotropes (e.g. amrinone, Amr) has occurred largely without attention to concomitant effects on pulmonary mechanics. Clinical situations arise (severe bronchospasm, ARDS, one lung ventilation) where decreased airway compliance and/or increased airway resistance (R_a) may significantly impair oxygenation, ventilation, or cardiac output especially in the heart with previously compromised contractility. We therefore investigated the in vivo effects of Amr on airway resistance in two populations of dogs.

Five Basenji-Greyhound dogs (BG) previously bred for their known airway hyperreactivity and 5 mongrel (M) dogs screened for equivalent baseline reactivity to histamine (H) were studied under thiopental-fentanyl anesthesia. Each dog underwent 2 studies: 1) Baseline H aerosol challenge consisting of 5 standardized breaths at each of 6 increasing concentrations of H (.01, .03, 0.1, 0.3, 1.0, 3.0 mg/ml), and 2) the same H challenge given after administering Amr as a 2mg/kg I.V. load with 10 μ g/kg/min maintenance infusion. Studies were performed in random order separated by a week. R_a was calculated from simultaneous pressure and flow measurements at points of zero flow. Transpulmonary pressure was estimated as the difference between the pressure

measurements of an esophageal balloon and a needle in the airway. Maximal changes in R_a were recorded after each H challenge. Data were analyzed by two way ANOVA with $p < .05$ considered significant. Data are Mean \pm SE.

M's and BG's responded similarly to initial H challenges. However, Amr attenuated the pulmonary response to H in M's but not in BG's. This response was observed at all H dose levels and was significant (Fig.). The attenuation was greatest at the 1.0 mg/ml H challenge (pre 7.2 ± 1.1 vs. 3.4 ± 0.5 cm H₂O/L/SEC post Amr, $p < 0.001$), and least at the .01 mg/ml challenge (pre $0.82 \pm .29$ vs. $0.28 \pm .08$ post Amr, $p < 0.05$).

We conclude Amr significantly attenuates H induced bronchoconstriction in M's but not in BG's. These differential responses may be due to receptor or enzymatic differences between the airways of the M's and BG's, a differential dose effect, and/or different levels of PDE inhibitor induced catecholamine release. These data suggest that Amr may be beneficial in critically ill patients with mixed cardiac and pulmonary complications. Supported by NIH HL38435.



A1167

TITLE: VENTILATORY EFFECTS OF DEXMEDETOMIDINE IN HUMANS

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Introduction. Dexmedetomidine (DEX), a centrally acting α_2 adrenergic agonist, produces complete or nearly complete anesthesia in animals (1). Thus, it is potentially a new anesthetic agent in humans.

Methods. We studied the ventilatory effects of placebo and 0.25, 0.5, 1.0, & 2.0 μ g \cdot kg⁻¹ of DEX infused over two minutes in 37 normal male subjects (consented and IRB approved). Prior to the infusion, two control CO₂ ventilatory response curves were determined while the subjects were breathing 50% O₂. The CO₂ challenge was repeated every 45 minutes starting approximately 15 minutes after the infusion. The slope and intercepts were determined by linear regression on the ventilation and PETCO₂ breath-by-breath data. Room air arterial blood gases were obtained prior to each CO₂ challenge. Ventilation, PETCO₂, and P_{ET}O₂ were measured continually during and immediately after DEX infusion and during normoxia just prior to each CO₂ challenge.

Results. DEX caused marked sedation in all subjects. No adverse reactions occurred. By four hours after the infusion, all subjects were fully awake and alert. Compared to the average of the two control periods, the peak ventilatory depression was seen on the second and third measurements after DEX. The maximum decrease in ventilation was 2.44 ± 1.33 l \cdot min⁻¹ (mean \pm s.d.) in the 2.0 μ g \cdot kg⁻¹ group by a reduction in tidal volume with little change in respiratory frequency. The P_aCO₂ increased by 1.3 ± 1.2 , 2.2 ± 2.2 , 5.0 ± 2.7 , & 4.2 ± 3.3 mmHg for the four increasing DEX doses (placebo showed an increase of 0.61 ± 2.4 mmHg). The increases for the two highest doses were significantly different from placebo. Figure 1 gives the results for the arterial P_{CO}₂ and the P_{CO}₂ response slopes and intercepts at the 2.0 μ g \cdot kg⁻¹ dose for all time periods.

There was a right shift and depression of the hypercapnic response. The hypoventilation slowly returned to normal and by the last two tests (4.5 and 5.25 hours after the infusion) there was no significant difference from the control experiments.

Discussion. DEX is a potent new α_2 adrenoceptor agonist, more specific and selective than either the antihypertensive agent clonidine or the animal anesthetic xylazine. We did not study DEX's analgesic properties in these experiments; however, all subjects showed a marked degree of sedation. The amount of respiratory depression was quite small considering the amount of sedation. Since there did not seem to be any significant difference in the degree of ventilatory depression between the two highest drug doses, this may indicate a ceiling effect. This lack of major ventilatory depression from DEX may make it useful as a perioperative anesthetic adjuvant.

1. Anesthesiology 69:818-823, 1988.

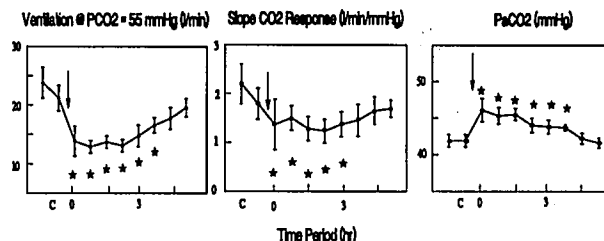


Figure 1: Mean (\pm s.e.m.) of the ventilation at a PETCO₂ of 55 mmHg, the slope of the CO₂ response and the P_aCO₂ for the 10 subjects receiving 2.0 μ g \cdot kg⁻¹ DEX. Two control runs (C) were made 45 minutes apart; DEX was infused at the 1, and the subsequent measurements were made at 45-minute intervals. * $p < 0.05$ different from the two control runs by ANOVA and Duncan's range test.