TITLE: DIFFERENTIAL EFFECTS OF AMINOLINE 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) 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 Basangi-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 continuous-fentanyl anesthesia. Each dog underwent 2 studies: 1) Baseline H aerosol challenge consisting of 5 standardized breaths at each of 5 increasing concentrations of H (.01, .03, .05, 1.0, 3.0 mg/ml), and 2) the same H challenge given after administering 2 mg/kg IV as a loading dose with 10 µg/kg/min maintenance infusion. Studies were performed in random order separated by a week. R, 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, were recorded after each H challenge. Data were analyzed by two way ANOVA with p<.05 considered significant. Data are Mean ± 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 ± .29 vs. 0.28 ± .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, 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.

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TITLE: VENTILATORY EFFECTS OF DEXMEDETOMIDINE IN HUMANS

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Introduction. Dexmedetomidine (DEX), a centrally acting α2 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 µg 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 60% O2. The CO2 challenge was repeated every 45 minutes starting approximately 16 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 PaCO2 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. For 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/min⁻¹ (mean ± s.d.) in the 2.0 µg kg⁻¹ group by a reduction in tidal volume with little change in respiratory frequency. The PETCO2 increased by 1.3 ± 2.9, 5.2 ± 7.9, 5.0 ± 4.7, and 6.3 ± 3.9 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 Pco2 and the Pco2 response slopes and intercepts at the 2.0 µg kg⁻¹ dose for all time periods.

There was a right shift and depression of the hypercarbic response. The hyperventilation slowly returned to normal by the last two tests (4.5 and 8.25 hours after the infusion) there was no significant difference from the control experiments.

Discussion. DEX is a potent new α2 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.


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Figure 1: Mean (± s.e.m.) of the ventilation at a PpetCO2 of 55 mmHg, the slope of the CO2 response and the Pco2 for the 10 subjects receiving 2.0 µg kg⁻¹ DEX. Two control runs (C) were made 45 minutes apart; DEX was infused at 1, and the subsequent measurements were made at 15 minute intervals. * p < 0.05 different from the two control runs by ANOVA and Duncan’s range test.