TITLE: EFFECTS OF ESMOLOL (E) ON PULMONARY REACTIVITY IN BASENJI-GREYHOUNDS (BG).

AUTHORS: JD Tobias MD, RA Sauder MD
CA Hirshman MD.

AFFILIATION: Depts. of Anesthesiology\CCM and EHS, Johns Hopkins University, Baltimore, MD.

β-adrenergic antagonists are frequently used in the perioperative period to control heart rate and blood pressure. Although these drugs are generally safe and effective, non-selective β-antagonists can provoke bronchospasm in patients with asthma. E is a short acting β-1 selective antagonist which may be safer than nonselective beta blockers in these patients. To further investigate this issue, we compared the effect of equipotent doses of propranolol (P) and E on pulmonary reactivity in BG dogs.

Seven BG dogs were anesthetized with thiopental and fentanyl (TF) and studied during three conditions: (1) control-TF anesthesia, (2) TF plus P, and (3) TF plus E. The three studies were performed in random order on separate days. After intubation and mechanical ventilation, pulmonary resistance (R_L) was calculated from simultaneous pressure and flow curves. P was administered as a bolus dose of 2 mg/kg. This dose was based on previous studies in these dogs. An equipotent dose of E was determined from a standardized isoproterenol sensitivity test which was performed on a separate day. E was administered as a bolus dose of 1 mg/kg followed by a continuous infusion of 0.4-0.5 mg/kg/min. Aerosol challenges consisted of increasing doses of methacholine (0.03,.075,.15,.3,.75,3.0 mg/ml). Data were analyzed using 2-way ANOVA.

Both E and P significantly decreased heart rate from baseline ($p<0.01$). Baseline heart rate was 162 $\pm$ 8.4 beats/minute and decreased to 103 $\pm$ 4.4 after P and to 98 $\pm$ 3.8 after E. P significantly increased R_L at all concentrations of MCH when compared to control while E did not (see figure). During the 3 conditions (control, TF+P, and TF+E) MCH 0.3 mg/ml increased R_L (cm H_2O/L/sec) from baseline: 4.4 $\pm$ .89, 7.9 $\pm$ .97, and 4.0 $\pm$ .39 respectively. These data suggest that in clinically applicable dose ranges, E is devoid of pulmonary effects in the BG model of asthma. Our study suggests that E is preferable to P in patients with reactive airway disease. Supported by NIH 38435.

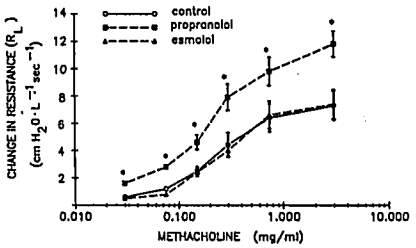

Fig. 1: The effect of propranolol and esmolol on airway responsiveness to MCH in BG dogs.

TITLE: REDUCED SENSITIVITY TO BETA-ADRENERGIC AGONISTS IS REVERSED BY METHYLPREDNISOLONE.

AUTHORS: RA Sauder MD, JD Tobias MD,
CA Hirshman MD.

AFFILIATION: Depts. of Anesthesiology\CCM and EHS, Johns Hopkins University, Baltimore, MD.

Although corticosteroids have become the mainstay of asthma therapy, the mechanism by which these drugs act in asthma is unknown. Basenji-greyhound dogs (BG), similar to humans with asthma, show a reduced sensitivity to β-adrenergic agonists in response to methacholine(MCH) challenge both <u>in vitro</u> and <u>in vivo</u>. To study the influence of corticosteroids on airway responsiveness, we investigated the effect of chronic methylprednisolone (MP) treatment (2 mg/kg/day) on altering the airway responses to MCH challenge in BG dogs pretreated with albuterol (A).

Five BG dogs were studied on 4 occasions during thiopental-fentanyl anesthesia, in random order. Airway responsiveness to MCH, alone and in the presence of A (1 μg/kg IV bolus), were determined prior to treatment with MP (control) and after 2 weeks of subcutaneous MP. Aerosol challenge consisted of 5 standardized breaths with increasing concentrations of MCH (.03, .075, .15, .3, .75, 3.0, and 10.0 mg/ml). Pulmonary resistance (R_L) 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_L were recorded after each MCH challenge. Data were analyzed by two way ANOVA and expressed as the ratio of post challenge to pre challenge R_L.

Chronic MP treatment did not alter airway responsiveness to MCH. However, the combination of A and chronic MP significantly attenuated ($p<0.05$) the pulmonary response to MCH. During the 4 study conditions (C, A, MP, A+MP) MCH .75 mg/ml, altered airway responsiveness from baseline: (mean $\pm$ SEM) 3.60 $\pm$ 0.58, 4.28 $\pm$ 0.42, 4.19 $\pm$ 0.68, 1.25 $\pm$ 0.05 fold respectively ($p<0.01$).

We conclude that chronic MP treatment reverses the insensitivity to β-adrenergic agonists, <u>in vivo</u>, in BG dogs. These data suggest that corticosteroids should be part of the premedication for asthmatic patients who may require beta-adrenergic agonists intraoperatively. Supported by NIH HL 38435.

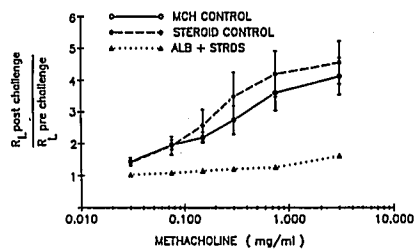

Fig. 1: The effect of albuterol (1μg/kg) on MCH challenge in steroid treated BG dogs.