

**TITLE:** IMPAIRED BETA ADRENERGIC-CHOLINERGIC INTERACTION LEADING TO AIRWAY HYPERREACTIVITY (AH) IN THE BASENJI-GREYHOUND (BG).

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

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

In the search for the etiology of airway hyperreactivity seen in asthmatics, most studies have focused on an abnormal response to constricting agonists. Recent *in vitro* studies in the BG model of asthma suggest that a defect exists in the mechanism controlling airway relaxation. To investigate this issue *in vivo*, 5 mongrel dogs (M) and 5 BG's with equivalent baseline responses to methacholine (MCH) and histamine (H) were anesthetized with thiopental-fentanyl and studied under 3 experimental conditions. Each study was performed in random order, separated by one week. The three conditions were: (1) control MCH or H, (2) MCH or H after albuterol (A) 1  $\mu\text{g}/\text{kg}$ , (3) MCH or H after A 2.5  $\mu\text{g}/\text{kg}$ . The dogs were intubated and mechanically ventilated. Pulmonary resistance ( $R_L$ ) was calculated from simultaneous pressure and flow curves. A (1.0 or 2.5  $\mu\text{g}/\text{kg}$ ) was administered intravenously over 15 minutes. Aerosol challenges consisted of increasing doses of MCH or H. Data were analyzed using 2-way ANOVA.

There was no difference in the control responses to MCH or H between the BG's and M's. Both doses of A significantly attenuated the increase in  $R_L$  after H

challenge in both BG's and M's. Both doses of A also attenuated the response to MCH in M's while only the larger dose (2.5  $\mu\text{g}/\text{kg}$ ) attenuated the response in BG's. Furthermore, the attenuation with A (2.5  $\mu\text{g}/\text{kg}$ ) in the BG's was significantly less ( $p < 0.05$ ) than that seen in the M's. During the 3 conditions in the M's, MCH 0.75 mg/ml increased  $R_L$  (cm H<sub>2</sub>O/L/sec) from baseline:  $7.5 \pm 1.3$ ,  $3.6 \pm .62$ , and  $1.7 \pm .43$  respectively. During the 3 conditions in the BG's, MCH 0.75 mg/ml increased  $R_L$   $6.7 \pm 1.3$ ,  $7.8 \pm 1.1$ , and  $3.4 \pm 0.58$ .

In conclusion, we found that although no difference exists between BG's and M's in the relaxation obtained with A during H challenge, A was significantly less effective in attenuating the response to MCH in BG's than in M's. These data suggest that an abnormal functional antagonism or interaction between the adrenergic and cholinergic system is present in BG and may be important to the AH in the BG model of asthma. Supported by NIH HL 38435.

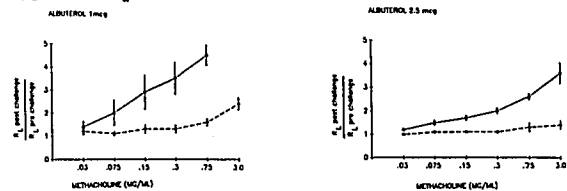


Fig. 1: Attenuation in airway responsiveness to MCH in BG (o-o) and mongrel (•-•) dogs with albuterol.

## A1161

**TITLE:** Barbiturate Induced Airway Constriction in Guinea Pig Trachea: Structure-Function Relationship

**AUTHOR:** C.Curry M.D., C.Lenox M.D., W.Mitzner Ph.D., C.Hirshman M.D.

**AFFILIATION:** Depts. of Anesthesiology/CCM and Env. Health Sci., The Johns Hopkins Med. Insts., Baltimore, MD 21205

Barbiturates are commonly used induction agents in anesthesia. Their effects on airway tone and reactivity are controversial, especially in the patient with reactive airway disease. We have previously shown that thiopental produced dose related constriction in guinea pig trachea (*Anesthesiology*, in press). It is not clear whether this constriction is a property of all barbiturates or is specific to thiopental. We therefore compared the effects of two other ultra short acting barbiturates, thiamylal (a thiobarbiturate) and methohexital (an oxybarbiturate) at increasing airway tone in an intact guinea pig tracheal preparation.

Whole tracheas were suspended between two cannula in 50cc tissue baths and perfused at a constant flow rate with Krebs Henseleit solution. The contractile responses were assessed by measuring the pressure differential between the tracheal inlet and outlet ports. Thiamylal and methohexital were added to the bath of each trachea followed by wash periods between each drug. Each drug was added to produce final bath concentrations of  $10^{-6}$ ,  $10^{-5}$ ,  $10^{-4}$ ,  $10^{-3}$ , and  $3 \times 10^{-3}\text{M}$ . All data were normalized to a concentration of carbachol ( $2 \times 10^{-6}\text{M}$ ) which has been shown to produce maximum constriction in this preparation. All data were expressed as a mean  $\pm$  SEM and were analyzed by one-

way ANOVA.

Thiamylal produced constriction beginning at  $10^{-4}\text{M}$  which reached a maximum at  $10^{-3}\text{M}$  ( $56.2 \pm 4.0\%$ ;  $p < 0.0001$ ). Methohexital did not produce any significant change in airway tone (Fig. 1). The dose-response relationships produced by thiamylal were similar to those previously observed with thiopental.

We conclude that thiobarbiturates, but not oxybarbiturates, constrict guinea pig trachea in concentrations similar to those achieved *in vivo*. The ability to constrict the airway is most likely related to the sulfur moiety of the thiobarbiturate structure. These data suggest that a nonbarbiturate or an oxybarbiturate may be indicated for patients at risk of bronchospasm. Supported by NIH HL 01342.

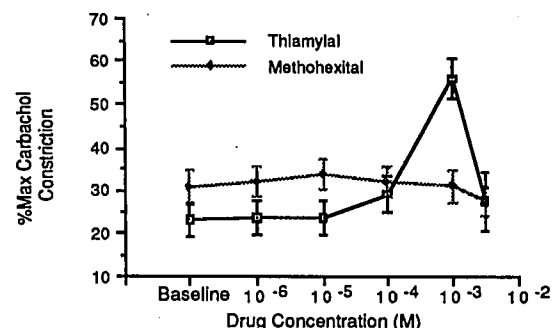


Fig. 1 Comparison of guinea pig tracheal constriction to thiamylal and methohexital.