

Title: AMINOPHYLLINE DOES NOT INHIBIT HYPOXIC PULMONARY VASOCONSTRICTION

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**INTRODUCTION:** Aminophylline is widely recognized as a clinically useful bronchodilator. Aminophylline is also a vasodilator and is commonly thought to inhibit hypoxic pulmonary vasoconstriction (HPV). The notion that aminophylline inhibits HPV constitutes a theoretical explanation for an occasional decrease in  $P_{O_2}$  following administration of aminophylline and therefore a theoretical impediment to greater clinical use of the drug. The purpose of this investigation was to directly examine the effects of aminophylline on HPV in an experimental model that allows direct examination of pharmacological influence on HPV.

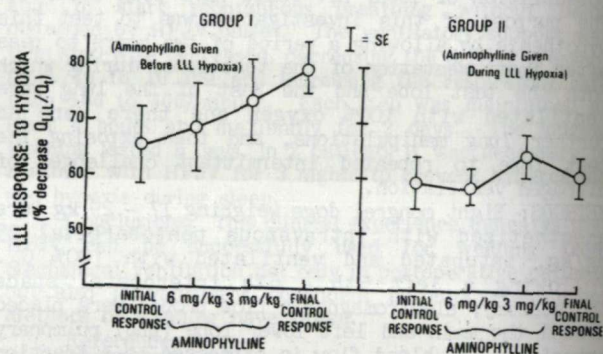
**METHODS:** Eight pentobarbital anesthetized dogs were intubated and ventilated with one side of a dual piston Harvard ventilator. Following a left thoracotomy, electromagnetic flow probes were placed around the main and left lower lobe (LLL) pulmonary arteries. The LLL bronchus was intubated distal to a ligature and ventilated independently and synchronously with the rest of the lung (RL) with the second piston of the respirator. Appropriate LLL and RL ventilation was achieved by manipulating the two tidal volumes and external dead spaces. The respiratory rate was adjusted so that  $P_{CO_2}$  was  $40 \pm 2$  torr. Blood pressure in the femoral and pulmonary arteries and left atrium were measured directly ( $P_{sa}$ ,  $P_{pa}$ ,  $P_{la}$ , respectively). The LLL was ventilated with 100%  $O_2$  or with 95%  $N_2$  and 5%  $CO_2$  to obtain LLL control hyperoxia (LLL- $O_2$ ) or LLL hypoxia (LLL- $N_2$ ) respectively. The rest of the lung was ventilated with 100%  $O_2$  throughout the experiment. We express blood flow to the LLL as a fraction of the cardiac output ( $Q_{LLL}/Q_t$ ). The LLL HPV response was computed as the maximum % decrease in  $Q_{LLL}/Q_t$  during LLL- $N_2$  from its LLL- $O_2$  value. Several LLL HPV responses were performed prior to the experimental sequence. The experimental sequence consisted of induction of LLL- $N_2$  (initial control LLL HPV response); return to LLL- $O_2$ ; administration of aminophylline 6 mg/kg i.v. over 10 min before (Group I; N=4) and after (Group II; N=4) establishment of LLL- $N_2$ ; return to LLL- $O_2$ ; administration of aminophylline 3 mg/kg i.v. over 5 min before (same 4 Group I dogs) and after (same 4 Group II dogs) establishment of LLL- $N_2$ ; return to LLL- $O_2$ ; induction of LLL- $N_2$  2 hours later (final control LLL HPV response). After each i.v. aminophylline bolus in both Group I and II, maintenance aminophylline was infused i.v. at 1 mg/kg/hr until the end of the appropriate LLL- $N_2$  period. Arterial and mixed venous serum theophylline levels were measured in every dog at the end of the LLL- $N_2$  period that followed each bolus administration.

**RESULTS:** Serum theophylline levels were not significantly different between Group I and II and are therefore reported together (Table)(mean  $\pm$  SE). Following the 6 mg/kg aminophylline bolus maximum hemodynamic changes consisted of increased cardiac output (from  $1913 \pm 389$  to  $2114 \pm 368$  ml/min;  $p < .025$ ), decreased systemic arterial pressure (from

SITE	POST AMINOPHYLLINE BOLUS (mg/kg)	SERUM THEOPHYLLINE LEVEL ( $\mu$ g/ml)
ARTERIAL	6	$15.1 \pm 0.7$
	3	$13.5 \pm 1.1$
VENOUS	6	$12.0 \pm 0.8$
	3	$14.1 \pm 0.7$

$119 \pm 6$  to  $116 \pm 7$  torr; NS), decreased systemic vascular resistance (from  $5374 \pm 604$  to  $3797 \pm 49$  dynes.s.cm $^{-5}$ ;  $p < 0.025$ ) and pulmonary vascular resistance (from  $497 \pm 71$  to  $483 \pm 65$  dynes.s.cm $^{-5}$ ; NS). The figure shows that in both Groups of dogs the magnitude of LLL HPV response during aminophylline infusion was no different from either the initial or final control LLL HPV response.

#### AMINOPHYLLINE AND LLL RESPONSE TO HYPOXIA



**DISCUSSION:** The aminophylline dosages employed in this experiment resulted in serum theophylline levels that were in the accepted therapeutic range for humans. These serum theophylline concentrations were unassociated with any change in the LLL HPV response. This negative result is surprising in that  $\beta$ -agonists (isoproterenol, ritodrine, salbutamol, and orciprenaline), glucagon, and  $ATP$  all increase cellular cAMP and markedly inhibit HPV whereas aminophylline also increases cellular cAMP but does not inhibit acute in-vivo lobar HPV. The basic scientific implication of these findings are that aminophylline may not increase cAMP levels in the canine pulmonary circulation. In addition, if aminophylline does not inhibit HPV in humans with bronchospastic disease (asthma and COPD), as our results suggest, then the small and varying effect of aminophylline on arterial oxygenation (see for example Table I of Stirt et al, Anes Analg 60:587, 1981) should be explained simply on the basis of changes in respiratory mechanics rather than some sort of summation of deleterious vasodilator and efficacious bronchodilator effects. The clinical implication of these findings, when viewed in the context of previous clinical experience, are that aminophylline may be used with increased confidence that major decreases in arterial oxygenation will not occur (i.e. pre-existing HPV will not be inhibited).