Aminophylline Does Not Attenuate Histamine-Induced Airway Constriction during Halothane Anesthesia

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The effects of aminophylline on the release of endogenous catecholamines and on airway reactivity to aerosol histamine challenge were evaluated during halothane and thiopental/fentanyl anesthesia in basenji-greyhound dogs. Responses to histamine aerosol challenge (0.01, 0.03, 0.1, 0.3, 1.0, and 3.0 mg/ml) were measured during six conditions: 1) thiopental/fentanyl anesthesia (control), 2) thiopental/ fentanyl with aminophylline infusion, 3) halothane anesthesia (1.5 MAC), 4) halothane anesthesia with aminophylline infusion, 5) thiopental/fentanyl anesthesia after pretreatment with iv propranolol, and 6) thiopental/fentanyl anesthesia with aminophylline infusion after pretreatment with iv propranolol. Prior to aerosol challenge baseline pulmonary resistance (R_L) did not differ in the six groups. Aminophylline significantly attenuated the pulmonary response to histamine and increased catecholamine concentrations during thiopental/fentanyl anesthesia. Although halothane itself significantly attenuated the pulmonary response to histamine, the administration of aminophylline during halothane anesthesia produced no additional protective effect and no increases in catecholamines were noted. Moreover, no protective effect was seen after aminophylline administration during thiopental/fentanyl anesthesia in the same dogs pretreated with propranolol. These data suggest that the protective effect of aminophylline on histamine reactivity results from release of endogenous catecholamines and that the use of aminophylline during halothane anesthesia, which blocks this release, is not warranted. (Key words: Anesthetics, intravenous: fentanyl; thiopental. Anesthetics, volatile: halothane. Antagonists, adrenergic: propranolol. Lungs, asthma: bronchoconstriction; pulmonary resistance. Pharmacology: aminophylline. Sympathetic nervous system, catecholamines: epinephrine, norepinephrine.)

ASTHMA is present in approximately 2–5% of the general population.[1,2] Thus, anesthesiologists are frequently faced with preventing and treating bronchospasm that develops intraoperatively. Inhalational anesthesia is often used in the anesthetic management of asthmatic patients, and aminophylline has long been advocated as a first line drug in treating asthmatic patients who develop acute bronchospasm during anesthesia. Whereas the potential risks of the combination of aminophylline and halothane (dysrhythmias) are well established,[3–6] the benefits (enhanced bronchodilator effects) are not.

Although the mechanism by which theophyllines exert their beneficial effects on airways are controversial, theophylline administration has been shown to acutely increase plasma epinephrine concentrations,[7] and this increase of plasma epinephrine is capable of reducing symptoms of asthma.[8] If this is indeed an important mechanism by which theophylline compounds exert their beneficial effects on airways, then theophylline preparations should be ineffective if used to treat bronchospasm during halothane anesthesia because halothane reduces the release of endogenous catecholamines.[9,10]

To delineate the role of endogenous catecholamine release in the mechanism of action of aminophylline on airways *in vivo* and the possible interactions between halothane (an agent that is known to block the release of endogenous catecholamines) and aminophylline, we evaluated the effects of aminophylline on pulmonary reactivity to histamine, and on endogenous catecholamine release during thiopental/fentanyl anesthesia, in the presence and absence of beta adrenergic blockade and during halothane (1.5 MAC) anesthesia in a dog model of asthma.[11]

Methods

GENERAL CONDITIONS

These studies were approved by the animal research committee of both the School of Medicine and the School of Hygiene and Public Health of the Johns Hopkins University. The animals employed in the study were five basenji-greyhounds (BG) ranging in age from 1 to 2 yr and in weight from 17 to 23 kg. Each dog was studied during six separate conditions performed in random order and separated by at least 1 week. These six conditions included 1) thiopental/fentanyl anesthesia, 2) thiopental/fentanyl anesthesia with aminophylline infusion, 3) halothane anesthesia (1.5 MAC), 4) halothane anesthesia with aminophylline, 5) thiopental/fentanyl anesthesia with iv propranolol (2 mg/kg), and 6) thiopental/fentanyl anesthesia with aminophylline infusion and iv propranolol. The dogs were fasted overnight, received no preanesthetic medicine, and were anesthetized while standing and supported in a sling. Anesthesia was induced in all conditions with intravenous thiopental (15 mg/kg) and intubation of the trachea was facilitated with succinylcholine (0.5 mg/kg). The dogs' tracheas were intubated with an 8.5 mm cuffed endotracheal tube and the lungs were mechanically ven-

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tilated (Harvard Apparatus, Millis, Massachusetts) with 100% oxygen at a tidal volume of 15 ml/kg. Respiratory rate was 20 breaths/min with an end-tidal CO_2 of 38–42 mmHg. Heart rate was continuously monitored with a needle electrode electrocardiogram (Tektronics 412, Beverton, Oregon) and blood pressure was measured with an automated blood pressure cuff (Datascope Accutor 1A, Paramus, New Jersey). In studies involving intravenously administered anesthetics (conditions 1, 2, 5, and 6), anesthesia was maintained by a continuous infusion of thiopental (0.2 mg $\cdot$ kg^{-1} $\cdot$ min^{-1})[12] and fentanyl (1 μg/kg) every 20 min until completion of the study (fig. 1). No additional muscle relaxants were used. In studies involving inhalational anesthesia (conditions 3 and 4), halothane was started immediately after intubation and was admin-

istered until a steady state end-tidal anesthesia concentration of 1.5 MAC was established (fig. 1). The MAC value of halothane in the dog was assumed to be 0.87%.[13] End-tidal halothane and CO_2 concentrations were sampled continuously using a Perkin Elmer 1100 mass spectrometer (Pomona, California).

In studies involving aminophylline, aminophylline (16 mg/kg) was administered as a loading dose over 20 min followed by a continuous infusion of 0.032 mg $\cdot$ kg^{-1} $\cdot$ min^{-1}, which was calculated to achieve a plasma concentration of 15–20 mg/1 (fig. 1).[14] Propranolol (2 mg/kg) was administered by slow iv injection over 5 min with the dogs awake, 5 min prior to the induction of anesthesia. This dose was selected because previous studies with these dogs demonstrated adequate beta-adrenergic blockade.[15,16]

MEASUREMENT OF AIRWAY MECHANICS

Airflow ($\dot{V}$) was measured by a pneumotachograph head (Fleisch type No. 1. OEM Medical Inc, Richmond, Virginia) and a differential pressure transducer (Validyne DP45-16, Northridge, California), which was connected to one channel of a pen recorder (Gould 2500S, Cleveland, Ohio). A balloon (Spectramed, Dayton, Ohio) was placed in the esophagus, filled with 0.8–1.0 ml of air and withdrawn to the point where end-expiratory pressure was most negative. A second catheter was placed alongside the balloon and connected to suction to keep the esophagus free of air and secretions. Transpulmonary pressure was recorded by connecting one side of a differential pressure transducer (Validyne MP 45-18, Northridge, California) to the esophageal balloon and the other side to a needle in the airway. The output of the pressure transducer was recorded on the second channel of the pen recorder. Both records were electronically integrated by a dedicated pulmonary mechanics microprocessor (Buxco Model 6, Sharon, Connecticut) to give values for lung resistance (R_L) and dynamic compliance (C_{dyn}), which was printed out averaged over the six preceding breaths by a computer (Texas Instruments, Model 703 Temple, Texas). Apparatus resistance (2 cmH$_2$O $\cdot$ l^{-1} $\cdot$ s^{-1}), determined by ventilating a mechanical lung analog with known parameters, was subtracted from the results to give R_L.

AEROSOL CHALLENGES

Thirty minutes after induction of anesthesia, inhalational challenges with incremental doses of histamine (0.01, 0.03, 0.1, 0.3, 1.0, and 3.0 mg/ml) were administered during each of the six different conditions (fig. 1). Aerosols were delivered by a Hudson 3000 nebulizer (Hudson, Temecula, California) driven by compressed
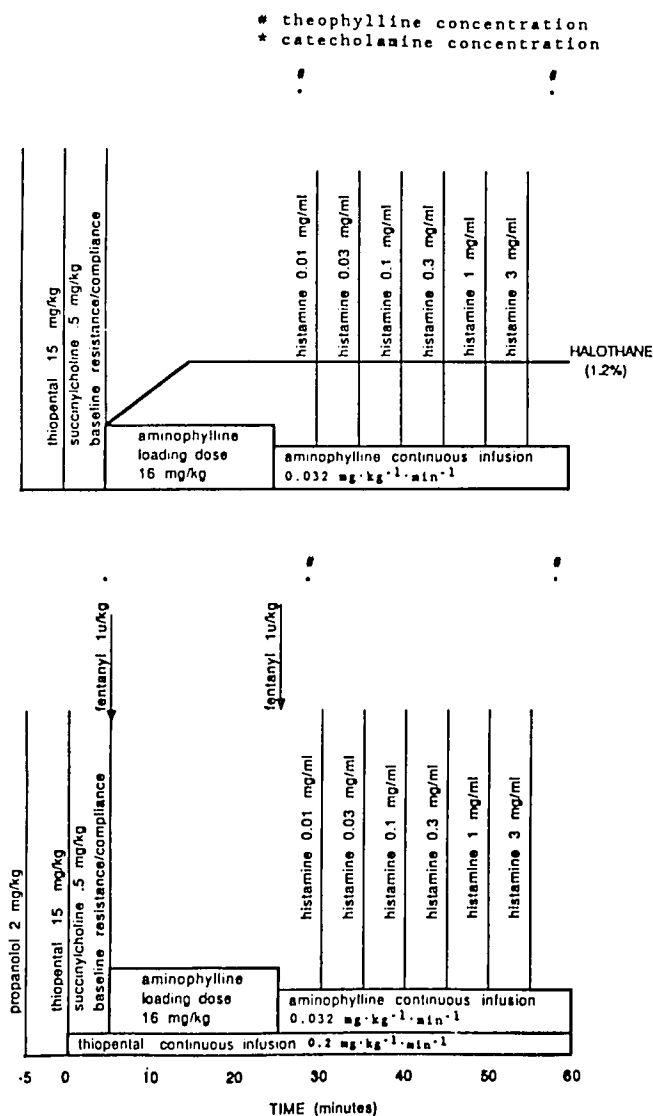

FIG. 1. Protocol for studies using halothane anesthesia (*above*) and thiopental/fentanyl anesthesia (*below*).

oxygen, which delivered aerosol particles with a mass median diameter of 5.7 μm. All solutions were dissolved in distilled water. Histamine was administered for five standardized breaths using an Ayre's t-tube inserted between the nebulizer and the endotracheal tube.[17] The expiratory port was occluded until an inflation pressure of 15 cmH_2O had been obtained. Maximal changes in R_L occurred within 5 min of challenge. Baseline R_L (obtained prior to histamine challenge) was subtracted from maximal R_L following each challenge to give change in R_L. Maximal C_{dyn} postchallenge was divided by C_{dyn} prechallenge $\times$ 100 to give percent decrease in C_{dyn}. Challenges with increasing histamine concentrations were administered at 5-min intervals until R_L reached three times the baseline value. Challenges were administered at 5-min intervals even if resistance had not returned to baseline values.

PLASMA CATECHOLAMINE AND THEOPHYLLINE CONCENTRATIONS

Venous blood was drawn for plasma epinephrine, norepinephrine, and theophylline concentrations from a limb not involved in continuous infusions immediately prior to the first histamine challenge and at completion of the final histamine challenge. An additional sample for catecholamine determination (baseline level) was drawn immediately after induction of anesthesia.

CATECHOLAMINE AND THEOPHYLLINE ANALYSIS

Three milliliters of plasma and 50 μl dihydroxybenzylamine (internal standard) were shaken for 5 min with 50 mg of acid-washed alumina and 1 ml Tris pH 8.7. The alumina was washed three times with 1 ml of water and transferred to a 2.5 ml microcentrifuge tube. Water was aspirated and replaced with 100 μl of 0.1 M perchloric acid. Tubes were then vortexed for 15 s and allowed to stand for 5 min after which they were vortexed for an additional 15 s and centrifuged for 30 s at 13,000 $\times g$. Fifty microliters of acid eluate was injected onto a 4.5 mm $\times$ 22 cm, 5 μm, C_{18} column and eluted with a mobile phase consisting of 70 mM monobasic sodium phosphate, 2.6 mM sodium octyl sulfate, 0.1 mM EDTA, and 8% acetonitrile. Epinephrine and norepinephrine were oxidized at 650 mV (vs. Ag/AgCl) on Bioanalytical Systems vitreous carbon working electrode. An integrator quantified catecholamines by the method of internal standard.

Theophylline concentrations were measured by high pressure liquid chromatography with a sensitivity of less than 1 mg/l.

STATISTICAL ANALYSIS

All data were expressed as the mean $\pm$ SEM of five dogs and analyzed using a two-way analysis of variance (ANOVA) with a P value of less than 0.05 considered as significant. The significant difference between paired groups was then tested by the least significance difference method.

Results

Prior to histamine challenge, there were no significant differences in baseline R_L and C_{dyn} values among the six conditions (table 1). The addition of halothane, aminophylline, or propranolol did not significantly increase R_L or decrease C_{dyn} from the baseline values.

Histamine produced dose-related increases in R_L and decreases in C_{dyn}, which became statistically significant at concentrations of 0.1 mg/ml. The increase in R_L was significantly attenuated in dogs that received thiopental/fentanyl/aminophylline (condition 2) (fig. 2), halothane (condition 3) (fig. 3), and halothane/aminophylline (fig. 3) (condition 4) compared with the thiopental/fentanyl control group (condition 1). This attenuation of the rise in R_L became statistically significant ($P < 0.01$) when comparing the response of conditions 1–4 to a histamine challenge of 0.3 mg/ml and 1.0 mg/ml. Although halothane itself significantly attenuated the response to histamine (condition 3), the addition of aminophylline during 1.5 MAC halothane (condition 4) produced no additional effect (fig. 3).

Although aminophylline attenuated the pulmonary response to histamine during thiopental/fentanyl anesthesia (condition 1 vs. condition 2), no attenuation was noted in dogs that received aminophylline after pretreatment with propranolol (condition 5 vs. 6) (fig. 4).

Serum theophylline values ranged from 15.1 to 21.1 mg/l in the five dogs. Heart rate and blood pressure responses were both significantly lower in the two groups that received halothane (conditions 3 and 4) ($P < 0.05$) when compared with the two groups anesthetized with thiopental/fentanyl without propranolol (conditions 1 and 2) with heart rates ranging from 80 to 100 beats/min and systolic blood pressures from 80 to 90 mmHg in the halothane groups. No significant change in heart rate or

TABLE 1. Baseline Values of Pulmonary Resistance (R_L) and Dynamic Compliance (C_{dyn})

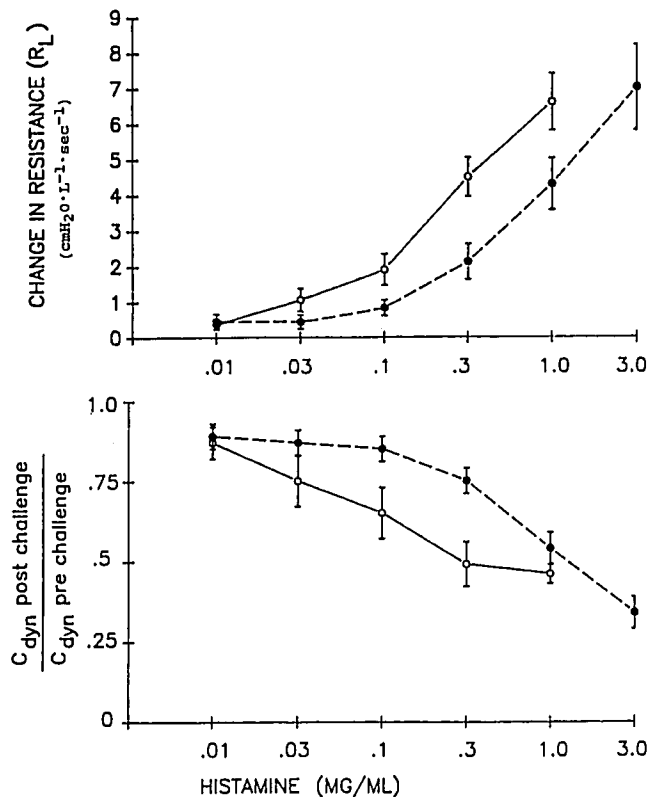|	R_L (cmH$_2$O·l^{-1}·s^{-1})	C_{dyn} (ml/cmH$_2$O)
Thiopental/fentanyl	2.60 ± 0.09	80.3 ± 2.7
Thiopental/fentanyl/ aminophylline	2.96 ± 0.18	82.0 ± 1.3
Halothane	3.00 ± 0.40	82.0 ± 1.3
Halothane/aminophylline	3.10 ± 0.40	83.2 ± 2.14
Thiopental/fentanyl/ propranolol	2.12 ± 0.24	90.0 ± 13.6
Thiopental/fentanyl/ propranolol/aminophylline	2.30 ± 0.28	85.0 ± 7.6

Values are mean ± SEM of five dogs.

FIG. 2. Change in pulmonary resistance (*above*) and decrease in dynamic compliance (*below*) in thiopental/fentanyl-anesthetized dogs in the absence (———) and presence (- - -) of aminophylline. Each point represents the mean ± SE of five dogs.

blood pressure was noted during the aminophylline infusion in the halothane group.

In the thiopental/fentanyl groups (conditions 1 and 2), heart rates ranged from 150 to 170 beats/min and systolic blood pressures from 130 to 150 mmHg. A significant increase in heart rate ($P < 0.05$) was noted during the aminophylline infusion in the thiopental/fentanyl-anesthetized dogs (condition 2) with an increase of heart rates to 190–210 beats/min. No significant change was noted in the systolic blood pressure. The administration of propranolol to the dogs (conditions 5 and 6) resulted in a significant slowing of heart rate from baseline values of 130–140 down to 90–100 beats/min. No significant change in systolic blood pressure was noted. In addition, unlike condition 2, no increase in heart rate was noted during aminophylline infusion in dogs pretreated with propranolol.

Catecholamine concentrations (pg/ml) obtained 5 min after induction of anesthesia and intubation and prior to the start of halothane or aminophylline were similar in all six groups (tables 2 and 3). Norepinephrine and epinephrine concentrations increased significantly ($P < 0.05$) in the dogs anesthetized with thiopental/fentanyl after aminophylline infusion (conditions 2 and 6). In contrast,

norepinephrine and epinephrine levels did not increase after aminophylline infusion in halothane-anesthetized dogs (tables 2 and 3).

Discussion

This study demonstrates that BG dogs react to histamine in a dose-related manner, that during thiopental/fentanyl anesthesia aminophylline increases plasma catecholamine concentrations and attenuates the bronchoconstrictive response, and that during halothane anesthesia aminophylline neither increases plasma catecholamine concentrations nor attenuates histamine-induced airway constriction.

BG dogs, similar to asthmatic people, demonstrate airway hyperreactivity to a variety of challenge aerosols, including methacholine and histamine. This means that the airways of these dogs and asthmatic persons react to concentrations of these agonists that are far lower than those concentrations effective in other dogs and normal people. As has been previously reported, we found no change in baseline R_L and C_{dyn} during halothane and thiopental/fentanyl anesthesia in the unstimulated airway.[18] This is not surprising because dogs in general, including BG, have little baseline tone.
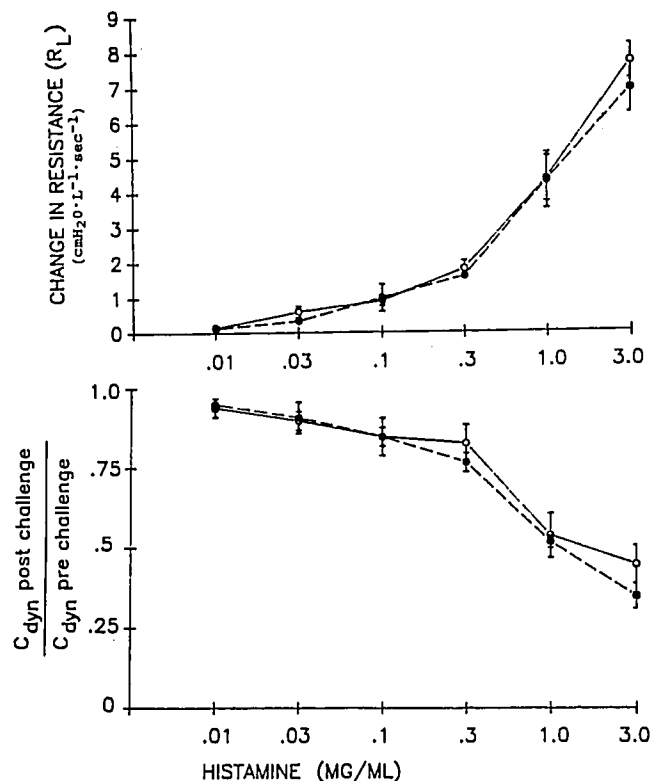

FIG. 3. Change in pulmonary resistance (*above*) and decrease in dynamic compliance (*below*) in halothane-anesthetized dogs in the absence (———) and presence (- - -) of aminophylline. Each point represents the mean ± SE of five dogs.
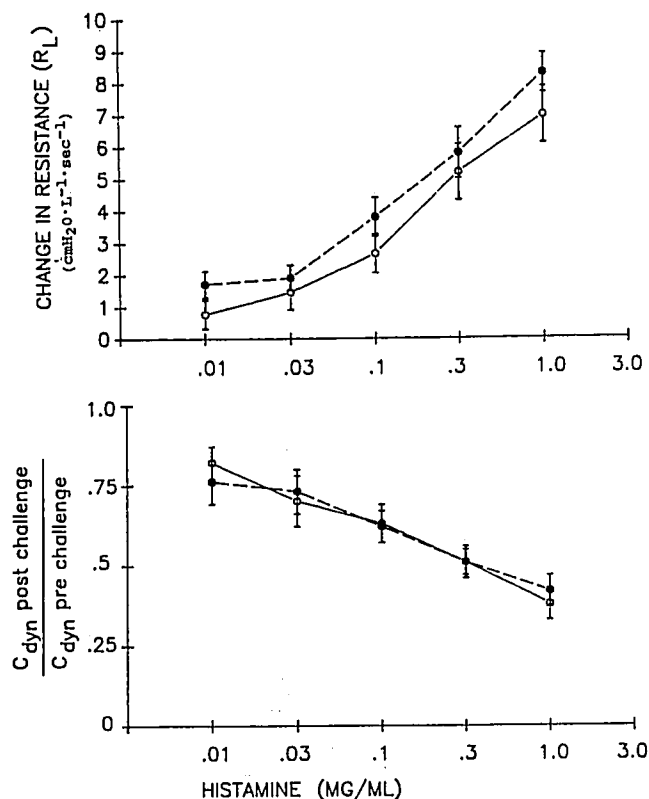
FIG. 4. Change in pulmonary resistance (*above*) and decrease in dynamic compliance (*below*) in thiopental/fentanyl-anesthetized dogs after pretreatment with propanolol in the absence (———) and presence (– – –) of aminophylline. Each point represents the mean ± SE of five dogs.

TABLE 2. Epinephrine Concentrations (pg/ml)

Condition 1 Thiopental/fentanyl	Condition 2 Thiopental/fentanyl/ aminophylline
1) 136 ± 34	1) 96 ± 11
2) 104 ± 14	2) 220 ± 69
3) 112 ± 13	3) 374 ± 64
Condition 3 Halothane	Condition 4 Halothane/ aminophylline
1) 140 ± 32	1) 101 ± 24
2) 88 ± 15	2) 88 ± 24
3) 109 ± 29	3) 104 ± 16
Condition 5 Thiopental/fentanyl/ propranolol	Condition 6 Thiopental/fentanyl/ aminophylline/ propranolol
1) 122 ± 41	1) 90 ± 22
2) 101 ± 26	2) 301 ± 80
3) 133 ± 24	3) 344 ± 91

1) = Five minutes after induction and intubation prior to start of aminophylline or halothane.

2) = Ten minutes after loading dose of aminophylline (groups 2, 4, and 6) and/or 15 min of halothane at end-tidal equal to 1.3% (groups 3 and 4), prior to histamine aerosol challenges.

3) = After completion of histamine aerosol challenges.

the range reported by other investigators in "well anesthetized" dogs.[22]

Inhalational agents, such as halothane, affect airway reactivity by both a direct effect on smooth muscle and by depression of airway reflexes.[23] It is possible that aminophylline may work through a similar mechanism and

In this study we measured R_L, which is the sum of tissue resistance (viscance) and airway resistance. Ludwig *et al.* have shown that the percentage of pulmonary resistance due to tissue resistance remains constant throughout the histamine concentration response curves.[19] Therefore, a linear correlation exists between increases in R_L and changes in airway caliber or resistance.

Several possibilities exist that might explain the lack of additive effect of halothane and aminophylline. Aminophylline reduces the depth of barbiturate anesthesia,[20] which may increase airway reactivity. This interaction is unlikely because aminophylline was effective in our study when administered to dogs anesthetized with thiopental/ fentanyl. Moreover, Nichols *et al.* demonstrated that halothane anesthetic requirements are not affected by aminophylline.[21] In addition, an adequate depth of anesthesia was demonstrated during both thiopental/fentanyl anesthesia (condition 1) and during halothane anesthesia (condition 3) because no rise in the concentration of endogenous catecholamines occurred (tables 2 and 3) and no movement was observed in unparalyzed dogs. Moreover, the plasma catecholamine concentrations were in

TABLE 3. Norepinephrine Concentrations (pg/ml)

Condition 1 Thiopental/fentanyl	Condition 2 Thiopental/fentanyl/ aminophylline
1) 280 ± 59	1) 244 ± 95
2) 278 ± 58	2) 1221 ± 563
3) 281 ± 52	3) 1477 ± 488
Condition 3 Halothane	Condition 4 Halothane/ aminophylline
1) 223 ± 37	1) 194 ± 39
2) 121 ± 20	2) 204 ± 72
3) 155 ± 35	3) 164 ± 49
Condition 5 Thiopental/fentanyl/ propranolol	Condition 6 Thiopental/fentanyl/ aminophylline/ propranolol
1) 261 ± 54	1) 244 ± 99
2) 244 ± 46	2) 988 ± 486
3) 244 ± 55	3) 1124 ± 466

1) = Five minutes after induction and intubation prior to start of aminophylline or halothane.

2) = Ten minutes after loading dose of aminophylline (groups 2, 4, and 6) and/or 15 min of halothane at end-tidal equal to 1.3% (groups 3 and 4), prior to histamine aerosol challenges.

3) = After completion of histamine inhalational challenges.

that this effect is maximal at 1.3% halothane or at aminophylline concentrations of 20 mg/l. If this were the case, the addition of a second agent would produce no further effect. This is unlikely; we are aware of no published data suggesting that aminophylline inhibits vagal reflexes. It is also unlikely that bronchodilatation is maximal at either 1.3% halothane or at aminophylline concentrations of 20 mg/l because both agents attenuated the response to histamine but by no means abolished it in this study and in previous studies with histamine in this model.[24]

Aminophylline and halothane may not produce additive effects because the actions of one will antagonize the actions of the other. Several mechanisms of action have been proposed for aminophylline's bronchodilatory properties. These have included 1) inhibition of cyclic AMP phosphodiesterase activity,[25] 2) an anti-adenosine property,[26] 3) a decrease in the intracellular availability of calcium,[27] 4) release of endogenous catecholamines,[7,8] and 5) an anti-inflammatory effect.[28]

The most likely explanation for our findings is that aminophylline acts through the release of endogenous catecholamines and that halothane blocks this effect.[9,10] During thiopental/fentanyl anesthesia we found an increase in the concentrations of norepinephrine and epinephrine during the administration of aminophylline. No such increase was noted during halothane anesthesia. This inhibition of the release of endogenous catecholamines prevents the protective action of aminophylline on airways. A similar result has been noted after surgical excision of the adrenals in animals.[29] Therefore, it is likely that the chemical adrenalectomy induced by halothane blocks aminophylline's ability to release endogenous catecholamines. The role of endogenous catecholamines in the protection afforded by aminophylline is further supported by the propranolol studies showing aminophylline to be ineffective in the presence of beta-adrenergic blockade during thiopental/fentanyl anesthesia (condition 6).

In conclusion, we found that the administration of aminophylline to dogs anesthetized with thiopental/fentanyl increased endogenous catecholamines and attenuated the bronchoconstrictor response to aerosolized histamine. This attenuation was blocked by pretreatment with propranolol. Although halothane alone attenuated the pulmonary response to histamine, aminophylline infusion during deep halothane anesthesia (1.5 MAC) produced no further attenuation in the response and no increase in catecholamine concentrations occurred. This relationship between the rise of endogenous catecholamines and the attenuation of histamine-induced bronchoconstriction suggests that aminophylline acts in vivo through the release of endogenous catecholamines. Although it is difficult to extrapolate these findings to humans, in view of the po-

tential morbidity from the interaction of halothane and aminophylline, other therapies, such as deepening the level of anesthesia or the use of beta$_2$ specific adrenergic agonists, may be more appropriate in the treatment of bronchospasm during deep halothane anesthesia (1.5 MAC) rather than the acute administration of aminophylline.

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